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Synthesis of 7,12-Benz[*a*]anthraquinones via Diels–Alder Reaction of 1,4-Phenanthraquinones

Bruce Irwin Rosen and William P. Weber*

Department of Chemistry, University of Southern California, Los Angeles, California 90007

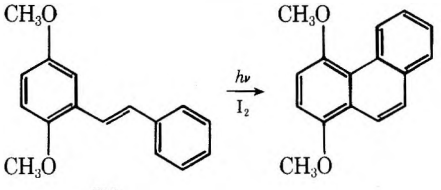
Received April 12, 1977

7,12-Benz[*a*]anthraquinones have been prepared by Diels–Alder reaction of 1,4-phenanthraquinones and 1,3-butadiene. The precursors, 1,4-phenanthraquinones, have been prepared in two ways. Photocyclization of 2,5 dimethoxystilbene under oxidizing conditions yields 1,4-dimethoxyphenanthrene, which is demethylated by trimethylsilyl iodide and directly oxidized to 1,4-phenanthraquinone. Diels–Alder reaction of styrenes and 1,4-benzoquinone yields 1,4-phenanthraquinones directly.

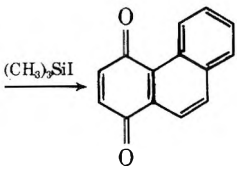
We have been interested in the preparation of substituted 7,12-dimethylbenz[*a*]anthracenes. It should be noted that 7,12-dimethylbenz[*a*]anthracene is one of the most potent carcinogens known.[1,2] 7,12-Dimethylbenz[*a*]anthracene has been prepared efficiently from 7,12-benz[*a*]anthraquinone.[3] Thus a versatile synthesis of substituted 7,12-benz[*a*]anthraquinones would provide a solution to this problem. 7,12-Benz[*a*]anthraquinone has been prepared by direct oxidation of benz[*a*]anthracene.[4] A more general method is the cyclization of *o*-(1-naphthoyl)benzoic acids by treatment with benzoyl chloride and a catalytic amount of sulfuric acid at 140–200 °C.[5–7] The required o-(1-naphthoyl)benzoic acids have been prepared by an aluminum chloride catalyzed Friedel–Crafts reaction between phthalic anhydrides and naphthalenes,[7] or by reaction of 1-naphthyl Grignard reagents with phthalic anhydrides.[6] Both methods possess limitations.

By analogy to the successful synthesis of 1,4-naphthoquinone from the Diels–Alder adduct of 1,3-butadiene (I) and 1,4-benzoquinone (II),[8] it appeared to us that the Diels–Alder reaction between 1,3-butadienes and 1,4-phenanthraquinones would provide adducts which could be converted into various 7,12-benz[*a*]anthraquinones. However, examination of the chemical literature revealed not a single example of a Diels–Alder reaction involving 1,4-phenanthraquinone (III). This is probably due to the fact that while III has been known for almost 50 years, its preparation by classical methods is difficult.[9,10] We should like to report two new methods to prepare III and the first example of its Diels–Alder reactivity.

Our first approach was based on the photochemical cyclization of stilbenes to phenanthrene derivatives under oxidizing conditions.[11–13] Thus, we have found that photolysis of a dilute solution of 2,5-dimethoxystilbene (IV)[14] in the presence of iodine with a 450-W medium-pressure Hanovia Hg lamp leads to production of 1,4-dimethoxyphenanthrene in 71% yield. The direct oxidation of this hydroquinone dimethyl ether with argentic oxide to III failed.[15] An alternative plan called for demethylation of 1,4-dimethoxyphenanthrene to the corresponding 1,4-dihydroxyphenanthrene, which could be oxidized to yield III. Demethylation, however, proved to be no trivial task. Among the demethylation procedures which failed were the use of LiI in collidine[16] and sodium ethyl thiolate in DMF.[17,18] Fortunately, trimethylsilyl iodide[19] proved a successful demethylating reagent.[20] Further, 1,4-dihydroxyphenanthrene must be easily oxidized, since under the reaction conditions (air was not rigorously excluded) the product isolated was III. Problems associated with this



IV



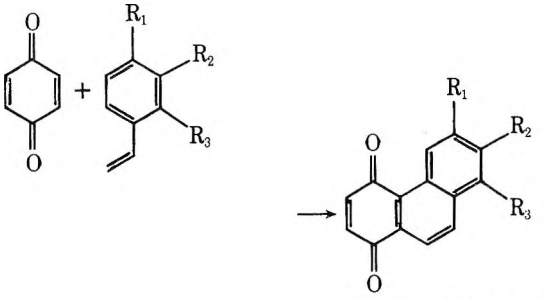
III

method are that quite dilute solutions of IV must be used (≃1 g/L) and relative long photolysis times. Further, neither IV (prepared from 2,5-dimethoxybenzaldehyde by a Wittig reaction) nor trimethylsilyl iodide are commercially available. Nevertheless, by comparison to previous methods this procedure provides a practical approach to 1,4-phenanthraquinones.

Our second systhesis of III is even more direct and over-

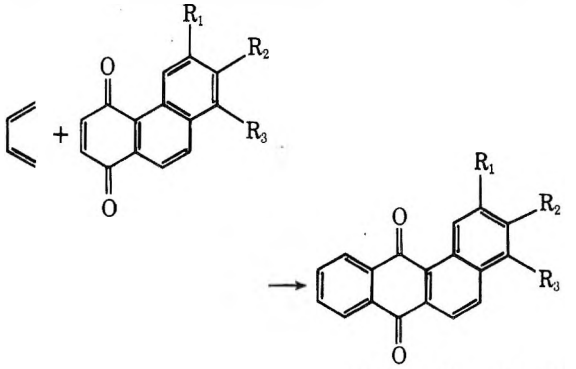
comes most of the limitations discussed above. Styrene is not usually thought of as a potential 1,3-diene system for Diels–Alder reactions; however, a limited number of such reactions have been reported.[21,22]

Thus, the direct Diels–Alder reaction of II with styrene should yield a tetrahydro adduct capable of facile oxidation to III. Examination of the literature reveals at least two reports of success with this type of Diels–Alder reaction.[23,24] Thus reaction of methoxy-II with styrene is reported to yield 3-methoxy-III.[24] On the other hand, reaction of styrene with II is reported to yield a 2:1 styrene/II adduct.[25] We find that heating dilute solutions of styrene and II in xylene at reflux leads to a 30% yield of III. Apparently the initial tetrahydro adduct is dehydrogenated under the reaction conditions, possibly by excess II, to yield III directly. Analogous reactions with *o*-,[26] *m*-,[27] *p*-,[27] and 3,4-dimethoxystyrene[27] led respectively to 8-methoxy-III, 7-methoxy-III, 6-methoxy-III, and 6,7-dimethoxy-III in 20–30% yields. It should be noted that *m*-methoxystyrene might be expected to react with II to yield two products: 7-methoxy-III and 5-methoxy-III. No 5-methoxy-III was detected. This is probably due to the well-known steric hindrance between the C-4 and C-5 positions in phenanthrenes. This is a limitation to the generality of this method.



III, $R_1 = R_2 = R_3 = H$
8-methoxy-III, $R_1 = R_2 = H$; $R_3 = OCH_3$
7-methoxy-III, $R_1 = R_3 = H$; $R_2 = OCH_3$
6-methoxy-III, $R_2 = R_3 = H$; $R_1 = OCH_3$
6,7-dimethoxy-III, $R_3 = H$; $R_1 = R_2 = OCH_3$

III smoothly underwent a Diels–Alder reaction with I under pressure at 90 °C to yield directly 7,12-benz[*a*]anthraquinone (V) in 90% yield. Apparently the initial tetrahydro adduct is easily oxidized on workup in air to yield V. Analogous reaction with 8-methoxy-III, 7-methoxy-III, 6-methoxy-III, and 6,7-dimethoxy-III led respectively to 4-methoxy-V, 3-methoxy-V, 2-methoxy-V, and 2,3-dimethoxy-V in 75–90% yields.



V, $R_1 = R_2 = R_3 = H$
4-methoxy-V, $R_1 = R_2 = H$; $R_3 = OCH_3$
3-methoxy-V, $R_1 = R_3 = H$; $R_2 = OCH_3$
2-methoxy-V, $R_2 = R_3 = H$; $R_1 = OCH_3$
2,3-dimethoxy-V, $R_3 = H$; $R_1 = R_2 = OCH_3$

Experimental Section

The National Cancer Institutes Safety Standards for Research Involving Chemical Carcinogens were followed.

IR spectra were determined with KBr pellets on a Beckman Acculab 2 spectrometer and were calibrated against known bands in a polystyrene film. NMR spectra were recorded on a Varian XL-100 spectrometer, using 10% solutions in $CDCl_3$ with an internal standard of Me_4Si. Ultraviolet spectra were obtained in 95% ethanol on a Beckman Acta M spectrometer. Melting points were taken on a Hoover-Thomas apparatus and are uncorrected. High resolution mass spectra were run at the California Institute of Technology Microanalytical Laboratory, Pasadena, Calif., on a DuPont 21-492 mass spectrometer.

Preparation of 1,4-Dimethoxyphenanthrene. A mixture of 1.0 g (4.15 mmol) of IV[14] and two crystals of iodine was dissolved in 700 mL of olefin-free hexane. This solution was photolyzed using a 450-W medium-pressure Hanovia lamp. The reaction mixture was then evaporated to dryness under reduced pressure. The crude product was dissolved in 20 mL of hexane, poured into a 2.5 × 10 cm column of alumina, and eluted with hexane/1% EtOAc followed by TLC. The eluent was evaporated to yield 0.70 g (71%) of 1,4-dimethoxyphenanthrene as white crystals, mp 118.5 °C: NMR δ 9.1 (m, 1 *H*), 8.2 (d, 1 H, *J* = 9 Hz), 7.8 (m, 2 H), 7.6 (m, 2 H), 6.95 (dd, 2 H, *J* = 12 and 9 Hz), 4.0 (s, 3 H), 3.9 (s, 3 H); IR C=C 1610 cm^{-1}; UV 2471 Å (ε 1.41 × 10^4), 2660 (1.07 × 10^4), 2790 (1.29 × 10^4), 3025 (6.7 × 10^3), 3140 (5.65 × 10^3), 3315 (2.34 × 10^3), 3480 (3.57 × 10^3), 3650 (3.84 × 10^3). Calcd for $C_{16}H_{14}O_2$, parent ion *m/e* 238.101; found 238.102.

Preparation of III. Method A: Oxidative Demethylation of 1,4-Dimethoxyphenanthrene. In a three-neck, 100-mL, round-bottom flask equipped with a Teflon stirring bar and a condenser was placed 35 mL of CCl_4, 0.22 g (0.925 mmol) of 1,4-dimethoxyphenanthrene, and excess $(CH_3)_3SiI$.[19,20] The reaction was refluxed for 48 h under an atmosphere of N_2 and then quenched with H_2O. The organic fraction was separated, dried ($MgSO_4$), filtered, and evaporated. The crude product was dissolved in 20 mL of hexane and poured into a 2.5 × 10 cm column of alumina and eluted with 5% EtOAc/hexane; the major fraction (yellow band) was collected and evaporated to yield 0.15 g (78%) of III as yellow crystals, mp 145 °C (lit. mp 148 °C):[8,9] NMR δ 9.5 (dd, 1 H, *J* = 9 and 2 Hz), 8.1 (s, 2 H), 7.9–7.5 (m, 3 H), 6.85 (s, 2 H); IR C=O 1670 cm^{-1}, 1660, C=C 1620; UV data was in agreement with literature.[9]

Preparation of III. Method B: Diels–Alder Reaction of Styrene and II. In a three-neck, 500-mL, round-bottom flask equipped with a pressure-equalizing addition funnel, a condenser, and a Teflon stirring bar was placed 5 g (50 mmol) of II in 250 mL of xylene. The solution was heated to reflux and to it was added dropwise over 5 h 4.9 g (47 mmol) of styrene. The solution was refluxed overnight. After cooling, the solvent was evaporated under reduced pressure. The crude product was dissolved in 10 mL of 5% EtOAc/hexane, poured into a 2.5 × 10 cm column of alumina, and eluted with 5% EtOAc/hexane; the major fraction (yellow band) was collected and evaporated to yield 1.4 g (14.3%) of III. Its properties were identical with those of samples prepared by method A.

6-Methoxy-III was prepared as above by the reaction of 2.0 g (15 mmol of *p*-methoxystyrene[27] and 2.8 g (26 mmol) of II to yield 1.1 g (31%) of 6-methoxy-III (orange crystals), mp 195 °C: NMR δ 9.0 (d, 1 H, *J* = 2 Hz), 8.01 (dd, 2 H, *J* = 12 and 8 hz), 7.75 (d, 1 H, *J* = 10 Hz), 7.3 (d, 1 H, *J* = 2 Hz), 6.9 (s, 2 H), 3.98 (s, 3 H); IR C=O 1655 cm^{-1}, C=C 1620; UV 2315 Å (ε 5.26 × 10^4), 2700 (1.60 × 10^4), 2900 (1.3 × 10^4), 3880 (4.96 × 10^3). Calcd for $C_{15}H_{10}O_3$, parent ion *m/e* 238.063; found 238.065.

7-Methoxy-III was prepared as above by the reaction of 2.5 g (19 mmol) of *m*-methoxystyrene[27] and 4.5 g (42 mmol) of II to yield 0.85 g (19%) of 7-methoxy-III (orange crystals), mp 140 °C: NMR δ 9.35 (d, 1 H, *J* = 10 Hz), 8.95 (dd, 2 H, *J* = 13 and 8 Hz), 7.25 (dd, 1 H, *J* = 10 and 4 Hz), 7.0 (d, 1 H, *J* = 4 Hz), 6.78 (s, 2 H), 3.76 (s, 3 H); IR C=O 1660 cm^{-1}, C=C 1620; UV 2334 Å (ε 3.53 × 10^4), 2600 (1.09 × 10^4), 2940 (1.04 × 10^4), 3023 (1.07 × 10^4). Calcd for $C_{15}H_{10}O_3$, parent ion *m/e* 238.063; found 238.062.

8-Methoxy-III was prepared as above by the reaction of 2.1 g (16 mmol) of *o*-methoxystyrene[26] and 4.3 g (40 mmol) of II to yield 1.15 g (30%) of 8-methoxy-III (dark red-brown crystals), mp 204 °C: NMR δ 9.05 (d, 1 H, *J* = 9 Hz), 8.65 (d, 1 H, *J* = 8 Hz), 8.1 (d, 1 H, *J* = 8 Hz), 7.58 (t, 1 H, *J* = 8 Hz), 6.9 (br s, 3 H), 3.98 (s, 3 H); IR C=O 1660 cm^{-1}, C=C 1615; UV 2210 Å (ε 2.46 × 10^4), 2584 (7.75 × 10^3), 3001 (1.03 × 10^4), 3679 (1.65 × 10^3). Calcd for $C_{15}H_{10}O_3$, parent ion *m/e* 238.063; found 238.065.

6,7-Dimethoxy-III was prepared as above by the reaction of 2.0 g (12.2 mmol) of 3,4-dimethoxystyrene[27] with 3.2 g (29 mmol) of II to yield 0.7 g (21%) of 6,7-dimethoxy-III (orange crystals), mp 236 °C dec: NMR δ 9.0 (s, 1 H), 7.0 (s, 2 H), 7.02 (s, 1 H), 6.82 (s, 2 H), 4.0 (s, 3 H), 3.96 (s, 3 H); IR C=O 1670 cm^{-1}, 1650, C=C 1620; UV 2450 Å (ε 8.25 × 10^4), 2900 (1.48 × 10^4), 3020 (1.01 × 10^4), 4273 (9.07 × 10^3).

Calcd for $C_{16}H_{12}O_4$, parent ion *m/e* 268.073; found 268.071.

Preparation of V. Into a pressure bottle was placed 0.09 g (0.43 mmol of III, 25 mL of benzene, and a Teflon stirring bar. The solution was cooled to −78 °C and excess I was condensed in. The bottle was capped and the reaction flask was heated to 90 °C and stirred overnight. The flask was then cooled and vented and the solvent was removed under reduced pressure. The crude product was dissolved in 5 mL of hexane and poured into a column of alumina. Elution with hexane removed butadiene polymer. This was followed by elution with 15% EtOAc/hexane to move the desired product from the column. The eluent was evaporated to yield 0.10 g (90%) of V (greenish crystals), whose spectral (UV, NMR) properties were identical with those of an authentic sample (Aldrich), mp 165–166 °C (lit. mp 166–167 °C).[4]

2-Methoxy-V was prepared as above by the reaction of 0.10 g (0.42 mmol) of 6-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.11 g (91%) of V (yellow crystals), mp 195 °C (lit. mp 200 °C):[28] NMR δ 9.2 (d, 1 H, J = 4 Hz), 8.3–8.0 (m, 4 H), 7.8–7.65 (m, 3 H), 7.3 (d, 1 H, J = 4 Hz), 4.0 (s, 3 H); IR C=O 1670 cm^{-1}, C=C 1625; UV 2236 Å (ε 1.93 × 10^4), 2555 (1.71 × 10^4), 2903 (9.5 × 10^3), 3010 (8.25 × 10^3), 4408 (1.69 × 10^3).

3-Methoxy-V was prepared as above by the reaction of 0.05 g (0.21 mmol) of 7-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.045 g (75%) of 3-methoxy-V (yellow crystals), mp 145 °C: NMR δ 9.5 (d, 1 H, J = 10 Hz), 8.3–7.9 (m, 4 h), 7.75–7.6 (m, 2 H), 7.3 (dd, 1 H, J = 10 and 3 Hz), 7.1 (d, 1 H, J = 3 Hz), 3.9 (s, 3 H); IR C=O 1670 cm^{-1}, C=C 1620; UV 2241 Å (ε 3.22 × 10^4), 2456 (2.13 × 10^4), 2530 (1.99 × 10^4), 3037 (2.95 × 10^4), 3841 (4.02 × 10^3). Calcd for $C_{19}H_{12}O_3$, parent ion *m/e* 288.079; found 288.076.

4-Methoxy-V was prepared as above by the reaction of 0.025 g (0.11 mmol) of 8-methoxy-III and excess 9.7 g (200 mmol) of I to yield 0.026 g (88%) of 4-methoxy-IV (red-orange crystals), mp 212 °C (lit. mp 220 °C):[29] NMR δ 9.22 (d, 1 H, J = 10 Hz), 8.7 (d, 1 H, J = 10 Hz), 8.3–8.18 (m, 3 H), 7.8–7.5 (m, 3 H), 6.9 (d, 1 H, J = 8 Hz), 3.98 (s, 3 H); IR C=O 1670 cm^{-1}, C=C 1590; UV 2184 Å (ε 2.71 × 10^4), 2461 (1.32 × 10^4) 2800 (8.69 × 10^3), 3007 (1.51 × 10^4), 4322 (1.22 × 10^3).

2,3-Dimethoxy-V was prepared as above by the reaction of 0.116 g (0.43 mmol) of 6,7-dimethoxy-III and excess 9.7 g (200 mmol) of I to yield 0.11 g (80%) of 2,3-dimethoxy-V (yellow crystals), mp 237 °C dec: NMR δ 9.2 (s, 1 H), 8.3–8.1 (m, 3 H), 7.94 (d, 1 H, J = 9 Hz), 7.8–7.65 (m, 2 H), 7.08 (s, 1 H), 4.1 (s, 3 H), 4.0 (s, 3 H); IR C=O 1660 cm^{-1}, 1650, C=C 1620; UV 2250 Å (ε 1.71 × 10^4), 2450 (1.11 × 10^4), 2571 (9.3 × 10^3), 2902 (5.9 × 10^3), 3025 (5.9 × 10^3), 3290 (2.27 × 10^3), 4225 (2.41 × 10^3). Calcd for $C_{20}H_{14}O_4$, parent ion *m/e* 318.089; found 318.087.

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Registry No.—I, 106-99-0; II, 106-51-4; III, 569-15-3; 6-methoxy-III, 63216-06-8; 7-methoxy-III, 63216-07-9; 8-methoxy-III, 63216-08-0; 6,7-dimethoxy-III, 63216-09-1; IV, 21889-09-8; 2-methoxy-V, 63216-10-4; 3-methoxy-V, 63216-11-5; 4-methoxy-V, 16277-48-8; 23-dimethoxy-V, 63216-12-6, 1,4-dimethoxyphenanthrene, 63216-13-7; *p*-methoxystyrene, 637-69-4; *m*-methoxystyrene, 626-20-0; *o*-methoxystyrene, 612-15-7; 3,4-dimethoxystyrene, 17055-36-6; styrene, 100-42-5.

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A General Synthesis of 1-, 2-, 3-, and 4-Substituted Benz[*a*]anthracene-7,12-diones

Wayne B. Manning,* Joseph E. Tomaszewski, Gary M. Muschik, and Ronald I. Sato

Chemical Carcinogenesis Program, NCI–Frederick Cancer Research Center, Frederick, Maryland 21701

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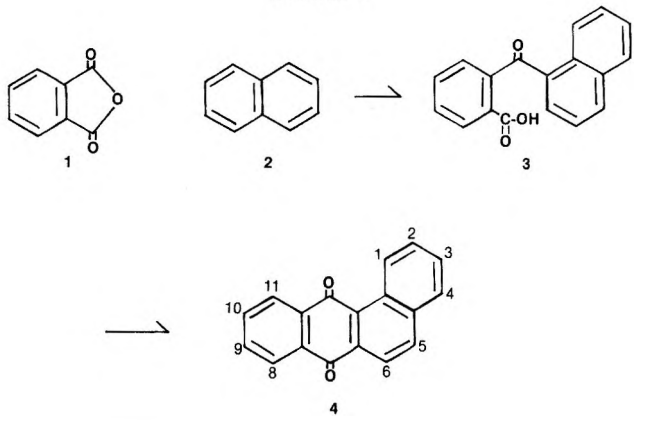
Various 1-, 2-, 3-, and 4-substituted derivatives of benz[a]anthracene-7,12-dione (4) have been prepared by reaction of ring-substituted styrenes and 1,4-naphthoquinone (5) in the presence of chloranil. Comparative reactions done with and without chloranil demonstrated that chloranil had a positive effect upon the yield of the substituted benz[a]anthracene-7,12-diones. The preparation of 1,4-dimethylbenz[a]anthracene-7,12-dione in yields comparable with those obtained for the monosubstituted diones demonstrated that certain steric problems of the Diels–Alder reaction could be overcome. Spectral data are discussed.

The current interest in the metabolites of benz[a]anthracene and 7,12-dimethylbenz[a]anthracene as potential carcinogens has prompted study into synthetic methods to prepare these compounds. Recent preparations of substituted benz[a]anthracenes and 7,12-dimethylbenz[a]anthracenes (DMBAs) have been based upon multistep syntheses using substituted naphthalenes and phthalic anhydrides in a Friedel–Crafts acylation, followed by cyclization of the re-

Scheme I



sulting keto acid **3** to the dione product[1,2] (Scheme I). This classical route for preparing 1-, 2-, 3-, and 4-substituted benz[*a*]anthracene-7,12-diones required substituted naphthalenes that often led to problems in orientation. Diels–Alder reactions between 1,4-naphthoquinone (**5**) and the appropriate styrenes were recently used[3] to prepare benz[*a*]anthracene-7,12-dione (BAD) and its 5-methyl derivative (5-MeBAD). This Diels–Alder reaction does not suffer from the problems inherent in the Friedel–Crafts method and, if general, provides a simple alternative. We now wish to report the generalization of this reaction to the formation of 1-, 2-, 3-, and 4-substituted BADs from which the corresponding benz[*a*]anthracenes could be prepared in one step[4] and the substituted DMBAs in two steps.[5]

The formation of these diones from 1,4-naphthoquinone and ring-substituted styrenes, represented by **6**, requires two dehydrogenations after the Diels–Alder adduct formation (Scheme II). The presence of 1,4-naphthalenediol in the reaction mixture, identified by TLC, suggested that 1,4-naphthoquinone served as the oxidizing agent. Addition of chloranil, with its higher oxidation potential[6] than **5**, aided the formation of the dione **9**.

Results and Discussion

For comparison, two solutions of equimolar amounts of styrene plus 1,4-naphthoquinone in toluene were set in an oil bath at 85–90 °C. One of these was treated with an equimolar amount of chloranil. The chloranil-treated reaction showed the presence of benz[*a*]anthracene-7,12-dione (BAD) by thin-layer chromatography (TLC) within 4 h. Comparable amounts of BAD appeared in the TLC analyses of the chloranil-free solution only after 2–4 days at 85 °C. When neither reaction exhibited any quantity of naphthoquinone by TLC, workup of the mixtures yielded 12% BAD in the unmodified reaction and 33% BAD in the chloranil-treated one.

Reaction of equimolar amounts of 2-chlorostyrene, **5**, and chloranil in a small volume of benzene for 6 days at 85 °C led to a 44% yield (method B) of 4-chlorobenz[*a*]anthracene-7,12-dione (4-ClBAD). In contrast, when an extra equivalent of **5** was used instead of the chloranil, the yield of 4-ClBAD was only 14%. This reaction mixture contained many components, three of which possessed parent ions in their mass spectra at *m/e* 292, 294, and 296. This suggested the presence of 4-chlorobenz[*a*]anthracene-7,12-dione (*m/e* 292), a "dihydro" intermediate (**8**, X = Cl) (*m/e* 294), and a "tetrahydro" intermediate (**7a**, X = Cl) (*m/e* 296). The diol tautomer **7a** was suggested for the "tetrahydro" component because of the lack of fragmentation attributable to CO loss, as would be expected for **7**.

The favorable yields produced by the addition of chloranil to the 2-chlorostyrene/1,4-naphthoquinone reaction prompted the use of chloranil in the preparation of the substituted BADs listed in Table I. With the exception of the 4-methoxy compound, the similarity in the yields suggested that the ring substituents did not have a profound effect upon the reactivity when chloranil was present. The low yield of 1-ClBAD was not unexpected because of the steric interaction between the chlorine atom and the quinone carbonyl in this approach of 3-chlorostyrene. The alternate attack should be energetically preferred and lead to a high proportion of 3-ClBAD.

Even these steric problems can be overcome in some cases. 1,4-Dimethylbenz[*a*]anthracene was prepared in 29% yield from 2,5-dimethylstyrene, **5**, and chloranil (method A). The one styrene approach leading to product exhibits steric interactions similar to those present for the formation of the 1-ClBAD, yet the yield of the reaction was comparable with that for the other substituted BADs.

Yields were further improved by oxygenation of the crude reaction mixtures,[7] as was done in method B. This treatment resulted in a much higher yield for the 4-ClBAD when compared with the other substituted BADs that were not oxygenated, and preliminary results indicated a 20% increase (13–16%) in the yield of 4-OMeBAD upon oxygenation.

The spectral characteristics of the diones synthesized were consistent with their assigned structures. Large parent ions were found in the mass spectra of all compounds except the 1-chloro isomer, which possessed a large (M − Cl) fragment.

Proton magnetic resonance spectra were particularly useful in establishing the positions of substitution in the angular benzene ring. Brown and Thomson[8] showed that the resonance signal of the proton in the one position of BAD occurred at δ 9.72 ($CDCl_3$), further downfield than that of any other proton. The position of this resonance and the effect of substitution upon its splitting pattern gave information useful in assigning the position of substitution.

In the cases of the 4-chloro-, 4-bromo-, and 4-fluorobenz[*a*]anthracene-7,12-diones, this proton signal appeared

Scheme II

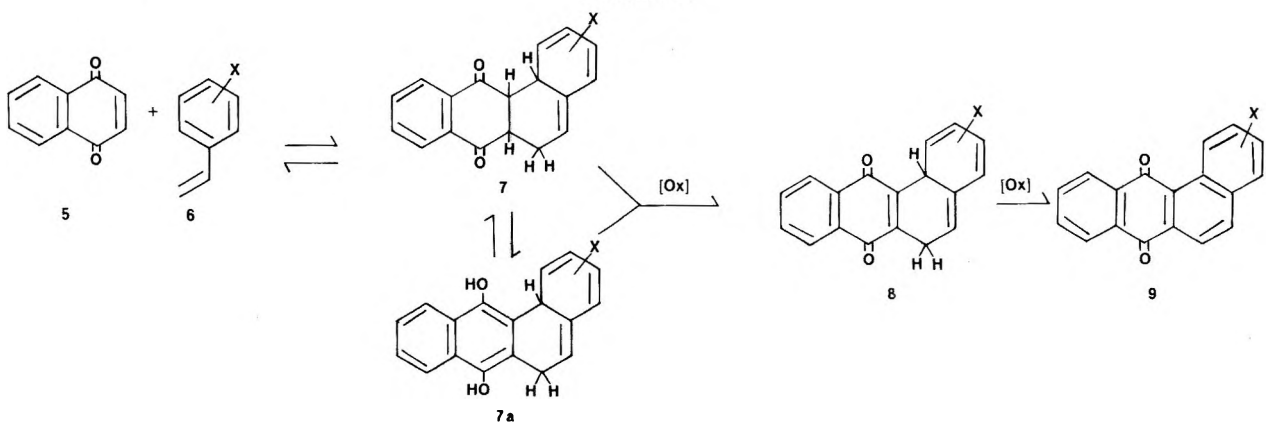


Table I. Substituted Benz[a]anthracene-7,12-diones Prepared from 1,4-Naphthoquinone and Substituted Styrenes

Reactant styrene	Registry no.	Product dione	Registry no.	Method	Scale, mol	Yield, mg (% theoretical)	Mp, °C	Lit. mp °C
2-F[a]	394-46-7	4-F	2712-26-7	A	0.005	300 (20%)	198–199	199–200[b]
4-Me[a]	622-97-9	2-Me	58024-07-0	A	0.010	600 (29%)	188.5–190.0	189–190[c]
2-Br[a]	2039-88-5	4-Br	63715-52-6	A	0.010	780 (30%)	234.5–235.5	230–232[c]
3-Cl[e]	2039-85-2	3-Cl	63715-53-7	A	0.010	680 (30%)	216–217	215–216[f]
3-Cl[e]		1-Cl	63715-54-8	A	0.010	50 (4%)	199–200	[g]
4-Cl[e]	1073-67-2	2-Cl	49600-94-4	A	0.010	720 (33%)	232–233	232–233[h]
2-Cl[e]	2039-87-4	4-Cl	63715-55-9	B	0.010	966 (44%)	232–233	226–227[i]
2-OMe[a]	612-15-7	4-OMe	16277-48-8	A	0.010	374 (13%)	219–220	220–221[j]
2,5-DiMe[k]	2039-89-6	1,4-DiMe	63715-56-0	A	0.010	630 (29%)	213–214	[g]

[a] Polysciences, Inc. [b] E. D. Bergmann, J. Blum, and S. Butanaro, *J. Org. Chem.*, **26**, 3211 (1961). [c] J. W. Cook, *J. Chem. Soc.*, 456 (1932). [d] C. M. Badger and A. R. M. Gibb, *J. Chem. Soc.*, 799 (1949). [e] Aldrich Chemical Co. [f] C. Marschalk and J. Dassigny, *Bull. Soc. Chim. Fr.*, 812 (1948). [g] Satisfactory elemental analyses were obtained (oxygen not analyzed). [h] T. Tsunoda, *Chiba Daigaku Kogakubu Kenkyu Hôkoku*, **7**, 19 (1956). [i] T. Tsunoda, *J. Soc. Org. Synth. Chem.*, **9**, 127 (1951). [j] Reference 5. [k] Leon Laboratories.

Table II. Characteristic Infrared Bands from the Fingerprint Region of Spectra of Substituted Benz[a]anthracene-7,12-diones (KBr)

Compd	IR bands (1000–700 cm^{-1})
4-BrBAD	900, 848, 784, 741, 712
4-ClBAD	990, 848, 785, 742, 711
4-FBAD	991, 848, 788, 743, 713
4-OMeBAD	850, 787, 781, 743, 718
2-ClBAD	857, 712
3-ClBAD	991, 881, 800, 712
1-ClBAD	850, 845, 752, 713, 701
2-MeBAD	870, 778, 712
1,4-DiMeBAD	840, 708

as a doublet (J = 9 Hz). In the cases of the 1-chloro- and the 1,4-dimethylbenz[a]anthracene-7,12-diones, the absence of the δ 9.72 signal confirmed the one-proton assignment. The 2-chloro isomer showed a singlet in this region, while the 2-methylbenz[a]anthracene-7,12-dione yielded a quartet (J = 1 Hz).

Although all of the BADs prepared contained infrared bands at 1655 and 1590 cm^{-1}, the infrared spectra of the 4-substituted isomers exhibited unique absorptions in the ranges of 782–788, 741–744, and 710–718 cm^{-1} (see Table II). In no other spectrum were all of these peaks present. The strength and sharpness of these peaks suggested their use for the differentiation of the 4-substituted BADs from the other isomers.

The ultraviolet spectra were distinct, but of no practical use for determining the position of substitution (see Table III). All of the monosubstituted BADs except the 4-methoxy isomer possessed a major absorption in the 283–287-nm range.

The overall success of this diene synthesis suggests that this method could be a general one for reaction of ring-substituted styrenes with 1,4-naphthoquinone. The results of ongoing investigations will be reported in the near future.

Experimental Section

All melting points were determined using a Fisher-Johns hot-stage apparatus and were uncorrected. Mass spectra were taken on a Finnegan 3300 mass spectrometer equipped with a Finnegan 6000 MS data system. A Cary 17 UV–vis spectrophotometer was used for the UV spectra. Proton magnetic resonance spectra were taken on a Varian XL-100 spectrometer using $CDCl_3$ (0.5% Me_4Si) as solvent, while the IR spectra were obtained on a Perkin-Elmer 467 spectrophotometer.

Method A. To 5–8 mL of toluene were added 0.01 mol (or 0.005 mol) of 1,4-naphthoquinone (recrystallized from alcohol) and equimolar amounts of the substituted styrene and chloranil. The mixture was placed in an 85–90 °C oil bath for ~1 week. When monitoring by thin-layer chromatography on silica gel GF plates, using benzene as development solvent, showed little or no naphthoquinone remaining, the reaction was stopped and the colored reaction mixture was chromatographed on Silicar CC-7 (Mallinckrodt) by elution with hexane, followed by 1:1 benzene–hexane. The progress of the components through the column was followed by long wavelength UV (λ 366 nm), with the diones exhibiting an orange or red-orange color. The BADs isolated in this manner were recrystallized from either benzene or benzene–ethanol.

Method B. The same as method A except that benzene was used as solvent and the reaction was heated in a 75–80 °C oil bath for 1 week. The mixture was then reduced to dryness on a rotary evaporator and 50 mL of a 5% solution of alcoholic potassium hydroxide (95% ethanol) was added to the resultant dark material. The flask was fitted with a reflux condenser and oxygen bubbled through for 24 h. The mixture was then neutralized with concentrated HCl and the crude product extracted with ether. After drying and removal of the ether by evaporation, the residue was chromatographed as in method A.

Acknowledgment. This research was supported by the National Cancer Institute under Contract No. N01-CO-25423 with Litton Bionetics.

Registry No.—5, 130-15-4.

Supplementary Material Available: Complete proton magnetic resonance spectra (9 pages). Ordering information is given on any current masthead page.

Table III. Ultraviolet Absorption Data of Substituted Benz[a]anthracene-7,12-diones (95% Ethanol)

Compd	λ_{max}, nm (log ϵ)				
4-BrBAD	286 (4.48)	254 (4.23)	248 (4.28)	233 (4.35)	217 (4.55)
4-ClBAD	284 (4.51)	254 (4.27)	247 (4.30)	232 (4.38)	217 (4.61)
4-FBAD	284 (4.58)	253 (4.27)	247 (4.29)		217 (4.55)
4-OMeBAD	300 (4.39)	247 (4.34)			218 (4.65)
2-ClBAD	283 (4.50)	253 (4.34)	248 (4.37)	237 (4.36)	217 (4.63)
3-ClBAD	287 (4.48)	254 (4.30)	250 (4.30)	238 (4.29)	218 (4.49)
1-ClBAD	284 (4.51)	255 (4.25)	245 (4.31)		215 (4.56)
2-MeBAD	287 (4.52)	253 (4.42)	248 (4.45)		218 (4.68)
1,4-DiMeBAD	300 (4.52)	248 (4.39)			221 (4.57)

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Preparations of Optically Active [8][8]- and [8][10]Paracyclophanes with Known Absolute Configurations[1]

Masao Nakazaki,* Koji Yamamoto, Masayuki Ito, and Shigeo Tanaka

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka, Japan

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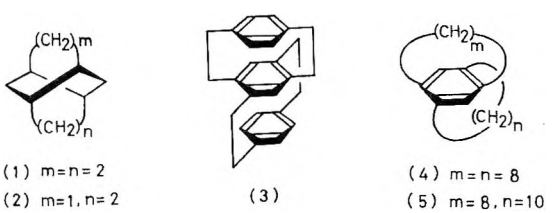
(+)-(*S*)-[8][8]Paracyclophane (**4**) was prepared from (+)-[8]paracyclophane-10-carboxylic acid (**6d**) whose absolute configuration was correlated to (+)-(*S*)-[2.2]paracyclophane-4-carboxylic acid (**20**). Preparations and absolute configurations of (−)-(*R*)-[8][10]paracyclophane (**5**) and related optically active paracyclophane derivatives are also reported.

As part of our continuing efforts to study the chiroptical properties and the biological transformations[2] of high-symmetry chiral (gyrochiral)[3] molecules,[4] the first successful syntheses of (+)-twistane (D_2 symmetry) (**1**),[5] (+)-twist brendane (C_2 symmetry) (**2**),[3] and (−)-[3]chochin (D_2 symmetry)[6] (**3**), all with known absolute configurations, have been reported from our laboratory (Chart I).

[3]Chochin (**3**) and [*m*][*n*]paracyclophane (**4** and **5**)[7] (D_2 symmetry with $m = n$, and C_2 symmetry with $m \neq n$) bear the twisted central benzene nucleus as a common structural unit, and our preceding papers[8] reported the preparation of unusually strained [8][8]paracyclophane (**4**) and [8][10]paracyclophane (**5**). This contribution reports the preparations of (+)-[8][8]paracyclophane (**4**) and (−)-[8][10]paracyclophane (**5**) together with the determination of their absolute configurations.

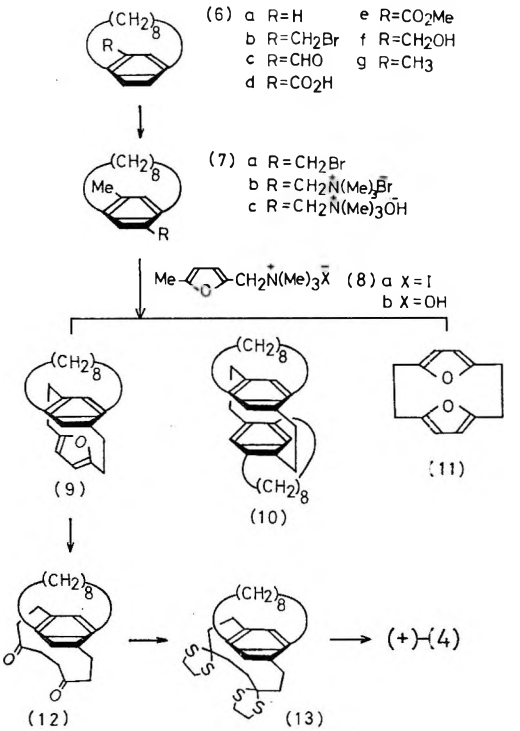
Chart I.



Results and Discussion

Preparation of (+)-[8][8]Paracyclophane (4) (Scheme I).[9] Bromomethylation[10] of [8]paracyclophane (**6a**)[11] afforded the 10-bromomethyl derivative **6b** which was treated with the sodium salt of 2-nitropropane[10] in ethanol to yield the aldehyde **6c.** Permanganate oxidation of the aldehyde **6c** in acetone gave (±)-[8]paracyclophane-10-carboxylic acid (**6d**), the optical resolution of which was accomplished by working with (+)-1-(β-naphthyl)ethylamine as the resolving agent. The (+)-carboxylic acid **6d,** $[\alpha]^{18}_D$ +18°, was converted to the methyl ester **6e** whose hydride reduction afforded the alcohol **6f.** Conversion to the bromide **6b** with phosphorus tribromide followed by reduction with lithium aluminum hydride furnished (+)-10-methyl[8]paracyclophane (**6g**), $[\alpha]^{19}_D$ +4.6°,

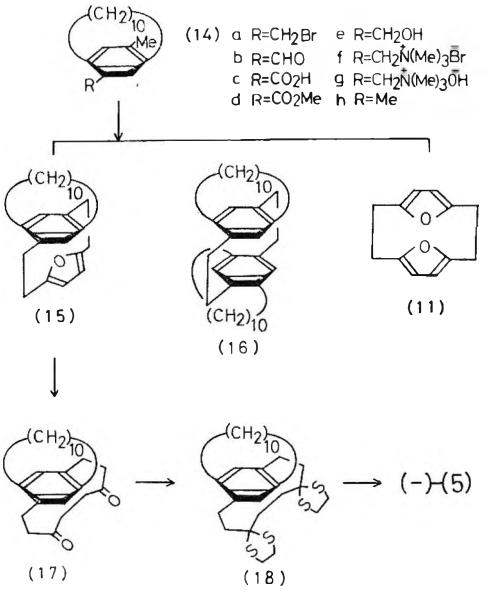
Scheme I



which was further bromomethylated to the bromide **7a.**

Construction of the second [8] bridge was carried out via the benzene–furan "hybrid" [2.2]paracyclophane **9.** The quaternary ammonium bromide **7b** ($[\alpha]^{20}_D$ −5.4°) prepared from the bromide **7a** was mixed with 5-methylfurfuryltrimethylammonium iodide (**8a**),[12] and the mixture was treated with silver hydroxide to give a mixture of Hofmann bases which was pyrolyzed in refluxing toluene. Since a preliminary experiment had revealed the rather labile character of the hybrid [2.2]-paracyclophane **9,** the pyrolysate was chromatographed on neutral alumina in a cold room (5 °C). Elution with hexane gave the doubly [8]-bridged [2.2]paracyclophane **10** ($[\alpha]^{20}_D$ −25°, 2.5% yield) which was followed by the hybrid [2.2]par-

Scheme II



acyclophane **9** (9% yield) and [2.2]furanophane (**11**) (16% yield).

The synthetic procedure and the observed optical activity necessitate that the doubly bridged [2.2]paracyclophane possess the staggered structure **10**, and the identity of the IR and mass spectra with those of the previously reported doubly bridged compound[8] from the racemic precursor confirms our previous assumption that formation of the staggered isomer should be preferred on steric grounds.

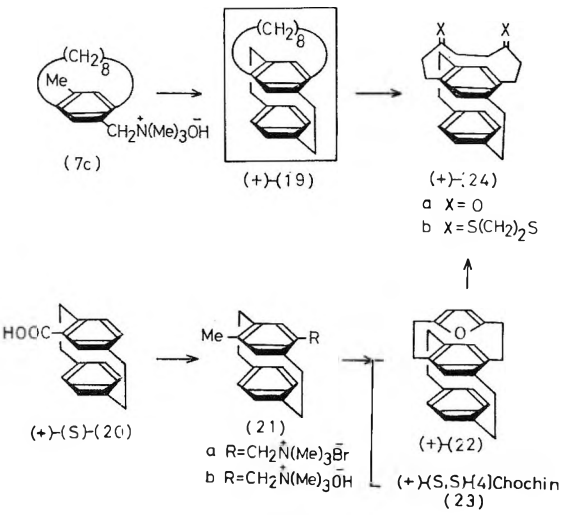
Because of the instability of the hybrid [2.2]paracyclophane **9**, the oily product, without further purification, was directly hydrolyzed with 10% sulfuric acid in acetic acid to afford the 1,4-diketone **12**: mp 149–150 °C, $[\alpha]^{20}_D$ +15°. In order to complete the synthesis, there remained the conversion of the 1,4-diketone bridge to the octamethylene bridge, and this was accomplished by desulfurization with Raney nickel of the bis(dithioketal) **13**. Treatment of the 1,4-diketone **12** with ethanedithiol and boron trifluoride in acetic acid solution yielded the bis(dithioketal) **13** which was heated with Raney nickel in ethyl acetate to afford (+)-[8][8]paracyclophane (**4**): bp 148–150 °C (1.0 mm), $[\alpha]^{20}_D$ +5.4°.

Preparation of (−)-[8][10]Paracyclophane (5) (Scheme II).[9] Optical instability[13] observed in [10]paracyclophane-12-carboxylic acid had warned us that optical resolution in this [10]paracyclophane series of compounds should be carried out on a 12,15-disubstituted [10]paracyclophane intermediate.

(±)-15-Methyl[10]paracyclophane-12-carboxylic acid (**14c**) was prepared from 12-bromomethyl-15-methyl[10]paracyclophane (**14a**) via the aldehyde **14b**, and its optical resolution was accomplished via the brucine salt. Esterification followed by hydride reduction of the levorotatory carboxylic acid **14c**, mp 134–135 °C, $[\alpha]^{21}_D$ −28°, gave the alcohol **14e** which was treated with phosphorus tribromide to furnish (−)-12-bromomethyl-15-methyl[10]paracyclophane (**14a**), $[\alpha]^{22}_D$ −24°.

An equimolar mixture of the quaternary ammonium salt **14f** prepared from the (−)-bromide **14a** and the 5-methylfurfuryltrimethylammonium iodide (**8a**)[12] was treated with silver hydroxide to give a mixture of Hofmann bases which was pyrolyzed in boiling toluene. The mixture was extracted with hexane, and the extract was chromatographed on neutral alumina to afford the following fractions: the doubly bridged [2.2]paracyclophane **16**, mp 219–221 °C, $[\alpha]^{21}_D$ +61° (5%); the benzene–furan hybrid [2.2]paracyclophane **15**, bp 154–156 °C (0.01 mm), $[\alpha]^{22}_D$ −21.3° (10%); and the [2.2]furanophane (**11**) (8%).

Scheme III



The furan moiety of the hybrid [2.2]paracyclophane **15** was modified to the octamethylene bridge as previously described for [8][8]paracyclophane (vide supra). The hybrid **15** was treated with 10% sulfuric acid in acetic acid to give the 1,4-diketone **17**, mp 159–160 °C, $[\alpha]^{21}_D$ −14.8°, which was then converted into the bis(dithioketal) **18**, mp 194–195 °C, $[\alpha]^{24}_D$ −6°, with ethanedithiol and boron trifluoride. Desulfurization with Raney nickel in boiling ethyl acetate converted the bis(dithioketal) **18** into (−)-[8][10]paracyclophane (**5**), bp 184–186 °C (2 mm), $[\alpha]^{25}_D$ −6.3°, the IR and mass spectra of which were found identical with those of the racemic form.[8]

Absolute Configurations (Scheme III). The [8]-bridged [2.2]paracyclophane **19** was selected as our key intermediate which correlates (+)-[8][8]paracyclophane **4** to (+)-(*S*)-[2.2]paracyclophane-4-carboxylic acid (**20**) with known absolute configuration.[14]

The levorotatory quaternary ammonium bromide **7b**, the precursor of (+)-[8][8]paracyclophane (**4**), was mixed with *p*-xylyltrimethylammonium bromide, and pyrolysis of a mixture of their Hofmann bases in boiling toluene afforded, beside [2.2]paracyclophane (8%), the (+)-[8]-bridged [2.2]-paracyclophane **19**, $[\alpha]^{20}_D$ +14.2° (5%).

This same dextrorotatory [8]-bridged [2.2]paracyclophane could also be obtained from (+)-[2.2]paracyclophane-4-carboxylic acid (**20**) to which the *S* absolute configuration had been assigned by Schlögl.[14] When the [2.2]paracyclophane ammonium base **21a**,[6] accessible from the (+)-(*S*)-[2.2]paracyclophane-4-carboxylic acid (**20**), was coupled with 5-methylfurfuryltrimethylammonium hydroxide (**8b**), the furan–benzene hybrid [3]chochin (**22**) (6%), mp 111–112 °C, $[\alpha]^{20}_D$ +137°, and (+)-(*S,S*)-[4]chochin (**23**)[6] (3%), mp 229–231°, $[\alpha]^{20}_D$ +245°, were isolated from the reaction mixture. Following the sequence of reactions described for the conversion of the furan–benzene hybrid [2.2]paracyclophane **9** into [8][8]paracyclophane (**4**), the furan moiety of the furan–benzene hybrid [3]chochin (**22**) was modified to an [8] bridge to give rise to (+)-[8]-bridged [2.2]paracyclophane **19**, mp 135–136 °C, $[\alpha]^{20}_D$ +33.2°. The infrared spectra of the two samples of **19**, prepared from the two different precursors **7** and **21**, were found to be indistinguishable. This configurational correlation enables us to assign the *S* configuration to (+)-[8]paracyclophane-10-carboxylic acid (**6d**), which eventually leads to the *S* configuration of (+)-[8][8]paracyclophane (**4**).

Chiroptical Properties. Figure 1 reproduces the CD spectra of (+)-(*S*)-[8][8]paracyclophane (**4**) and (−)-[8][10]-paracyclophane (**5**), and their antipodal patterns clearly indicate the *R* configuration to (−)-[8][10]paracyclophane. This conclusion is further supported by the more complicated but

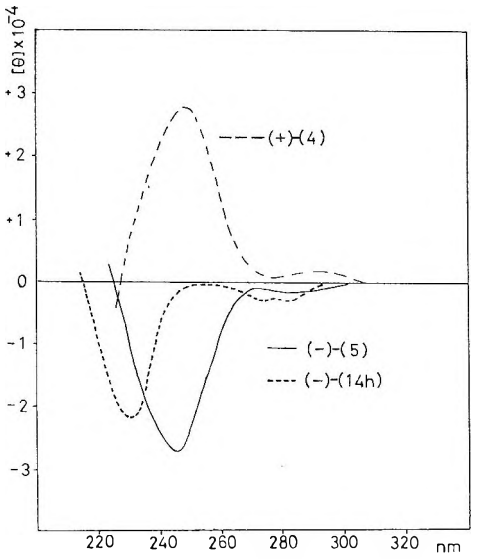


Figure 1. CD spectra of (+)-**4**, (−)-**5**, and (−)-**14h** in isooctane.

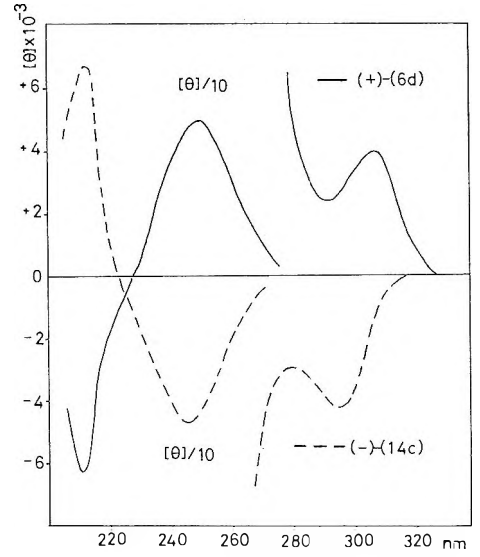


Figure 2. CD spectra of (+)-**6d** and (−)-**14c** in methanol.

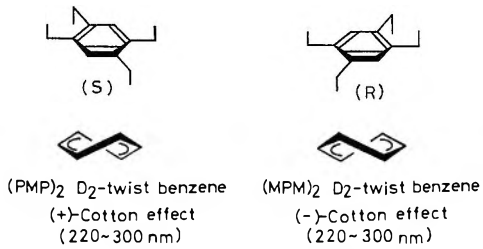


Figure 3. Conformational chirality of D_2-twist benzene and planar chirality of the benzene rings in [*m*][*n*]paracyclophane.

again enantiomeric CD curves shown by their respective precursors (Figure 2): (+)-(*S*)-[8]paracyclophane-10-carboxylic acid (**6d**) and (−)-[10]paracyclophane carboxylic acid (**14c**).

In our preceding paper[6] on optically active multilayered [2.2]paracyclophanes, we extended the Cahn–Ingold–Prelog's nomenclature[15] for conformational chirality to specify the chiralities of the enantiomeric D_2-twist benzene as shown in Figure 3. Inspection of molecular models reveals that the benzene ring in (+)-[8][8]paracyclophene (**4**) with *S*-planar chirality suffers a distortion corresponding to the $(MPM)_2$ D_2-twist benzene ring, whereas (−)-[8][10]paracyclophane (**5**) with *R*-planer chirality is deformed to have the enantiomeric $(PMP)_2$ D_2-twist benzene ring.

From analyses of the CD curves of various D_2-[*n*]chochins, we have drawn the conclusion that the $(PMP)_2$ D_2-twist benzene ring exhibits a (+) Cotton effect at 240–360 nm, and the enantiomeric $(MPM)_2$ D_2-twist benzene ring exhibits a (−) Cotton effect at the same region.

The observed (+) Cotton effect in (+)-(*S*)-[8][8]paracyclophane (**4**) with $(PMP)_2$ D_2-twist benzene confirms this generalization. In Figure 1 is also reproduced the CD curve of (−)-(*R*)-12,15-dimethyl[10]paracyclophane (**14h**) which was prepared by hydride reduction of the (−)-bromide **14a**, and examination of the Cotton curves shown by three paracyclophanes in Figure 1 suggests that the observed bathochromic effect undoubtedly reflects the degree of distortion of the benzene rings in these molecules. Lastly, it would appear to be appropriate to mention here that Schlögl[16] recently suggested the opposite configuration to [*m*][*n*]paracyclophanes based mainly on the theoretical analyses of their CD spectra.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectral data and nuclear magnetic resonance spectra were obtained from a Hitachi EPI-S2 spectrophotometer and a JNM-MH-100 spectrometer, respectively. Ultraviolet spectra were recorded on a Hitachi EPS-3T spectrometer. Circular dichroism data were measured on a JASCO J-20 spectropolarimeter with a CD attachment. Mass spectral data were measured on a Hitachi HMS-4 spectrometer. Elemental analyses were performed by Yanagimoto CHN-Corder Type II.

[8]Paracyclophane-10-carboxaldehyde (6c). 2-Nitropropane (15 g, 0.17 mol) was added to a solution of sodium ethoxide, prepared from sodium (3.4 g-atoms) and absolute ethanol (100 mL). The nitronate salt was brought into solution by the addition of absolute ethanol (190 mL). To this ethanolic solution, the bromide **6b**[6] (41 g, 0.146 mol) was added and the mixture was stirred for 30 h. The reaction mixture was poured into cold water (1 L) and then extracted with ether. The etheral extract was washed with 10% sodium hydroxide solution, water, and then dried. After evaporation of the solvent, the product was distilled to give **6c** (28 g, 89%), bp 126–129 °C (0.3 mm), n^{20}_D 1.5642; IR (film) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.11; H, 9.40.

The 2,4-dinitrophenylhydrazone of the aldehyde **6c** showed mp 224–225 °C after recrystallization from ethanol–benzene.

Anal. Calcd for $C_{21}H_{24}O_4N_4$: C, 63.62; H, 6.10; N, 14.13. Found: C, 63.48; H, 5.93; N, 14.13.

[8]Paracyclophane-10-carboxylic Acid (6d). Powdered potassium permanganate (3 g) was added to a solution of the aldehyde **6c** (28 g) in acetone (400 mL), and the mixture was stirred at 35 °C until the purple color disappeared. To the solution freed from the precipitated manganese dioxide, potassium permanganate (3 g) was added and stirring was continued to give a colorless supernatant. After removal of the manganese dioxide, oxidation was continued with a further 3 g of potassium permanganate until the purple color persisted for several hours. The combined manganese dioxide cakes were extracted with three 100-mL portions of 1% potassium hydroxide solution. The combined extracts were made strongly acidic with concentrated hydrochloric acid to precipitate crystallines which were dried in a vaccum oven (50 °C) and recrystallized from methanol to afford **6d** (18 g, 60%), mp 152–153 °C; IR (KBr) 2980, 2920, 2840, 1670, 1598, 1554, 1483, 1457, 1435, 1394, 1288, 1263, 1207, 922, 910, 777, 705 cm^{-1}; NMR ($CDCl_3$) τ −1.65 (br s, 1 H), 2.03 and 2.95 (AB quartet, J_{ab} = 8 Hz, 2 H), 2.62 (s, 1 H), 6.84 (t, 2 H), 7.42 (t, 2 H), 8.18–8.52 (m, 4 H), 8.60–9.53 (m, 8 H).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.37; H, 8.66.

Resolution of the Acid 6d. A mixture of **6d** (18 g, 0.077 mol) and (+)-1-(β-naphthyl)ethylamine (13.3 g, 0.077 mol) ($[\alpha]^{18}_D$ +17.5°) in 95% ethanol (100 mL) was warmed to give a clear solution. After standing at room temperature for 24 h, the mixture yielded 3.8 g of a crystalline solid, mp 115–121°. The filtrate was reduced in volume to 50 mL and was kept at room temperature for another 24 h to give 3.6 g of a crystalline solid, mp 112–118 °C. Recrystallization of the

combined crops from 95% ethanol afforded the salt, 6.4 g (20%): mp 141–143 °C; $[\alpha]$ $^{23}_{D}$ −14.7° (c 0.68, $CHCl_3$). The purified salt was dissolved in chloroform (10 mL), and 5% hydrochloric acid (30 mL) was added with vigorous shaking. The chloroform extract was washed with water and then dried. Evaporation of the solvent afforded a white solid which was recrystallized from methanol–water to give (+)-**6d** (3.5 g): mp 139–140 °C; $[\alpha]^{18}_{D}$ +18.1° (c 0.52, $CHCl_3$); CD (CH_3OH), $[\theta] \times 10^{-4}$ (nm), −6.38 (212), 0 (228), +4.97 (248), +0.24 (290), +0.41 (305), 0 (327).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.48; H, 8.65.

(+)-10-Carbomethoxy[8]paracyclophane (6e). To a solution of **6d** (3.4 g, 14.6 mmol) in ether (20 mL) was added diazomethane solution prepared from 6 g of *p*-tosyl-*N*-methyl-*N*-nitrosoamide. After evaporation of the solvent, the residual oil was distilled to give **6e** (3.4 g, 94.5%): bp 135–137 °C (1.0 mm); n^{18}_{D} 1.5458; $[\alpha]^{18}_{D}$ +16.8° (c 0.72, $CHCl_3$); IR (film) 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.10; H, 8.96.

(−)-10-Hydroxymethyl[8]paracyclophane (6f). A solution of (+)-**6e** (3.4 g, 13.8 mmol) in dry tetrahydrofuran (15 mL) was added dropwise to a suspension of lithium aluminum hydride (1.2 g, 32 mmol) in dry tetrahydrofuran (60 mL). The mixture was stirred for 5 h, and the excess reducing reagent was decomposed by addition of ethyl acetate. Dilute hydrochloric acid was added to dissolve the precipitated complex, and the mixture was extracted with ether. The ether solution was washed with 3% sodium bicarbonate solution and water, and then dried. Evaporation of the solvent gave an oil which was distilled to yield **6f** (2.8 g, 93%): bp 141–143 °C (0.8 mm); n^{19}_{D} 1.5586; $[\alpha]^{21}_{D}$ −5.8° (c 0.98, $CHCl_3$); IR (film) 3620 cm^{-1} (OH).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.41, H, 10.20.

(+)-10-Bromomethyl[8]paracyclophane (6b). To a stirred solution of the alcohol **6f** (2.1 g, 10 mmol) in dry ether (30 mL) was added dropwide a solution of phosphorus tribromide (3.0 g, 11 mmol) in dry ether (20 mL) at room temperature. After the mixture was stirred for 6 h at room temperature, water (150 mL) was slowly added. The separated ether layer was washed with dilute sodium bicarbonate solution and water, and then dried. Removal of the ether afforded an oil which was distilled to give **6b** (2.6 g, 96%): n^{21}_{D} 1.5793; $[\alpha]^{19}_{D}$ +5.3° (c 0.86, $CHCl_3$).

Anal. Calcd for $C_{15}H_{21}Br$: C, 64.06; H, 7.53; Br, 28.41. Found: C, 63.92; H, 7.58; Br, 28.49.

(+)-10-Methyl[8]paracyclophane (6g). A solution of (+)-**6b** (2.6 g, 10 mmol) in dry tetrahydrofuran (5 mL) was added dropwise to a suspension of lithium aluminum hydride (0.11 g, 30 mmol) in dry tetrahydrofuran (10 mL). The mixture was refluxed with stirring for 7 h, and the excess reducing reagent was decomposed with ethyl acetate (1 mL). After hydrochloric acid was added to dissolve the precipitated complex, the organic phase was extracted with ether. The ether solution was washed with water, 3% sodium bicarbonate solution, and again with water, and was dried. After evaporation of the solvent, the residual oil was distilled to give **6g** (1.7 g, 91.5%): bp 142–143 °C (0.1 mm); n^{17}_{D} 1.5418; $[\alpha]^{19}_{D}$ +4.6° (c 0.96, $CHCl_3$).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.86; H, 10.79.

(−)-10-Trimethylammoniomethyl-13-methyl[8]paracyclophane Bromide (7b). A mixture of **6g** (1.7 g, 8.4 mmol), paraformaldehyde (0.75 g, 16.8 mmol of formaldehyde), acetic acid (7 mL), 85% phosphoric acid (2 mL), and 47% hydrobromic acid (6 mL) was refluxed with stirring for 15 min. The cooled mixture was poured into cold water and extracted with ether. The etheral solution was washed with water, 3% sodium bicarbonate solution, and again water, and was dried. After removal of the solvent, the resulting crude bromide **7a** (2.2 g) was dissolved in ether (20 mL) and then treated with excess anhydrous trimethylamine (5 mL). The resulting salt was collected by filtration, washed with ether, and dried to afford **7b** (2.0 g, 69% from **6g**). An analytical sample was recrystallized from methanol–ether: mp 163–164 °C; $[\alpha]^{20}_{D}$ −5.4° (c 0.96, $CHCl_3$).

Anal. Calcd for $C_{19}H_{42}NBr$: C, 64.39; H, 9.71; N, 3.95; Br, 22.55. Found: C, 64.47; H, 9.76; N, 3.99; Br, 22.61.

Benzene–Furan Hybrid [2.2]Paracyclophane 9 and (−) Doubly Bridged [2.2]Paracyclophane 10. A mixture of **7b** (2 g, 5.6 mmol) and 5-methylfurfuryltrimethylammonium iodide (**8a**) (2.8 g, 10 mmol) was dissolved in water (100 mL), and freshly prepared silver oxide (from 10 g of silver nitrate) was added. After removal of the precipitate, the resulting hydroxides solution was mixed with toluene (100 mL) containing phenothiazine (20 mg), and the mixture was heated with stirring. Water was removed by azeotropic distillation, and the reaction mixture was refluxed for 3 h. Freed from insoluble polymer by filtration, the solution was concentrated under vacuum. The concentrate was chromatographed on neutral alumina in a cold room (5 °C). Elution with hexane gave (−)-**10** (30 mg, 2.5%), which when recrystallized from ethanol gave mp 204–206 °C; $[\alpha]^{20}_{D}$ −25° (c 0.31, $CHCl_3$); CD (isooctane), $[\theta] \times 10^{-4}$ (nm), 0 (229), +16.3 (245), 0 (258), −5.88 (284), 0 (356), −1.68 (308).

Anal. Calcd for $C_{32}H_{44}$: C, 89.65; H, 10.35. Found: C, 89.56; H, 10.36.

Elution with hexane–benzene (9:1) produced **9** (0.16 g, 9% based on **7b**) as an oil [MS *m/e* 308 (M^+)] which was found unstable and was converted directly into (+)-3,6-diketo[8][8]paracyclophane (**12**) without further purification. Further elution with hexane–benzene (5:1) gave [2.2]furanophane (**11**) (0.38 g, 16%), mp 180–181 °C.

(+)-3,6-Diketo[8][8]paracyclophane (12). A mixture of **9** (0.16 g, 0.5 mmol), acetic acid (5 mL), water (0.1 mL), and 10% sulfuric acid (0.1 mL) was heated at 65 °C with stirring for 1 h. The reaction mixture was poured into water (20 mL), and the separated organic phase was extracted with chloroform. The extract was washed with water, 3% sodium bicarbonate solution, and again with water, and was dried. After removal of the solvent, the residue was chromatographed on neutral alumina. Elution with dichloromethane afforded **12** (50 mg, 30%), which when recrystallized from hexane gave mp 149–150 °C; $[\alpha]^{20}_{D}$ +15.4° (c 0.71, $CHCl_3$).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.82; H, 8.99.

(+)-[8][8]Paracyclophane (4). A solution of **12** (40 mg, 0.12 mmol) in acetic acid (4 mL) was combined with a solution of ethanedithiol (0.1 g, 10 mmol) in acetic acid (2 mL). After 47% boron trifluoride etherate (1 mL) was added, the mixture in a tightly sealed bottle was allowed to stand for 2 days at room temperature. The mixture was poured into water (30 mL), and the product was extracted with chloroform. The extract was washed with 3% sodium bicarbonate solution and water, and then dried. Evaporation of the solvent afforded the crude bis(ethanedithioketal) **13** which was desulfurized directly without further purification. To a solution of the crude bis(dithioketal) **13** (45 mg) in ethyl acetate (6 mL) was added W-5 Raney nickel (0.5 g). The mixture was refluxed for 1 h, cooled, and filtered. After concentration of the filtrate, the oily product was subjected to alumina column chromatography. Elution with hexane gave **4** (15 mg, 42%): bp 148–150 °C (1.0 mm); $[\alpha]^{20}_{D}$ + 5.4° (c 0.66, $CHCl_3$); CD (isooctane), $[\theta] \times 10^{-4}$ (nm), −2.34 (218), 0 (227.5), +2.84 (247.5), +0.19 (292), 0 (307).

Anal. Calcd for $C_{22}H_{34}$: C, 88.52; H, 11.48. Found: C, 88.47; H, 11.46.

15-Methyl[10]paracyclophane-12-carboxaldehyde (14b). Preparation of the aldehyde **14b** was carried out by the same method described for the preparation of **6c**, utilizing 12-bromomethyl-15-methyl[10]paracyclophane (**14a**) (34 g, 0.105 mol), 2-nitropropane (15 g, 0.17 mol), sodium (2.5 g, 0.11 g-atom), and absolute ethanol (160 mL). Distillation of the product gave **14b** (26 g, 95%): n^{18}_{D} 1.5536; MS *m/e* 258 (M^+); IR (film) 1686 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.56; H, 10.18.

The 2,4-dinitrophenylhydrazone of the aldehyde **14b** showed mp 208–209 °C after recrystallization from ethanol–benzene.

Anal. Calcd for $C_{24}H_{30}O_4N_4$: C, 65.73; H, 6.90; N, 12.78. Found: C, 65.31; H, 6.86; N, 12.73.

15-Methyl[10]paracyclophane-12-carboxylic acid (14c). Oxidation of **14b** (25.9 g, 0.095 mol) was carried out by the same procedure described for the preparation of **6d**. The product was recrystallized from ethanol–water to give **14c** (16.2 g, 59%): mp 168–169 °C; IR (KBr) 2980, 2880, 2830, 1672, 1600, 1550, 1492, 1451, 1402, 1262, 935, 757, 698 cm^{-1}; NMR ($CDCl_3$) τ −1.63 (br s, 1 H), 2.17 (s, 1 H), 3.00 (s, 1 H), 6.05–6.37 (m, 1 H), 6.94–7.23 (m, 1 H), 7.44–7.90 (m, 2 H), 7.65 (s, 3 H), 8.22–8.61 (m, 4 H), 8.72–9.10 (m, 4 H), 9.15–9.72 (m, 8 H).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55. Found: C, 78.91; H, 9.55.

Resolution of the Acid 14c. A mixture of **14c** (7.9 g, 0.029 mol) and brucine (12.5 g, 0.029 mol) in methanol (200 mL) was warmed until solution was complete. After standing at room temperature for 48 h, the mixture yielded 11.7 g of a solid, mp 93–99 °C; $[\alpha]^{25}_{D}$ −38.6° (c 0.53, CH_3OH), which was recrystallized from methanol three times to yield 6.4 g of white needles: mp 118–124 °C; $[\alpha]^{26}_{D}$ −41.4° (c 0.79, CH_3OH). This salt was dissolved in chloroform (80 mL), and 5% hydrochloric acid (70 mL) was added with vigorous shaking. The separated chloroform layer was washed with water and then dried. After evaporation of the solvent, the crude (−)-acid obtained was recrystallized from ethanol–water to give (−)-**14c** (2.9 g): mp 134–135 °C; $[\alpha]^{21}_{D}$ −28° (c 0.94, CH_3OH); CD (CH_3OH), $[\alpha] \times 10^{-4}$ (nm), +6.82

(213), 0 (224), −3.84 (245), −0.33 (380), −0.43 (294), 0 (315).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.88; H, 9.51.

(−)-12-Carbomethoxy-15-methyl[10]paracyclophane (14d). The (−)-acid **14c** (1.7 g, 6.2 mmol) was dissolved in ether (20 mL) and esterified with diazomethane. After evaporation of the solvent, the methyl ester was distilled to give **14d** (1.6 g, 90%) as an oil: bp 141–143 °C (0.1 mm); $n^{21}D$ 1.5386; $[\alpha]^{21}D$ −20.6° (c 0.81, $CHCl_3$); IR (film) 1712 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{28}O_2$: C, 72.12; H, 9.79. Found: C, 72.26; H, 9.72.

(+)-12-Hydroxymethyl-15-methyl[10]paracyclophane (14e). A solution of (−)-**14d** (1.6 g, 5.6 mmol) in dry tetrahydrofuran (7 mL) was added dropwise to a suspension of lithium aluminum hydride (0.4 g, 10 mmol) in dry tetrahydrofuran (30 mL). The mixture was heated under reflux for 6 h, and the excess reducing reagent was decomposed with ethyl acetate. The mixture was acidified with dilute hydrochloric acid, and the organic phase was extracted with ether. The ether solution was washed with water, 3% sodium bicarbonate solution, and again with water, and was dried. The solvent was removed to give an oil, which was distilled to give **14e** (1.35 g, 94%): bp 145–147 °C (0.1 mm); $n^{22}D$ 1.5432; $[\alpha]^{26}D$ +8.1° (c 0.85, $CHCl_3$); IR (film) 3330 cm^{-1} (OH).

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.91; H, 10.90.

(−)-12-Bromomethyl-15-methyl[10]paracyclophane (14a). To a stirred solution of the alcohol **14e** (1.3 g, 5.0 mmol) in dry ether (15 mL) was added dropwise a solution of phosphorus tribromide (1.4 g, 5.1 mmol) in dry ether (10 mL) at room temperature. After stirring for 3 h at room temperature, the mixture was poured into cold water (50 mL). The separated organic phase was washed with 3% sodium bicarbonate solution and water, and was dried. After removal of the solvent, the residue was distilled to give **14a** (1.4 g, 88%): bp 138–140 °C (0.1 mm); $n^{21}D$ 1.5669; $[\alpha]^{22}D$ −24° (0.76, $CHCl_3$); MS *m/e* 323 (M^+).

Anal. Calcd for $C_{18}H_{27}Br$: C, 66.86; H, 8.42; Br, 24.72. Found: C, 66.97; H, 8.51; Br, 24.60.

(+)-12-Trimethylammoniomethyl-15-methyl[10]paracyclophane Bromide (14f). A solution of (−)-**14a** (1.2 g, 3.7 mmol) in ether (30 mL) was treated with excess anhydrous trimethylamine (5 mL). The resulting salt was collected by filtration, washed with ether, and dried to afford **14f** (1.3 g, 91.6%). An analytical sample was recrystallized from methanol–ether: mp 252–254 °C; $[\alpha]^{21}D$ +14° (c 0.84, $CHCl_3$).

Anal. Calcd for $C_{21}H_{36}NBr$: C, 65.95; H, 9.49; N, 3.66; Br, 20.88. Found: C, 66.00; H, 9.53; N, 3.62; Br, 20.83.

(−)-12,15-Dimethyl[10]paracyclophane (14h). A mixture of (−)-**14a** (0.18 g, 0.56 mmol) in dry tetrahydrofuran (5 mL) was added dropwise to a suspension of lithium aluminum hydride (0.2 g, 5.3 mmol) in dry tetrahydrofuran (15 mL). The mixture was heated under reflux for 10 h, and the usual work up furnished the product which was distilled to give **14h** (0.12 g, 88%): bp 174–176 °C (3 mm); $n^{25}D$ 1.5408; $[\alpha]^{25}D$ −7.2° (c 0.96, $CHCl_3$); CD (isooctane), $[\theta] \times 10^{-4}$ (nm), 0 (217), 2.22 (229), −0.27 (274), −0.29 (282), 0 (294).

Anal. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55. Found: C, 88.49; H, 11.51.

(−)-Benzene–Furan Hybrid [2.2]Paracyclophane 15 and (+) Doubly Bridged [2.2]Paracyclophane 16. A solution (70 mL) of the mixed quaternary ammonium hydroxides, **14g** and **8b**, prepared from a mixture of **14f** (1.3 g, 3.4 mmol) and **8a** (1.6 g, 5.7 mmol) in the usual manner, was mixed with toluene (50 mL) containing phenothiazine (10 mg). After pyrolysis, the same procedure described for the [8]paracyclophane series of compound **9** afforded the crude product which was chromatographed on neutral alumina. Elution with hexane afforded **16** (41 mg, 5%), which when recrystallized from hexane gave mp 219–220 °C; $[\alpha]^{21}D$ +61.3° (c 0.77, $CHCl_3$); CD (isooctane), $[\theta] \times 10^{-4}$ (nm), +13.8 (210), 0 (22.5), −19.4 (234.5), 0 (252), +3.68 (273), +1.27 (297), 0 (320).

Anal. Calcd for $C_{36}H_{52}$: C, 89.19; H, 10.81. Found: C, 89.15; H, 10.79.

Elution with hexane–benzene (9:1) produced a colorless oil, which was distilled to give **15** (120 mg, 10% based on **14f**): bp 154–156 °C (0.01 mm); $[\alpha]^{22}D$ −21° (c 0.83, $CHCl_3$); $[\alpha] \times 10^{-4}$ (nm) +1.22 (220), +4.66 (229), 0 (241), −1.57 (257), 0 (290).

Anal. Calcd for $C_{24}H_{32}O$: C, 85.66; H, 9.59. Found: C, 85.25; H, 9.68.

Further elution with hexane–benzene (5:1) gave [2.2]furanophane (**11**) (45 mg, 8%).

(−)-3,6-Diketo[8][10]paracyclophane (17). Ring opening of the furan ring in **15** was carried out by the method described for the preparation of the [8]paracyclophane series of compound **12**, utilizing **15** (120 mg, 0.36 mmol), water (0.1 ml), acetic acid (5 mL), and 10% sulfuric acid (0.1 mL). The resulting product was chromatographed on neutral alumina. Elution with dichloromethane produced **17** (75 mg, 59%), which was recrystallized from hexane to give mp 159–160 °C; $[\alpha]^{21}D$ −14° (c 0.79, $CHCl_3$).

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.65. Found: C, 81.12; H, 9.74.

(−)-Bis(ethanedithioketal) (18). A solution of **17** (70 mg, 0.2 mmol) in acetic acid (6 mL) was mixed with a solution of ethanedithiol (3 mL) in acetic acid (4 mL) which contained 47% borontrifluoride etherate (2 mL). After standing for 2 days at room temperature, the reaction mixture was poured into water (20 mL) and extracted with chloroform. The chloroform solution was washed with water and then dried. Removal of the solvent yielded a crystalline solid which on crystallization from ethanol gave **18** (79 mg, 79%): mp 149–150 °C; $[\alpha]^{24}D$ −6° (c 0.75, $CHCl_3$).

Anal. Calcd for $C_{28}H_{42}S_4$: C, 66.34; H, 8.36. Found: C, 66.41; H, 8.35.

(−)-[8][10]Paracyclophane (5). To a solution of **18** (70 mg, 0.173 mmol) in ethyl acetate (5 mL) was added W-5 Raney nickel (1.0 g), and the mixture was refluxed for 1 h. The mixture was freed of Raney nickel and concentrated under vacuum to give an oil which was chromatographed on neutral alumina. Elution with hexane afforded a colorless oil, which was distilled to give **5** (35 mg, 62%): bp 184–186 °C (2 mm): $[\alpha]^{25}D$ −6.3° (c 0.92, $CHCl_3$); MS *m/e* 326 (M^+); CD (isooctane), $[\theta] \times 10^{-4}$ (nm), +6.37 (215), 0 (225), −2.72 (243), −0.17 (285).

Anal. Calcd for $C_{24}H_{38}$: C, 88.27; H, 11.73. Found: C, 88.30; H, 11.69.

(+)-[8]-Bridged [2.2]Paracyclophane 19 (from 7c). A solution (40 mL) of the quaternary ammonium hydroxides prepared from a mixture of **7c** (0.5 g, 1.4 mmol) and *p*-xylyltrimethylammonium bromide (1.0 g, 4.1 mmol) was mixed with toluene (30 mL) containing phenothiazine (5 mg). After pyrolysis, the crude product was chromatographed on neutral alumina. Elution with hexane yielded (+)-**19** (22 mg, 5%), which when recrystallized from hexane–benzene gave mp 138–139 °C; $[\alpha]^{20}D$ +14.2° (c 0.67, $CHCl_3$); MS *m/e* 318 (M^+); IR (KBr) 2980, 2880, 2840, 2820, 1585, 1494, 1431, 1407, 1078, 928, 888, 902, 715 cm^{-1}; UV (isooctane) λ_{max} 220, 280, 325 sh nm (log ϵ 3.83, 3.22, 2.04); CD (isooctane), $[\theta] \times 10^{-4}$ (nm), +1.6 (205), +10.7 (217), 0 (227), −13.7 (242), 0 (256), +4.19 (265), +0.76 (285), +2.21 (302), +0.45 (325 sh), 0 (355); NMR ($CDCl_3$) τ 3.51 (s, 4 H), 3.95 (s, 2 H), 6.55–8.15 (m, 12 H), 8.20–10.06 (m, 10 H), 10.20–10.92 (m, 2 H).

Anal. Calcd for $C_{24}H_{30}$: C, 90.50; H, 9.50. Found: C, 90.41; H, 9.52.

Further elution with hexane–benzene (5:1) gave [2.2]paracyclophane (34 mg, 8%).

(+)-Triple-Layered [2.2]Paracyclophane 22. A solution (60 mL) of the quaternary ammonium hydroxides from a mixture of (+)-(*S*)-4-trimethylammoniomethyl-7-methyl[2.2]paracyclophane bromide (**21a**)[6] (3 g, 8.2 mmol) and **8a** (3 g, 10.7 mmol) was mixed with toluene (100 mL) containing phenothiazine (10 mg). After pyrolysis, the product was chromatographed on neutral alumina. Elution with hexane–benzene (10:1) gave [2.2]furanophane (**11**) (80 mg, 8%). Further elution with hexane–benzene (7:1) produced the (+)-triple-layered compound **22** (188 mg, 6%), which when recrystallized from hexane gave mp 111–112 °C; $[\alpha]^{20}D$ +137° (c 0.58, $CHCl_3$); MS *m/e* 328 (M^+); IR (KBr) 2970, 2880, 2820, 1584, 1532, 1493, 1486, 1452, 1419, 1171, 1128, 1010, 943, 934, 792, 713, 623 cm^{-1}; UV (isooctane) λ_{max} 222, 278, 314, 333 nm (log ϵ 4.09, 3.79, 2.85, 2.80); NMR ($CDCl_3$) τ 3.76 (s, 4 H), 4.27 (s, 2 H), 4.73 (s, 2 H), 6.65–7.85 (m, 16 H); CD (isooctane), $[\theta] \times 10^{-4}$ (nm) 0 (205), +21.0 (217), 0 (234), −25.9 (245.5), 0 (262.5), +3.88 (269), 0 (285.5), −0.56 (288), 0 (291), +3.88 (306), +1.46 (337), 0 (360).

Anal. Calcd for $C_{24}H_{24}O$: C, 87.76; H, 7.36. Found: C, 87.81; H, 7.34.

Elution with hexane–benzene (5:1) gave (+)-(*S,S*)-[4]chochin[6] (57 mg, 3%), which gave mp 229–231 °C after recrystallization from hexane–benzene: $[\alpha]^{20}D$ +245° (c 0.53, $CHCl_3$); MS *m/e* 468 (M^+); UV (isooctane), $[\theta] \times 10^{-4}$ (nm) 0 (211), −31.0 (217.5), −25.9 (232.5), 0 (249), +4.56 (260), +6.23 (272), +3.29 (311), +3.95 (339), +2.60 (355), 0 (385).

Anal. Calcd for $C_{36}H_{36}$: C, 92.26; H, 7.74. Found: C, 92.28; H, 7.73.

(+)-3,6-Diketone 24a. Hydrolysis of **22** was carried out by the method described for the preparation of **12**, utilizing **22** (180 mg, 0.55 mmol), water (5 mL), acetic acid (30 mL), and 10% sulfuric acid (0.5 mL). The resulting product was chromatographed on neutral alumina. Elution with dichloromethane produced **24a** (110 mg, 58%), which

after recrystallization from hexane gave mp 195–197 °C; $[\alpha]^{32}_D$ +17.5° (c 0.78, $CHCl_3$); IR (KBr) 2998, 2920, 2830, 1693, 1588, 1423, 1407, 1316, 1141, 1092, 1068, 899, 863, 789, 713 cm^{-1}; NMR ($CDCl_3$) τ 3.58 (s, 4 H), 4.03 (s, 2 H), 6.50–7.97 (m, 16 H), 8.10–8.85 (m, 4 H).

Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.57; H, 7.46.

(+)-[8]-Bridged [2.2]Paracyclophane (19) (from 24). The bis(ethanedithiol) **24b** was prepared by the method described for the preparation of **13**, utilizing **24a** (100 mg, 0.29 mmol), acetic acid (15 mL), ethanedithiol (3 mL), and 47% borontrifluoride (1 mL). To a solution of crude **24b** (0.14 g) in ethyl acetate (15 mL) was added W-5 Raney nickel (0.5 g). Refluxing followed by removal of the Raney nickel and concentration gave a solid which was subjected to alumina column chromatography. Elution with hexane–benzene gave **19**: mp 135–136 °C; $[\alpha]^{20}_D$ +33.2° (c 0.84, $CHCl_3$).

Anal. Calcd for $C_{24}H_{30}$: C, 90.50; H, 9.50. Found: C, 90.44; H, 8.54.

Registry No.—(*S*)-(+)-**4**, 54059-74-4; (*R*)-(−)-**5**, 36757-10-5; (±)-**6b**, 63534-00-9; (+)-**6b**, 63534-01-0; (±)-**6c**, 63534-02-1; (±)-**6c** DNP, 63534-03-2; (±)-**6d**, 63534-04-3; (*S*)-(+)-**6d**, 63597-46-6; (*S*)-(+)-**6d** (+)-α-(β-naphthylethylamine), 63597-47-7; (+)-**6e**, 63534-05-4; (−)-**6f**, 63534-06-5; (+)-**6g**, 63534-07-6; (±)-**7a**, 63534-08-7; (−)-**7b**, 63534-09-8; **8a**, 1197-60-0; **8b**, 32543-06-9; (±)-**9**, 63534-10-1; (−)-**10**, 63597-48-8; (±)-**11**, 5088-46-0; (+)-**12**, 63534-11-2; (±)-**13**, 63534-12-3; (±)-**14a**, 36659-11-7; (−)-**14a**, 63534-13-4; (±)-**14b**, 36659-12-8; (±)-**14b** DNP, 63534-14-5; (±)-**14c**, 63534-15-6; (−)-**14c**, 36659-13-9; (−)-**14c** brucine, 63534-16-7; (−)-**14d**, 36757-09-2; (+)-**14e**, 36659-14-0; (+)-**14f**, 36659-16-2; (±)-**14g**, 63534-17-8; *R*-(−)-**14h**, 63534-18-9; (−)-**15**, 36659-18-4; (+)-**16**, 63597-49-9; (−)-**17**, 36659-19-5; (−)-**18**, 36659-20-8; (+)-**19**, 63534-19-0; (*S*)-(+)-**21a**, 63534-20-3; (+)-**22**, 63534-21-4; (*S,S*)-(+)-**23**, 36659-04-8; (+)-**24a**, 63534-22-5; (+)-**24b**, 63534-23-6; (+)-α-(β-naphthyl)ethylamine, 3906-16-9; brucine, 357-57-3; *p*-xylyltrimethylammonium bromide, 16814-21-4.

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Synthesis of Methyl *dl*-Jasmonate and Its Related Compounds from Methyl (*E*)- and (*Z*)-4,4-Dimethoxy-2-butenoates

Sigeru Torii,* Hideo Tanaka, and Yuichi Kobayasi

Department of Industrial Chemistry, School of Engineering, Okayama University, Okayama, Japan 700

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A synthesis of methyl *dl*-jasmonate (**1b**) and its dehydro derivatives **2b** and **3b** from methyl (*E*)- and (*Z*)-4,4-dimethoxy-2-butenoates (**4**) is described. Dimethyl 2-acetyl-3-dimethoxymethylglutarate (**5**) could be obtained by Michael addition of **4** with methyl acetoacetate in excellent yields. Deacetalization of dimethyl 2-acetyl-3-dimethoxymethyl-2-(2-pentynyl)glutarate (**7a**) followed by cyclization with base after alkylation of **5** (R′ = Me) with 2-pentynyl bromide afforded 5-methoxycarbonyl-4-methoxycarbonylmethyl-5-(2-pentynyl)-2-cyclopentenone (**10a**). Reduction of **10** (R′ = Me) with $NaBH_4$ in MeOH giving 2-methoxycarbonyl-3-methoxycarbonylmethyl-2-(2-pentynyl)cyclopentanol (**13a**) and subsequent oxidation of **13** with chromic acid gave 2-methoxycarbonyl-3-methoxycarbonylmethyl-2-(2-pentynyl)cyclopentanone (**14a**), a precursor of **1b**. Cis hydrogenation of **7a** → **7b**, **10a** → **10b**, **13a** → **13b**, and **14a** → **14b** using Lindlar catalyst proceeded in quantitative yields. Direct demethoxycarbonylation of **10b** (R = 2-*cis*-pentenyl) with Me_2SO–H_2O–NaCl in a sealed tube afforded a mixture of **2b** and **3b**. However, acid-catalyzed de-*tert*-butoxycarbonylation of **10b** (R′ = *t*-Bu), prepared from **5** (R′ = *t*-Bu) by alkylation followed with cyclization, under reflux in benzene gave **2b** as a sole product. Hydrogenation of **10a** with palladium on charcoal afforded **14c** (R = pentyl). The products **2b** and **3b** could be converted into **1b** smoothly.

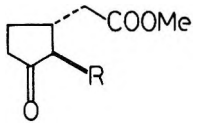
Our continuing interest in the jasmonoid syntheses[1] has led to discovering an economically significant method in obtaining methyl *dl*-jasmonate (**1b**)[2] and methyl dehydrojasmonates (**2b** and **3b**) without using troublesome reagents. In the course of our efforts to investigate the electrolysis of 2-substituted furans, we have found an effective, one-step preparative way of methyl (*E*)- and (*Z*)-4,4-dimethoxy-2-butenoates (**4**).[3] It should be noted that the butenoates **4** are expected to be a powerful Michael acceptor and they are indeed smoothly obtained in good yield by the simple electrolyses of furfuryl alcohol, furfural, and 2-furoic acid. We now report a straightforword synthesis of the jasmonates **1b**, **2b**, and **3b** from **4** via the intermediates **5**, **7**, **10**, **13**, and **14**.

When the butenoates **4** were allowed to react with methyl acetoacetate using alkali metal carbonates in methanol (Table I, runs 1, 2, and 3), the yield of **5** (R′ = Me) was in the ranges of 0–35% yields along with the formation of **6** (6–11% yields). A successful Michael addition of methyl acetoacetate to **4** was

Table I. Constituents of the Michael Adducts of 4 with Methyl Acetoacetate

Run	Substrate	Base	Time (h)	Yield of products, % 5 (R′ = Me)	6	4[a]
1	4(Z)	Li_2CO_3	20	35	6	29
2	4(Z)	Na_2CO_3	5	22	9	18
3	4(Z)	K_2CO_3	16		11	
4	4(Z)	KF	72	97		
5	4(E)	KF	72	98		

[a] The recovered substrates 4.



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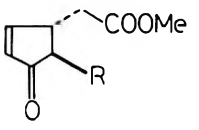

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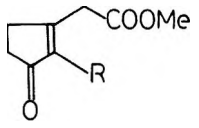
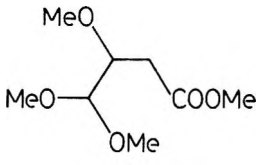
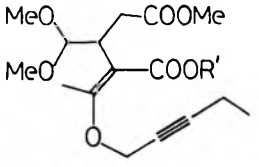


3

a: R = $-CH_2C{\equiv}CEt$
b: R = $-CH_2CH\overset{cis}{=}CHEt$
c: R = $-(CH_2)_4Me$



6



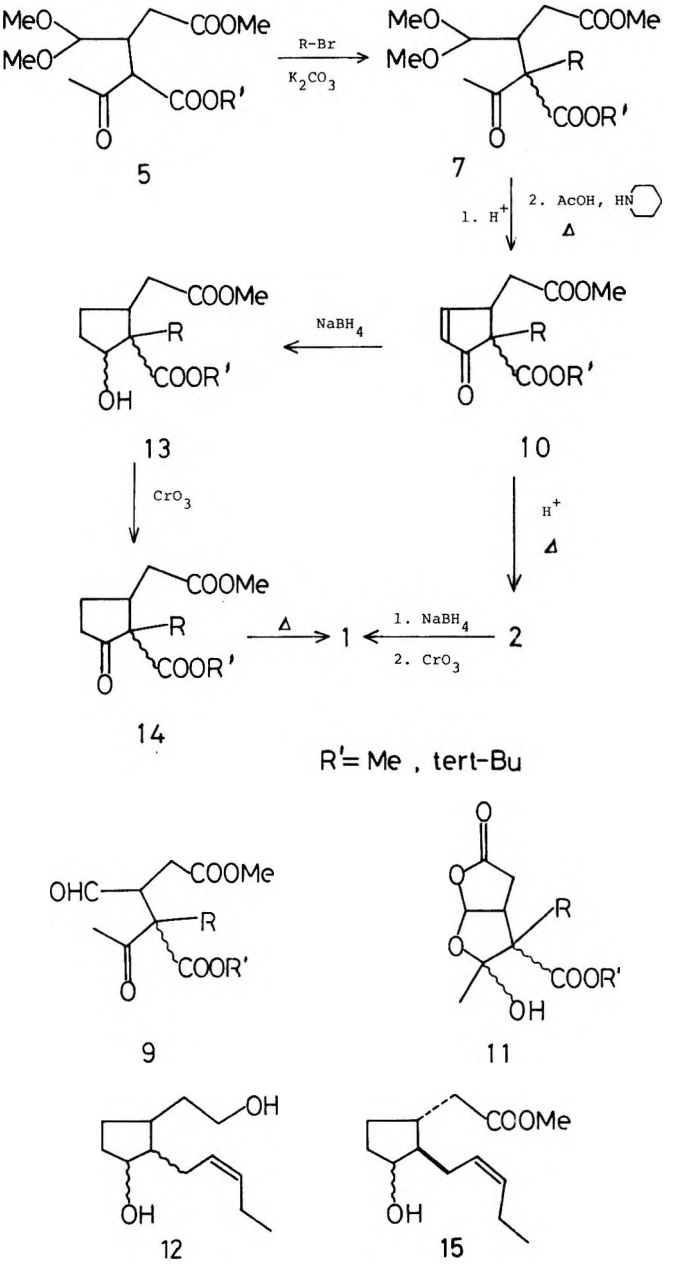
8

accomplished in 97–98% yields by using potassium fluoride in methanol as shown in Table I (runs 4 and 5). In contrast to our results, an earlier report demonstrates that fluoride ion is considered to be a strong base in aprotic solvents because of lack of hydrogen bonding.[4]

Alkylation of **5** (R′ = Me) with pentynyl bromide using potassium carbonate in acetone afforded the desired C-alkylated **7a** (R′ = Me, 72% yield) together with the O-alkylated **8a** (R′ = Me, 27% yield), whereas the yield of **7a** (R′ = Me) increased to 81% by addition of a catalytic amount of potassium iodide. The products **7a** and **8a** could be separated by column chromatography.

An aqueous THF solution of **7** (R′ = Me) was hydrolyzed with 1% perchloric acid at 26–28 °C, giving **9** (R′ = Me), and subsequent base-catalyzed cyclization with piperidine–acetic acid in benzene afforded **10** (R′ = Me) in 52–56% yield (based on **7**) after removal of water azeotropically. However, the prolonged heating of the aqueous THF solution of **7a** (R′ = Me) with 3–4% perchloric acid over 33 °C provided the lactone derivative **11a** preferentially. Cis hydrogenation of **7a → 7b, 10a → 10b, 13a → 13b,** and **14a → 14b** in a mixed solvent of hexane and acetone using Lindlar catalyst[5] proceeded in quantitative yields.

The hydride reduction of 2-cyclopenten-1-ones[6] has been well investigated; however, selective 1,4 reduction of the enones has not yet been reported, in contrast to the cases of 2-cyclohexen-1-ones.[7] The reduction of the mixed products **2b** and **3b** (5:1) to the diol **12** with 14 equiv of metal lithium in liquid ammonia and subsequent oxidation and esterification, giving **1b,** has been discussed by Ducos and Rouessac.[8] In an effort to ascertain how the double bond in the ring of **10** could



be selectively reduced, the following several examinations were attempted. Thus, reduction of **10b** (R′ = Me) with 4 equiv of lithium tri-*tert*-butoxyaluminumhydride[6a] in THF at 5 °C for 18 h afforded a mixture of **13b** (R′ = Me, 51%) and **14b** (R′ = Me, 26%) (Table II, run 1). Similarly, reduction of **10b** (R′ = Me) with 2 equiv of sodium borohydride in methanol and/or in dioxane under reflux for 1 h afforded the alcohol **13b** (R′ = Me, 80 and 41% yields) (Table II, runs 2 and 3). On the other hand, catalytic hydrogenation of **10b** (R′ = Me) with palladium on charcoal or palladium on barium sulfate in methanol at 24 °C for 30 min gave **14c** (R′ = Me) in 88–97% yields (runs 4 and 5).

The Jones oxidation of both **13a** (R′ = Me), derived from **10a** (R′ = Me), and **13b** (R′ = Me) with chromic acid–sulfuric acid in methylene chloride gave the corresponding cyclopentanones **14a** and **14b** in 71–84% yields, and subsequent demethoxycarbonylation in aqueous dimethylsulfoxide (Me_2SO) containing a small amount of sodium chloride (NaCl)[2d] in a sealed tube led to the jasmonates **1a–b,** smoothly.

Methyl dehydrojasmonate (**2b**), isolated from jasmine absolutes of Italian[9] and Spanish[10] jasmines (*Jasminum grandiflorum L.*), has received considerable attention as new odorous stuff.[1a] However, in a synthetical sense, it is lacking

Table II. Reduction of 10b (R′ = Me) with Various Reducing Reagents

Run	Reagent	Solvent	Temp, °C	Time, h	Yield of products, % 13b	14b	14c
1	$Li(t\text{-}BuO)_3AlH$	THF	5	18	51	26	
2	$NaBH_4$	Dioxane	102	1	41		
3	$NaBH_4$	MeOH	65	1		80	
4	Pd/C	MeOH	20	0.8			97
5	$Pd/BaSO_4$	MeOH	24	0.5			88

in the literature in obtaining **2b** except for the paper regarding the simultaneous formation of **2a** and **3a** in the retro-Diels–Alder reaction of 3-oxo-4-(2-pentynyl)-5-methoxycarbonylmethyl-*endo*-tricyclo[5.2.1.$0^{2,6}$]-8-decene.[8] In our experiment, demethoxycarbonylation of **10b** (R′ = Me) in aqueous Me_2SO-NaCl in a sealed tube at 170–175 °C for 4 h afforded a mixture of **2b** and **3b** (2:1)[11] in 46% yield, whereas the cyclopentenone **10b** (R′ = *t*-Bu), prepared by alkylation of the Michael adduct **5** (R′ = *t*-Bu) followed by cyclization, underwent acid-catalyzed decomposition under reflux in benzene for 20 min, to give pure **2b** in 83% yield. This reaction condition[12] may provide thermodynamically stable trans-isomer **2b.** Supporting evidence for the configuration of **2b** comes from the results of the ^{13}C NMR spectra of **2b** and **1b,** showing homogeneous peaks in very fine detail, and from the following conversion of **2b** to **1b.**[13] Conversion of **2b** and/or the mixture **2b** and **3b** into **1b** via **15** was carried out by reduction with sodium borohydride in methanol followed with Jones oxidation. An alternative route to **1b** from **10b** (R′ = *t*-Bu) via **13b** (R′ = *t*-Bu) and **14b** (R′ = *t*-Bu) was also examined in a similar manner to that described for **10b** (R′ = Me).

Experimental Section

Boiling points are uncorrected. ^1H NMR spectra were determined at 60 MHz with a Hitachi R-24 spectrometer and the chemical-shift values are expressed in δ value (ppm) relative to a Me_4Si internal standard. ^{13}C NMR spectra were taken at 25.05 MHz in the Fourier mode using a JEOL FX-100 spectrometer. Samples were dissolved in $CDCl_3$ containing Me_4Si as an internal standard. IR spectra were determined with a Japan Spectroscopic Co. Ltd., IRA-I, infrared recording spectrophotometer fitted with a grating. The mass spectra were obtained with a JEOL Model JMS-OIBM-2, ionizing voltage 75 eV.

Dimethyl 2-Acetyl-3-dimethoxymethylglutarate (5, R′ = Me). A mixture of **4**(*Z*) (2.22 g, 13.8 mmol), KF (2.5 g, 43.0 mmol), and $AcCH_2CO_2Me$ (2.7 g, 23.2 mmol) in MeOH (5 mL) was vigorously stirred for 3 days under reflux. The mixture was allowed to cool to room temperature and the solvent was evaporated in vacuo. The residue was poured into brine and extracted with AcOEt. The extracts were dried (Na_2SO_4) and concentrated. After removal of the solvents, the residue was chromatographed (SiO_2, benzene–AcOEt, 10/1) to give **5** (R′ = Me, 3.69 g, 97%): bp 88–91 °C (1.9 mm); ^1H NMR ($CDCl_3$) δ 2.24 (s, 3, CH_3CO), 2.41–2.64 (m, 2, CH_2CO), 2.77–3.22 (m, 1, CH), 3.31, 3.35 (2, s, 6, CH_3O), 3.66 (s, 3, CH_3O), 3.72 (s, 3, CH_3O), 3.79 (d, 1, *J* = 6 Hz, CHCO), 4.38 (t, 1, *J* = 6 Hz, OCHO); IR (neat) 1735 (C=O), 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30. Found: C, 52.32; H, 7.40.

Similarly, upon heating to reflux a mixture of **4**(*E*) and $AcCH_2CO_2Me$ in the presence of KF in MeOH afforded **5** (R′ = Me) in 98% yield.

Dimethyl 2-Acetyl-3-dimethoxymethyl-2-(2-pentynyl)-glutarate (7a, R′ = Me). A mixture of K_2CO_3 (2.08 g, 15.1 mmol), **5** (R′ = Me, 553 mg, 2.0 mmol), pentynyl bromide (320 mg, 2.18 mmol), and KI (444 mg, 2.67 mmol) in acetone (30 mL) was stirred at room temperature for 1 h and then refluxed for an additional 12 h. The mixture was allowed to stand to room temperature. The insoluble material was separated by centrifugation and the organic layer was concentrated. The residue was chromatographed (SiO_2, benzene–AcOEt, 8/1) to give **7a** (R′ = Me, 558 mg, 81%) and **8a** (R′ - Me, 88 mg, 13%).

The C-alkylation product **7a** boiled at 97–101 °C (0.08 mm): ^1H NMR (CCl_4) δ 1.11 (t, 3, *J* = 7 Hz, CH_3), 1.81–2.26 (m, 5, $CH_2C{\equiv}C$, CH_3CO), 2.26–2.55 (m, 2, CH_2CO), 2.55–2.85 (m, 2, CH_2 C≡C), 2.98–3.48 (m, 7, CH_3O, CH), 3.61 (s, 3, CH_3O), 3.65 (s, 3, CH_3O), 4.15–4.34 (m, 1, OCHO); IR (neat) 2837 (CH_3O), 1729 (C=O), 1710 cm^{-1} (C=O); MS *m/e* (rel intensity) 342 (M^+, 0.8), 311 (19), 279 (5), 267 (37), 221 (16), 219 (17), 207 (13), 191 (8), 181 (5), 161 (10), 160 (24), 130 (19), 101 (20), 91 (7), 75 (100).

Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.67; H, 7.76.

The O-alkylation product **8a** (R′ = Me) boiled at 85–89 °C (0.005 mm): ^1H NMR (CCl_4) δ 1.13 (t, 3, CH_3), 1.87–2.60 (m, 4, $CH_2C{\equiv}C$, CH_2CO), 2.29 (s, 3, CH_3CO), 3.12, 3.25 (2 s, 6, CH_3O), 3.11–3.78 (m, 1, CHC=C), 3.55, 3.66 (2 s, 6, CH_3OCO), 4.41–4.66 (m, 3, $OCH_2C{\equiv}C$, OCHO); IR (neat) 2832 (CH_3O), 1737 (C=O), 1708 (C=O), 1619 cm^{-1} (C=C).

Anal. Calcd for $C_{17}H_{26}O_7$: C, 59.64; H, 7.65. Found: C, 59.42; H, 7.44.

Dimethyl 2-Acetyl-3-dimethoxymethyl-2-(*cis*-2-pentenyl)-glutarate (7b, R′ = Me). A mixture of Lindlar catalyst (208 mg) and **7a** (R′ = Me, 194 mg, 0.57 mmol) in hexane (1 mL) and acetone (1 mL) was stirred under 1 atm of hydrogen at room temperature. After 40 min, hydrogen uptake stopped and the mixture was filtered free from the catalyst and concentrated in vacuo. Column chromatography of the residue (SiO_2, benzene–AcOEt, 5/1) gave **7b** (R′ = Me, 195 mg, 100%), bp 82–87 °C (0.14 mm): ^1H NMR (CCl_4) δ 0.95 (t, 3, CH_3), 1.76–2.32 (m, 5, CH_3CO, CH_2C=C), 2.37–2.86 (m, 4, CH_2C=C, CH_2CO), 2.95–3.50 (m, 7, CH_3O, CH), 3.66, 3.71 (2 s, 6, CH_3O), 4.27 (m, 1, OCHO), 4.82–5.77 (m, 2, HC=CH); IR (neat) 2835 (CH_3O), 1733 (C=O), 1708 cm^{-1} (C=O); MS *m/e* (rel intensity) 344 (M^+, 0.33), 313 (27), 312 (12), 270 (14), 269 (48), 253 (24), 242 (28), 238 (11), 237 (30), 221 (15), 209 (14), 207 (11), 183 (35), 181 (14), 160 (13), 153 (29), 130 (50), 101 (18), 75 (100).

Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 59.14; H, 8.44.

5-Methoxycarbonyl-4-methoxycarbonylmethyl-5-(2-pentynyl)-2-cyclopentenone (10a, R′ = Me). A solution of **7a** (R′ = Me, 53 mg, 0.15 mmol) in THF (2 mL) and aqueous 1% $HClO_4$ (2 mL) was stirred for 12 h at 26–28 °C. The solution was neutralized with aqueous $NaHCO_3$ and concentrated to ca. 2 mL of total volume under reduced pressure. The residue was poured into brine and extracted with AcOEt. The extracts were dried (Na_2SO_4) and evaporated in vacuo to give the crude aldehyde **9a** (R′ = Me, 50 mg): ^1H NMR (CCl_4) δ 9.65 (CHO); IR (neat) 2841 (CHO), 1733, 1716 cm^{-1} (C=O). Without further purification, the oily product was subjected to the following cyclization reaction. A stirred mixture of **9a** (50 mg) in a mixed solution of AcOH (0.1 mL), piperidine (0.1 mL), and benzene (25 mL) was refluxed for 6 h. After cooling to room temperature most of the solvent was removed by a rotary evaporator. The residue was diluted with AcOEt (20 mL), washed with 10% HCl, aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. Column chromatography of the residue (SiO_2, benzene–AcOEt, 12/1) gave **10a** (R′ = Me, 24 mg, 56%). From the next running fraction, **7a** (R′ = Me, 4 mg) was recovered. The cyclopentenone **10a** (R′ = Me) boiled at 110–115 °C (0.15 mm): ^1H NMR (CCl_4) δ 1.05 (t, 3, CH_3), 1.80–2.30 (m, 2, CH_2C=C), 2.34–2.86 (m, 4, CH_2C=C, CH_2CO), 2.86–3.50 (m, 1, CH), 3.61, 3.67 (2 s, 6, CH_3O), 6.14 (dd, 1, *J* = 6 Hz, *J* = 2 Hz, C=CHCO), 7.59 (dd, 1, *J* = 6 Hz, *J* = 2 Hz, HC=CCO); IR (neat) 1732, 1710 (C=O), 1595 cm^{-1} (C=C); MS *m/e* (rel intensity) 279 (M^+ + 1, 29), 278 (M^+, 100), 247 (60), 246 (44), 219 (97), 215 (23), 205 (77), 189 (19), 187 (39), 179 (33), 159 (66), 147 (24), 145 (26), 131 (36), 117 (23), 115 (23), 91 (26).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.64; H, 6.30.

5-Methoxycarbonyl-4-methoxycarbonylmethyl-5-(*cis*-2-pentenyl)-2-cyclopentenone (10b, R′ = Me). Method A. A solution of **7b** (R′ = Me, 250 mg, 0.73 mmol) in THF (3 mL) and aqueous 1.5% $HClO_4$ (2 mL) was stirred for 12 h at 26–28 °C. The mixture was neutralized with aqueous $NaHCO_3$ and concentrated to ca. 2 mL of total volume under reduced pressure. The workup of the residue was similar to that employed for the preparation of **10a** (R′ = Me) described above, giving **9b** (R′ = Me, 248 mg): ^1H NMR (CCl_4) δ 9.56, 9.65 (CHO); IR (neat) 1735, 1717 cm^{-1} (C=O). Without further purification, the oily product was subjected to the following cyclization reaction. A mixture of **9b** (R′ = Me, 248 mg) in a mixed solution of AcOH (0.1 mL) and piperidine (0.1 mL) in benzene (30 mL) was refluxed for 6 h under stirring. After workup in the usual manner as described above there was obtained **10b** (R′ = Me, 105 mg, 52%) after

chromatography (SiO_2, benzene–AcOEt, 12/1). From the next running fraction, **7b** (R′ = Me, 5.4 mg) was recovered. The cyclopentenone **10b** (R′ = Me) boiled at 81–85 °C (0.005 mm): ^1H NMR (CCl_4) δ 0.97 (t, 3, CH_3), 2.05 (q, 2, J = 7 Hz, $CH_2C{=}C$), 2.27–3.51 (m, 5, $CH_2C{=}C$, CH_2CO, CH), 3.62, 3.66 (2 s, 6, CH_3O), 4.76–5.75 (m, 2, HC=CH), 6.09 (dd, 1, J = 5 Hz, J = 2 Hz, C=CHCO), 7.47 (dd, 1, J = 5 Hz, J = 2 Hz, HC=CCO); IR (neat) 1736, 1710 (C=O), 1597 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.07; H, 7.35.

Method B. The cyclopentenone **10b** (R′ = Me) was prepared by hydrogenation of **10a** (R′ = Me, 45 mg, 0.16 mmol) in hexane (1 mL) and acetone (0.1 mL) using Lindlar catalyst (68 mg). Column chromatography (SiO_2, benzene–AcOEt, 5/1) of the product gave **10b** (R′ = Me, 43 mg, 95%), whose spectral data were identical with those of the specimen obtained in the preceding experiment.

2-Methoxycarbonyl-3-methoxycarbonylmethyl-2-(*cis*-2-pentenyl)cyclopentanol (13b, R′ = Me) from 10b (R′ = Me). A solution of **10b** (R′ = Me, 11 mg, 0.039 mmol) and $NaBH_4$ (3.0 mg, 0.079 mmol) in MeOH (2 mL) was refluxed at ca. 80 °C for 1 h. The solution was allowed to cool to room temperature and then 4 drops of AcOH was added. After stirring for an additional 30 min, the solution was concentrated in vacuo and the residue was passed through a short silica gel column (2 × 0.9 cm, benzene–AcOEt, 2/1, 15 mL). Evaporation of the solvents followed by column chromatography (SiO_2, benzene–AcOEt, 5/1) gave **13b** (R′ = Me, 8.9 mg, 80%): bp 74–78 °C (0.01 mm); ^1H NMR (CCl_4) δ 0.93 (t, 3, CH_3), 1.40–2.90 (m, 12), 3.59, 3.66 (2 s, 6, CH_3O), 3.85–4.12 (m, 1, CHO), 4.95–5.75 (m, 2, HC=CH); IR (neat) 3506 (OH), 1727 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.47; H, 8.78.

2-Methoxycarbonyl-3-methoxycarbonylmethyl-2-(2-pentynyl)cyclopentanol (13a, R′ = Me). A solution of **10a** (R′ = Me, 20.0 mg, 0.072 mmol) and $NaBH_4$ (5.4 mg, 0.143 mmol) in MeOH (2 mL) was refluxed at 80 °C for 1 h under N_2. After the usual workup, there was obtained **13a** (R′ = Me, 17.5 mg, 86.3%): bp 70–75 °C (0.005 mm); ^1H NMR (CCl_4) δ 1.11 (t, 3, CH_3), 1.38–2.95 (m, 12), 3.60, 3.68 (2 s, 6, CH_3O), 3.90–4.45 (m, 1, HCO); IR (neat) 3433 (OH), 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.90; H, 8.02.

The Cyclopentanol 13b (R′ = Me) from 13a (R′ = Me). A mixture of **13a** (R′ = Me, 28 mg, 0.01 mmol) and Lindlar catalyst (44 mg) in hexane (1 mL) and acetone (0.1 mL) was stirred under 1 atm of hydrogen at room temperature. After 1 h, the hydrogen uptake stopped and the mixture was filtered free from the catalyst and concentrated in vacuo. Column chromatography of the residue (SiO_2, benzene–AcOEt, 5/1) gave **13b** (R′ = Me, 21.5 mg, 77%), bp 74–78 °C (0.01 mm), which was identical in all respects with those of the product obtained in the preceding experiment.

2-Methoxycarbonyl-3-methoxycarbonylmethyl-2-(*cis*-2-pentenyl)cyclopentanone (14b, R′ = Me). To a solution of **13b** (R′ = Me, 6.8 mg, 0.024 mmol) in CH_2Cl_2 (2 mL), 100 mg of aqueous 2 M chromic acid was added dropwise. The mixture was stirred at room temperature for 12 h under a heterogeneous system. The yellow-orange solution was taken up in AcOEt and washed with brine, aqueous $NaHCO_3$, and brine. The AcOEt layer was dried (Na_2SO_4) and concentrated. Column chromatography (SiO_2, benzene–AcOEt, 10/1) of the residue gave **14b** (R′ = Me, 5.7 mg, 84%), bp 73–77 °C (0.007 mm) [lit.[2d] bp 84.0–85.0 °C (0.0 15 mm)], whose spectral data were identical with those of an authentic sample.

Methyl *dl*-Jasmonate (1b) from 14b (R′ = Me). Demethoxycarbonylation of **14b** (R′ = Me, 130 mg, 2.2 mmol) in aqueous Me_2SO–NaCl at 176 °C for 4 h gave **1b** (69 mg, 86%), whose spectral data (IR, ^1H NMR, and MS) were identical with those of an authentic sample.

2-Methoxycarbonyl-3-methoxycarbonylmethyl-2-(2-pentynyl)cyclopentanone (14a, R′ = Me). To a solution of **13a** (R′ = Me, 17 mg, 0.06 mmol) in CH_2Cl_2 (2 mL), aqueous 2 M chromic acid (ca. 0.2 mL) was added dropwise and the mixture was stirred at room temperature for 12 h. After the usual workup, there was obtained **14a** (R′ = Me, 12 mg, 71%), bp 78–82 °C (0.008 mm) [lit.[2d] bp 78–80 °C (0.02 mm)], whose IR and ^1H NMR spectra were identical with those of an authentic sample.

2-Methoxycarbonyl-3-methoxycarbonylmethyl-2-pentylcyclopentan-1-one (14c, R′ = Me). A mixture of **10b** (R′ = Me, 32 mg, 0.11 mmol) and palladium on charcoal (60 mg) in MeOH (2 mL) was stirred under 1 atm of hydrogen at room temperature. After 50 min, hydrogen uptake stopped and the mixture was filtered free from catalyst and concentrated. Column chromatography of the residue (SiO_2, benzene–AcOEt, 5/1) gave **14c** (31 mg, 97%), whose IR and ^1H NMR spectra were identical with those of an authentic sample.[2d]

Methyl 4-*tert*-Butoxycarbonyl-3-dimethoxymethyl-5-oxohexanoate (5, R′ = *t*-Bu). A mixture of **4**(*Z*) (1.66 g, 10.4 mmol), KF (2.0 g, 34.4 mmol), and $AcCH_2CO_2$-*t*-Bu (1.81 g, 11.5 mmol) in *t*-BuOH (2 mL) was vigorously stirred for 2 days under reflux. After the same workup as described for **5** (R′ = Me), there was obtained **5** (R′ = *t*-Bu, 2.86 g, 86%): bp 72–76 °C (0.014 mm); ^1H NMR (CCl_4) δ 1.43 (br s, 9, CH_3), 2.17 (s, 3, CH_3CO), 2.30–2.60 (m, 2, CH_2CO), 2.60–3.19 (m, 1, AcCHCO), 3.19–3.38 (m, 6, CH_3O), 3.58–3.72 (m, 3, CH_3OCO), 3.19–3.72 (m, 1, CH), 4.31 (t, 1, J = 5 Hz, OCHO); IR (neat) 1736 (C=O), 1715 cm^{-1} (shoulder, C=O).

Anal. Calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23. Found: C, 56.65; H, 8.13.

5-*tert*-Butoxycarbonyl-4-methoxycarbonylmethyl-5-(2-pentynyl)-2-cyclopentenone (10a, R′ = *t*-Bu) from 5 (R′ = *t*-Bu) via 7a. A mixture of K_2CO_3 (1.38 g, 9.99 mmol), **5** (R′ = *t*-Bu, 450 mg, 1.42 mmol), pentynyl bromide (270 mg, 1.84 mmol), and KI (308 mg, 1.86 mmol) in acetone (30 mL) was refluxed for 12 h. After the usual workup as described above, there was obtained 478 mg of an oily product, whose ^1H NMR spectrum indicated that the product consisted of **7a** (R′ = *t*-Bu, 75%) and **8a** (R′ = *t*-Bu, 13%). Without further purification, the mixture was subjected to the following cyclization reaction. A solution of the mixture **7a** and **8a** (60 mg, 0.16 mmol) in THF (3 mL) and aqueous 1.5% $HClO_4$ (2.5 mL) was stirred for 12 h at 28–29 °C. The workup of the reaction mixture was similar to that employed for the preparation of **10a** (R′ = Me), giving an oily material (79 mg), which was subjected to reflux in a mixed solution of AcOH (0.1 mL), piperidine (0.1 mL), and benzene (5 mL) for 4 h. Upon evaporation of the solvent, the residue was worked up in the usual manner as described above. After chromatography (SiO_2, benzene–hexane–AcOEt, 6/3/1), there was obtained 22 mg (48% based on **7a**, R′ = *t*-Bu) of **10a** (R′ = *t*-Bu): bp 82–86 °C (0.006 mm); ^1H NMR (CCl_4) δ 1.02 (t, 3, CH_3), 1.37 (br s, 9, CH_3), 1.76–2.73 (m, 6, $CH_2C{=}C$, CH_2CO), 3.33–3.58 (m, 1, CH), 3.66 (s, 3, CH_3O), 6.10 (dd, 1, J = 5, 2 Hz, C=CHCO), 7.50 (dd, 1, J = 5, 2 Hz, HC=CCO); IR (neat) 1734, 1711 (C=O), 1595 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.36; H, 7.70.

5-*tert*-Butoxycarbonyl-4-methoxycarbonylmethyl-5-(*cis*-2-pentenyl)-2-cyclopentenone (10b, R′ = *t*-Bu). Hydrogenation of **10a** (R′ = *t*-Bu, 69 mg, 0.22 mmol) in hexane (0.5 mL) and acetone (0.5 mL) in the presence of Lindlar catalyst (320 mg) afforded **10b** (R′ = *t*-Bu, 70 mg, 100%): bp 81–84 °C (0.005 mm); ^1H NMR (CCl_4) δ 0.97 (t, 3, CH_3), 1.42 (s, 9, CH_3), 2.05 (q, J = 7 Hz, 2, $CH_2C{=}C$), 2.34–2.71 (m, 4, $CH_2C{=}C$, CH_2CO_2), 3.26 (m, 1, CH), 3.66 (s, 3, CH_3O), 4.79–5.69 (m, 2, HC=CH), 6.09 (dd, 1, J = 5 Hz, J = 2 Hz, C=CHCO), 7.50 (dd, 1, J = 5 Hz, J = 2 Hz, HC=CCO); IR (neat) 1734, 1712 (C=O), 1596 cm^{-1} (C=C).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.91; H, 8.36.

Methyl Dehydrojasmonate (2b). A mixture of **10b** (R′ = *t*-Bu, 54 mg, 0.17 mmol) and a catalytic amount of anhydrous *p*-toluenesulfonic acid in benzene (2 mL) was refluxed for 20 min. The mixture was quenched with $NaHCO_3$ (powder, 10 mg). After removal of the solvent under reduced pressure, the residue was chromatographed (SiO_2, benzene–AcOEt, 10/1) to give **2b** (31 mg, 83%): bp 88–92 °C (2.5 mm); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3, CH_3), 1.88–3.18 (m, 8), 3.70 (s, 3, CH_3O), 4.95–5.75 (m, 2, HC=CH), 6.15 (dd, 1, J = 6, 1.6 Hz, C=CHCO), 7.60 (dd, J = 6, 2 Hz, HC=CCO); ^{13}C NMR (multiplicity, carbon no.) δ 14.1 (q, 12), 20.5 (t, 11), 27.7 (t, 8), 38.1 (t, 2), 43.2 (d, 3), 51.0 (d, 7), 51.8 (q, 13), 124.4 (d, 9), 133.7 (d, 5 or 10), 134.4 (d, 10 or 5), 165.3 (d, 4), 171.7 (s, 1), 210.0 (s, 6); IR (neat) 1736, 1706 (C=O), 1599 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.06; H, 8.19.

3-Methoxycarbonylmethyl-2-(*cis*-2-pentenyl)cyclopentanol (15) from 2b. A solution of **2b** (18 mg, 0.08 mmol) and $NaBH_4$ (9 mg, 0.2 mmol) in MeOH (2 mL) was refluxed at 80 °C for 1 h. After the usual workup, there was obtained **15** (16 mg, 87%) after chromatography (SiO_2 benzene–AcOEt, 5/1): bp 63–67 °C (0.01 mm); ^1H NMR (CCl_4) δ 0.99 (t, 3, CH_3), 1.22–2.88 (m, 13), 3.61 (s, 3, CH_3O), 3.67–4.22 (m, 1, CHO), 5.20–5.52 (m, 2, HC=CH); IR (neat) 3400 (OH), 1735 (C=O), 1722 cm^{-1} (shoulder).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.00; H, 9.75.

Methyl *dl*-Jasmonate (1b) from 15. To a solution of **15** (15 mg, 0.066 mmol) in CH_2Cl_2 (1 mL) aqueous 2 M chromic acid (0.2 mL) was added dropwise. The mixture was stirred at 18–20 °C for 12 h and then worked up in the usual manner as described for the Jones oxidation of **13** to give **1b** (10 mg, 68%) after chromatography (SiO_2, benzene–

hexane–THF, 11/5/1): bp 92–96 °C (2.7 mm) [lit.[2d] bp 110–112 °C (5 mm)].

2-*tert*-Butoxycarbonyl-3-methoxycarbonylmethyl-2-(*cis*-2-pentenyl)cyclopentanol (13b, R′ = *t*-Bu). A solution of **10b** (R′ = *t*-Bu, 37 mg, 0.11 mmol) and $NaBH_4$ (6 mg, 0.16 mmol) in MeOH (1.5 mL) was refluxed for 1 h. The mixture was quenched with AcOH (0.1 mL) and concentrated in vacuo. Column chromatography (SiO_2, benzene–AcOEt, 5/1) of the residue gave **13b** (R′ = *t*-Bu, 36 mg, 96%): bp 75–79 °C (0.005 mm); ^1H NMR (CCl_4) δ 0.98 (t, 3, CH_3), 1.20–2.69 (m, 21), 3.60 (s, 3, CH_3O), 3.96 (m, 1, CHO), 5.21–5.54 (m, 2, HC=CH); IR (neat) 3509 (OH), 1721 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.28; H, 9.50.

2-*tert*-Butoxycarbonyl-3-methoxycarbonylmethyl-2-(*cis*-2-pentenyl)cyclopentanone (14b, R′ = *t*-Bu). To a solution of **13b** (R′ = *t*-Bu, 15 mg, 0.046 mmol) in CH_2Cl_2 (1 mL) was added dropwise 2 M chromic acid (0.1 mL). The mixture was stirred at 16–20 °C for 12 h and then diluted with AcOEt. Upon the usual workup as described for the oxidation of **15**, there was obtained **14b** (R′ = *t*-Bu, 10 mg, 67%) after column chromatography (SiO_2, benzene–hexane–AcOEt, 10/5/1): bp 79–83 °C (0.01 mm); ^1H NMR (CCl_4) δ 0.97 (t, 3, CH_3), 1.29–2.79 (m, 11), 1.45 (s, 9, CH_3), 3.64 (s, 3, CH_3O), 4.94–5.59 (m, 2, HC=CH); IR (neat) 1738 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.87; H, 8.94.

Methyl *dl*-Jasmonate (1b) from 14b (R′ = *t*-Bu). A solution of **14b** (R′ = *t*-Bu, 7.2 mg, 0.022 mmol) in benzene (1 mL) containing a catalytic amount of *p*-toluenesulfonic acid was refluxed for 20 min. After the usual workup, the residue was chromatographed (SiO_2, benzene–AcOEt, 10/1) to give **1b** (4.5 mg, 90%): ^{13}C NMR (multiplicity, carbon no.) δ 14.1 (q, 12), 20.6 (t, 11), 25.5 (t, 4), 27.2 (t, 8), 37.8 (t, 2 or 5), 38.0 (d, 3), 38.8 (t, 5 or 2), 51.6 (q, 13), 54.0 (d, 7), 124.9 (d, 9), 134.0 (d, 10), 172.5 (s, 1), 218.8 (s, 6); IR and ^1H NMR data were identical with those of an authentic sample.

Registry No.—**1b**, 20073-13-6; **2b**, 63569-04-0; (*E*)-**4**, 32815-00-2; (*Z*)-**4**, 75314-31-5; **5** (R′ = Me), 63528-42-7; **5** (R′ = *t*-Bu), 63528-43-8; **7a** (R′ = Me), 63528-44-9; **7a** (R′ = *t*-Bu), 63528-45-0; **7b** (R′ = Me), 63528-46-1; **8a** (R′ = Me), 63528-47-2; **8a** (R′ = *t*-Bu), 63528-48-3; **9a** (R′ = Me), 63528-49-4; 9b (CR′ = Me), 63528-50-7; **10a** (R′ = Me), 63528-51-8; **10a** (CR′ = *t*-Bu), 63528-52-9; **10b** (R′ = Me), 63528-53-0; **10b** (R′ = *t*-Bu), 63528-54-1; **13a** (R′ = Me), 63528-55-2; **13b** (R′ = Me), 63534-37-2; **13b** (R′ = *t*-Bu), 63528-56-3; **14a** (R′ = Me), 55254-74-5; **14b** (R′ = Me), 55254-73-4; **14b** (R′ = *t*-Bu), 63528-57-4; **15**, 51388-61-5; $AcCH_2CO_2Me$, 105-45-3; pentynyl bromide, 16400-32-1; $AcCH_2CO_2$-*t*-Bu, 1694-31-1.

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Cyclodimerization of Styrene

Arnold R. Taylor,[1a,b,c] Gary W. Keen,[1c] and Edmund J. Eisenbraun*[1b,d]

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074 and Research and Development Department, Continental Oil Company, Ponca City, Oklahoma 74601

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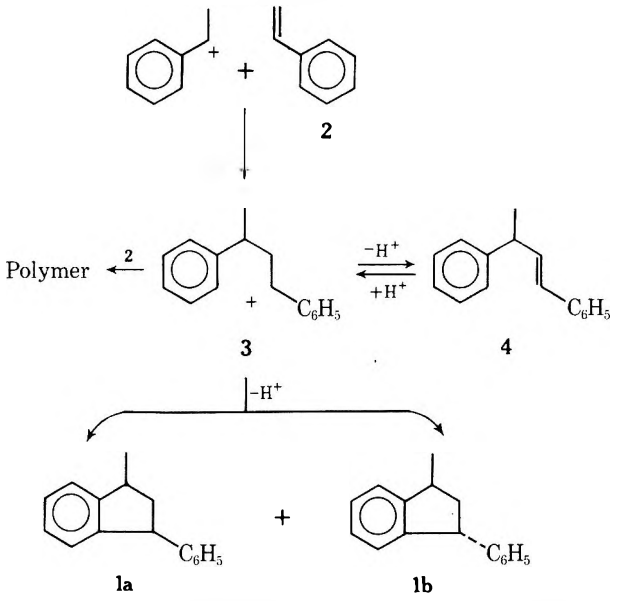
The cyclodimerization of styrene in the presence of sulfuric acid or Amberlyst-15 resin yields a 1:1 mixture of *cis*- and *trans*-1-methyl-3-phenylindan (**1a** and **1b**) via (*E*)-1,3-diphenyl-1-butene (**4**). 1-Methyl-3-phenylindene (**8**) and 3-methyl-1-phenylindene (**9**) were synthesized and converted to **1a** and **1b**. Base-catalyzed equilibration of **1a** and **1b** as well as **8** and **9** gave **1a:1b** (80:20) and **8:9** (30:70), respectively.

cis- and *trans*-1-methyl-3-phenylindan (**1a** and **1b**) can be obtained by cyclodimerization of styrene (**2**) with sulfuric acid,[2a-g] phosphoric acid,[3a-d] polyphosphoric acid (PPA),[3b] alumina–silica,[3a] perchloric acid,[3d] chlorosulfonic acid,[3d] or by passing styrene over hot promoted B_2O_3.[4] This reaction may proceed through the cation **3**, which can eliminate a proton to form the alkene **4**, cyclize to **1a** and **1b**, or yield polymer, as shown in Scheme I.

The low-temperature dimerization kinetics of **2** to **1a** and **1b** have been reported to be second order, whereas high-temperature kinetics are complex.[3d] Two isomeric forms of **1** have been reported[5] and identified[6] as **1a**, mp 9.5 °C, and **1b**, mp 25.5 °C. It has been reported that **1a:1b** as a 50:45 mixture was converted to a 62:38 ratio by stirring with 10% $AlBr_3$[7] and that **1a** is isomerized to an 82:18 ratio of **1a:1b** with $AlCl_3$.[5] The tertiary, twice-benzylic hydrogen of **1** is reported to be more reactive in forming a radical intermediate than the tertiary benzylic hydrogen.[8]

We sought **1a** and **1b** in order to study their stereochemistry and clarify their relative thermodynamic stability. The structure and stability of **1a** and **1b** were studied through equilibration experiments and by preparations from indenes. Sulfuric acid, ethylaluminum dichloride ($EtAlCl_2$),[9] and Amberlyst-15 (A-15),[10] an insoluble sulfonic acid resin, were tested as catalysts for the cyclodimerization reaction. Using A-15 allowed convenient monitoring of this reaction. Samples were periodically withdrawn from the A-15-catalyzed reactions and analyzed by GC.[11] The linear dimer **4** appears to be

Scheme I



an initial product and it slowly disappears as **1a:1b** (1:1) form. The reaction conditions were varied, but the combined yield of **1a** and **1b** from the A-15-catalyzed cyclodimerization remained at about 20%.

A sulfuric acid catalyzed reaction[2f] was used for production of the **1a:1b** mixture required for the equilibration studies. The yield was 69–80%; some **4** always remained. A diluted sulfuric acid solution and a lower temperature allowed isolation of **4** in good yields.[2g] Amberlyst-15 and PPA were used to show that **4** is converted to **1a** and **1b**. A similar conversion of **4** to **1a** and **1b** has been accomplished via a supported H_3PO_4 catalyst at 200 °C.[12] The cyclization of **4** to **1** with A-15 in 80% yield is a more facile reaction than direct conversion of **2** to **1** with A-15 (20% yield). This suggests that the A-15 catalyst becomes coated with polystyrene when **2** is present.

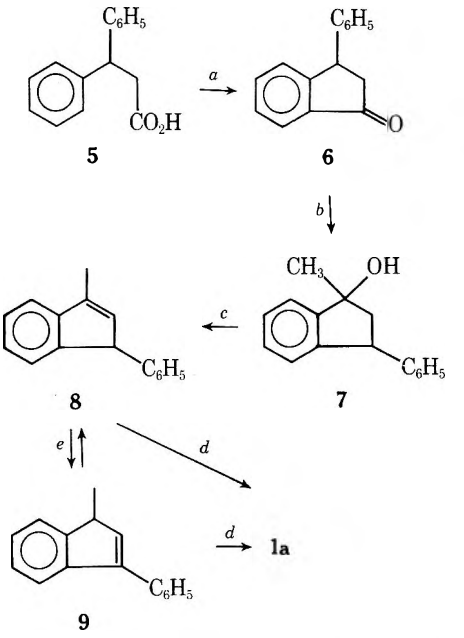
A series of reactions was run to determine whether $EtAlCl_2$[13] would be useful in the dimerization of styrene, since the dimerization of α-methylstyrene had been successfully carried out with this catalyst,[14] but $EtAlCl_2$ was less convenient to handle and gave a product of lower purity. Its use was not studied further.

The ^1H NMR signals of **1a** and **1b** could not be confidently assigned from mixtures, so individual samples of **1a** and **1b** were prepared as shown in Scheme II. Isomer **1b** was obtained in approximately 95% purity by recrystallizing a **1a:1b** mixture from petroleum ether, bp 60–68 °C, slowly cooled in dry ice. Dehydration and distillation of **7** yielded 1-methyl-3-phenylindene (**8**) and 3-methyl-1-phenylindene (**9**) in a 30:70 ratio, respectively. Hydrogenation of **8** or a mixture of **8** and **9** over Pd/C catalyst produced only **1a**.[5,6] When **8** was treated with a 5% KOH solution in methanol, an equilibrated mixture of **8:9** (30:70) was obtained.

3-Methyl-1-phenylindene (**9**) was synthesized as shown in Scheme III to further the equilibration studies and ^1H NMR assignments of **1a, 1b, 8,** and **9.** None of **8** was observed in the preparation of **9.** Isomerization of **9** by a 5% solution of KOH in methanol gave the same equilibrated mixture of **8:9** (30:70) as obtained from **8.** The reduction of **8** and **9** by sodium in liquid ammonia gives mixtures of **1a** and **1b,** as shown in Table I.

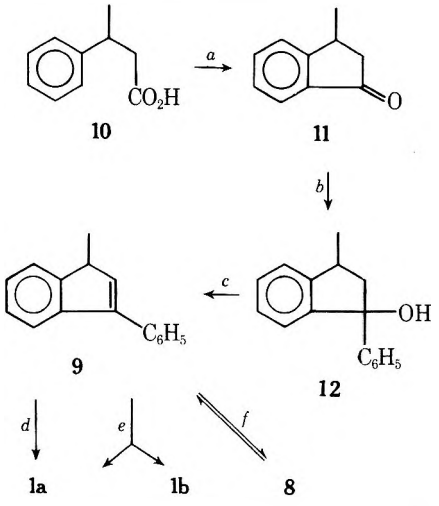
No isomerization was observed on treatment of **1a** with methanolic hydrochloric acid or sodium ethoxide at room temperature, but treatment with sodium amide produced **1a:1b** (80:20). Isomer **1b** showed similar behavior. Models of **1a** and **1b** show that the methyl and phenyl groups of **1a** may

Scheme II



[a] PPA, 90 °C. [b] CH_3MgBr, ether. [c] Toluene, Δ. [d] Pd/C, H_2. [e] 5% KOH in CH_3OH.

Scheme III



[a] PPA, Δ. [b] C_6H_5MgBr. [c] Δ. [d] H_2, Pd/C. [e] Na, NH_3. [f] 5% KOH in CH_3OH.

lie on the equatorial plane of the five-membered ring, whereas in **1b** only the methyl or the phenyl can occupy an equatorial position at one time. This suggests that **1a** has the greater thermodynamic stability.

In summary, the major intermediate (**4**) in the acid-catalyzed cyclodimerization of styrene is accessible by adjusting the temperature and/or the reaction time. Though A-15 is a superior catalyst for the cyclodimerization of α-methylstyrene,[15] only a low yield of cyclodimerization products is realized with styrene. However, sulfuric acid[2f] is effective in the dimerization of styrene to **1a** and **1b** (1:1). The base-catalyzed equilibrium ratio of indenes **8** and **9** (30:70) and indans **1a** and **1b** (80:20) were determined.

Experimental Section

Cyclodimerization of Styrene (2) by A-15. Several runs were made varying the reactant, catalyst, solvent ratios, and the length of the run. These ratios and times are given in Table II. The reaction mixtures were refluxed under a nitrogen atmosphere, filtered through Dicalite, and distilled to give a maximum yield of a mixture of 20% of **1a** and **1b,** bp 115–117 °C (1 mm), in a 1:1 ratio.

Table I. Reduction of Isomeric Methylphenylindenes with Sodium in Liquid Ammonia

	Sample, g	Sodium, g	% 1a	% 1b
8	1.5	0.7	77	23
8	1.0	0.4	79	21
9	1.0	0.4	82	18
9	1.0	1.0	84	16

Table II

2, mol	A-15, g	Cyclohexane, mL	Time, h
1.0	25	2.5	8
1.0	25	2.0	12
0.2	5	0.5	24
6.6	25	1.5	18
0.9	80	1.0	12

Table III

Time, h	% 1a,1b	% 4
4.0	13.5	86.5
8.5	59.4	40.6
16.0	86.2	13.8
24.0	99.0	1.0

The various runs were sampled and analyzed by gas chromatography[11] as shown in Table III. The product showed: IR (neat) 3025, 1600, 1495, 1455, 750 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 208 (M^+, 100), 193 (70), 179 (31), 178 (30), 130 (41), 115 (49).

Cyclodimerization of 2 to 1 by H_2SO_4. Freshly distilled **2** (400 g, 3.8 mol) was stirred into 1 L of a 62% solution of H_2SO_4 and treated as described.[2f] Distillation yielded 285 g (82%) of **1a:1b** (1:1), bp 114–116 °C (1 mm).

Dimerization of 2 to (*E*)-1,3-Diphenyl-1-butene (4). This dimerization was carried out as described[3a] to give a 77% yield of **4**: bp 123–125 °C (1 mm); IR (neat) 2780, 1440, 1005, 957, 737 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 208 (M^+, 90), 193 (93), 178 (28), 130 (22), 115 (100), 91 (57); ^1H NMR ($DCCl_3$) δ 7.3 (m, 10, ArH), 6.4 (s, 2, HC=CH), 3.62 (m, 1, ArCH), 1.44 (d, 3, CH_3). A computer-controlled peak and intensity search of the Cyphernetics Mass Spectral file (27 000 spectra) identified the spectrum as that of **4**. This spectrum was then directly compared with that of our reaction product, and they were found to be identical.

Cyclization of 4 to 1. By PPA.[3a] A 16-g sample of **4** was stirred into 20 g of PPA preheated to 150 °C, and the mixture was allowed to stir at this temperature under a nitrogen atmosphere for 3 h. An 80% yield of **1a:1b** (1:1)[11] was obtained.

By A-15. A 40-g sample of **4** was dissolved in 200 mL of cyclohexane, and 20 g of A-15 was added. The mixture was heated at reflux temperature under a nitrogen atmosphere for 4 h to give **1a:1b** (1:1)[11] in 80% yield.

Cyclodimerization of 2 by Ethylaluminum Dichloride. $EtAlCl_2$ (0.02 mol, 2.77 g) was dissolved in benzene and slowly added to a stirred benzene solution (600 mL) containing 20 g of **2** (0.2 mol) under a nitrogen atmosphere.[13,14] A red color developed immediately. Samples were removed periodically and analyzed by GC to determine the concentration of **1a** and **1b**.[11] The solution was stirred for 1 h at room temperature and 4 h at reflux temperature. The excess $EtAlCl_2$ was destroyed by adding 4 mL of methanol. The solution was washed with water and HCl, dried ($MgSO_4$), and filtered. The yield was low (24%), and other compounds were formed. The reaction was repeated as above using 0.2 mol of $EtAlCl_2$ (60% yield of product mixture).

Recrystallization of 1b. A 119-g sample of **1a:1b** was recrystallized as described[5] to give **1b** in 95% purity: mp 25 °C (lit.[5] 25.5 °C); IR (film) 747 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 208 (M^+, 100), 193 (71), 130 (61), 115 (54), 91 (30); ^1H NMR δ 7.1 (m, 9, ArH), 4.3 (t, 1, Ar_2CH), 3.3 (m, 1, ArCH), 2.1 (q, 2, CH_2), 1.3 (d, 3, CH_3).

Synthesis of 1-Methyl-3-phenylindene (8). The benzene for this experiment was purified by refluxing it in the presence of $AlCl_3$ for 20 h, cooling, filtering through Na_2CO_3, and distilling. Cinnamic acid (8.1 mol, 1203 g), 15.6 kg of benzene, and aluminum chloride (1824 g) were combined and treated as described.[5] Instead of cyclizing the 3,3-diphenylpropionic acid (**5**) via the acid chloride, 3 mol (675 g) of **5** was added to 6700 g of PPA that had been preheated to 90 °C. The mixture became yellow, and after 1.5 h of stirring, it was cooled to 70 °C, poured into ice water, and extracted with ether. The combined ether layers were washed with NaOH solution to remove acid, and then with water. The NaOH solution was later acidified to yield 223 g (33%) of **5**. The ether layer was dried ($MgSO_4$), filtered, and distilled to yield a residual orange solid. After two recrystallizations from methanol 298 g of yellow crystals of 3-phenylindanone (**6**) was obtained (48% conversion, 72% yield), mp 74.5–75.5 °C (lit.[5] 76.5–77.5 °C).

A 270-g (1.8-mol) sample of **6** dissolved in 900 mL of ether was added to 238 g of CH_3MgBr in 1500 mL of ether over a 20-min period. A green color developed which slowly faded to light yellow. The reaction mixture was heated at reflux for 2.5 h and then cooled. A 33% solution of NH_4Cl (300 mL) was added slowly to decompose the Grignard complex, and a 20% solution of HCl (200 mL) was used to dissolve salts. The product mixture was poured into ice water containing HCl and then extracted with ether (2 × 1.5 L). The combined ether layers were washed with water, Na_2CO_3, and water, then dried over $MgSO_4$ and filtered. Upon stripping the ether, some dehydration of **7** to **8** occurred. This dehydration was completed through use of refluxing toluene and a Dean–Stark trap.

Upon distillation, dehydration of the product mixture occurred to give 216 g of **8:9** (3:1). Several recrystallizations gave pure **8**: mp 59–61 °C (lit.[5] mp 63–64 °C); IR (KBr) 1600, 1070, 875, 845, 787, 765, 753, 695 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 206 (M^+, 100), 205 (17), 191 (56), 189 (15), 165 (11); ^1H NMR ($DCCl_3$) δ 7.2 (m, 9, ArH), 6.24 (d, 1, =CH), 4.52 (m, 1, ArCH), 1.2 (s, 3, CH_3).

Hydrogenation of 8 to 1a. A 51.3-g sample of **8** was dissolved in 95% ethanol containing 10% (by weight) of 5% Pd/C catalyst. This mixture was hydrogenated at 25 psi with shaking until the pressure drop ceased (15–20 min). The suspension was filtered (Dicalite), concentrated, and distilled using a Kugelrohr apparatus to give **1a** (39.5 g): IR (film) 731 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 208 (M^+, 100), 193 (70), 178 (30), 130 (41), 115 (49); ^1H NMR ($DCCl_3$) δ 7.1 (m, 9, ArH), 4.1 (q, 1, Ar_2CH), 3.1 (m, 1, ArCH), 2.6 (m, 1, *trans*-HCH to Ph), 1.6 (m, 1, *cis*-HCH to Ph), 1.2 (d, 3, CH_3). A 70:30 mixture of **8** and **9** also gave only **1a** when hydrogenated as above.

Synthesis of 3-Methyl-1-phenylindene (9). A 30-g sample of 3-phenylbutanoic acid (**10**) was added to 700 g of PPA preheated to 90 °C under a nitrogen atmosphere. A workup as described above and distillation gave 25 g (83%) of 3-methyl-1-indanone (**11**). A 30-g sample of **11** (25 g from the previous reaction plus 5 g prepared earlier) was dissolved in 50 mL of ether and then added slowly to 56 g of phenylmagnesium bromide in 500 mL of ether. After a workup similar to that described above, including dehydration by distilling, 32.5 g (92%) of **9** was obtained: mp 35–36 °C (lit.[16] 36–37 °C); IR (KBr) 2850, 1340, 910, 820, 690 cm^{-1}; ^1H NMR ($DCCl_3$) δ 7.40 (m, 9, ArH), 6.48 (d, 1, =CH), 3.56 (m, 1, ArCH), 1.38 (d, 3, CH_3).

General Procedure for Equilibration. Erlenmeyer flasks (125-mL) with a side arm were used in all the equilibration experiments. The top opening contained a one-hole neoprene stopper fitted with glass tubing, and nitrogen was passed through the side arm and out the stopper to a bubbler. A Teflon-enclosed magnetic stirring bar was used for agitation. The flasks were filled one-eighth with solvent and the other components were than added. Four flasks were used simultaneously and all were sampled periodically, using a pipet. Each sample was worked up in a 1-dram vial by adding water, then benzene, and shaking. The aqueous layer was removed by pipetting and the organic layer was washed three times with water. After the last aqueous layer was removed, a small amount of Na_2SO_4 was added to dry the benzene solution. GC studies were then carried out.[11]

Equilibration of 8 by 5% KOH. A 0.2-g sample of **8** was added to a stirred solution of 4.2 g of KOH dissolved in 25 g of methanol. After 30 min, a ratio of 30:70 (**8:9**) was observed. This ratio remained constant during 2 days of observation.

Equilibration of 9 by 5% KOH. A 0.2-g sample of **9** was added to 4.2 g of KOH dissolved in 25 g of methanol, and the resulting solution was stirred for 3.5 h. A ratio of 30:70 (**8:9**) was observed.

General Procedure for Reduction of 8 or 9 with Sodium in Liquid Ammonia.[17a,b] A 5 × 15 cm cylindrical Pyrex reaction vessel containing a polyethylene-enclosed magnetic stirring bar, ₹ openings for ammonia, a pressure-equalizing dropping funnel, a cold-finger reflux condenser, and a soda-lime guard tube was used to carry out the reduction.[17b] The apparatus was dried by heating and passing nitrogen through it, and then ammonia was allowed to flow through the vessel for 10 min. Dry ice and acetone were added to the condenser, and ammonia was condensed. Sodium was added to the vessel via Gooch tubing. Once the sodium had disappeared, a dropping funnel

containing the compound (8 or 9) dissolved in ether was attached, and the solution was slowly added with stirring. After the mixture had been stirred from 1 to 1.5 h, NH_4Cl crystals were cautiously added until the blue color disappeared. Ammonia was allowed to evaporate, and the residue was poured into water and extracted by ether. The ether layer was dried ($MgSO_4$), filtered, and concentrated to give an oil, which was analyzed by GC. The data from duplicate runs on 8 and 9 are given in Table I.

Reduction of 8. Sodium (0.7 g) was dissolved in 50 mL of ammonia and a blue color developed immediately. A 1.5-g sample of 8 dissolved in 15 mL of dry ethyl ether was then added via a dropping funnel. No color change occurred in the solution. After stirring 1.5 h, the reaction mixture was worked up to give 1.3 g of oil. Gas chromatography analysis showed **1a:1b** (77:23).[11]

The reduction of 1 g of 8 was repeated using 0.4 g of sodium to give **1a:1b** (79:21).[11]

Reduction of 9. A 1-g sample of 9 and 0.4 g of sodium treated as above gave **1a:1b** (82:18). This was repeated using 1 g of sodium, which resulted in **1a:1b** (84:16).[11]

Equilibration of 1a by $NaNH_2$. The apparatus described in the reduction procedure was used. A 1-g sample of **1a** dissolved in 15 mL of dry ether was slowly added to a solution containing 0.3 g of sodium dissolved in 50 mL of liquid ammonia, which contained a crystal of $FeSO_4$. When GC studies showed no composition change, the solution was worked up as described in the reduction procedure to yield 1 g of an oil. GC analysis showed that this oil contained **1a:1b** (82:18).[11]

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Registry No.—**1a**, 14568-75-3; **1b**, 14568-76-4; **2**, 100-42-5; **4**, 7302-01-4; **5**, 606-83-7; **6**, 16618-72-7; **8**, 22360-63-0; **9**, 22360-6-9; **10**, 4593-90-2; **11**, 6072-57-7; cinnamic acid, 621-82-9.

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Preparation and Properties of $RMgH$ and RMg_2H_3 Compounds

E. C. Ashby* and A. B. Goel

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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A series of alkyl- and arylmagnesium hydrides, RMgH (where R = Me, Et, *i*-Pr, Cp, and Ph), has been prepared by the reaction of R_2Mg compounds with an active form of magnesium hydride slurry in THF. These products could also be prepared by the reaction of RLi compounds with hydridomagnesium halide (HMgX, where X = Cl and Br), as demonstrated by the preparation of methylmagnesium hydride by the reaction of CH_3Li with HMgCl in THF. Preparation of compounds of the type RMg_2H_3 (where R = Me and Ph) has also been carried out. Contrary to earlier reports, the RMgH compounds have been found to be soluble and quite stable in THF at room temperature. A band in the region 1250–1300 cm^{-1} in the infrared spectrum of these compounds has been assigned to Mg–H stretching. This band is shifted to 940 cm^{-1} in the deuterio analogues, RMgD. Molecular weight studies of methyl- and ethylmagnesium hydride show these compounds to be dimeric in dilute solution.

The existence of compounds of the type RMgH has been the subject of interest and speculation for many years, as these compounds are analogues of Grignard reagents. Rice and coworkers[1] in 1956 reported the formation of PhMgH by the reaction of PhMgBr with $LiAlH_4$ in 4:1 ratio in ether. Later we showed[2] that the products of this reaction were not the same as reported by Rice. In a communication in 1962, Bauer[3] reported the preparation of C_2H_5MgH by the reaction of silane with $(C_2H_5)_2Mg$ in ether (eq 1).

$$Mg(C_2H_5)_2 + SiH_4 \rightarrow HMgC_2H_5 + H_3SiC_2H_5 \quad (1)$$

However, he provided no characterization of the product. Sometime later, Coates and Heslop[4] reported evidence for the formation of C_2H_5MgH as an intermediate in the reaction of $(C_2H_5)_2Mg$ and $NaB(C_2H_5)_3H$ (eq 2); however, they reported that the compound was stable only at −78 °C and dissociated at −20 °C to give MgH_2 and $(C_2H_5)_2Mg$ (eq 3).

$$NaEt_3BH + Et_2Mg \rightarrow EtMgH + NaEt_4B \quad (2)$$

$$2EtMgH \rightarrow Et_2Mg + MgH_2 \quad (3)$$

Our earlier attempts[5] to prepare C_2H_5MgH by the reaction of $LiAlH_4$ with $(C_2H_5)_2Mg$ in ether in 1:4 ratio and by the reaction of MgH_2 with $(C_2H_5)_2Mg$ in ether were not successful in that MgH_2 was recovered in both cases. In this communi-

cation, we wish to report for the first time the successful preparation of pure RMgH compounds.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[6] Filtration and other manipulations were carried out in a glove box equipped with a recirculating system.[7]

Infrared spectra were obtained using a Perkin-Elmer 621 spectrophotometer. Solutions were studied in matched 0.10-mm pathlength NaCl or KBr cells. X-ray powder data were obtained on a Phillips-Norelco x-ray unit using a 114.6-mm camera with nickel-filtered CuK_α radiation. Samples were sealed in 0.5-mm capillaries and exposed to x-rays for 6 h. The "d" spacings were read on a precalibrated scale equipped with viewing apparatus. Intensities were estimated visually. Proton magnetic resonance spectra were obtained on a Varian A-60 spectrometer equipped with a standard variable temperature unit. Ebullioscopic molecular-association studies were carried out in THF under vacuum (240 mmHg abs) using the technique developed earlier.[8]

Analytical. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump.[6] Methane and ethane in the presence of hydrogen were determined using a previously described tensimeter. Magnesium was analyzed by EDTA titration at pH 10. Phenyl groups present in the complexes were determined as benzene by hydrolysis of the samples with water and analyzing the filtrate by GLC using a SE 30 column at 70 °C. Mesitylene was used as the solvent and hexanol was used as the internal standard.

Materials. Solvents were distilled immediately prior to use over $LiAlH_4$ (ether) or $NaAlH_4$ (THF, benzene, and mesitylene).

Diphenylmagnesium (Ph_2Mg) was prepared by heating a mixture of triply sublimed magnesium (Dow Chemical Co.) and diphenylmercury at 155 °C for 40 h. The crude reaction mixture was extracted with freshly distilled ether or THF and the resulting solution standardized by magnesium analysis. Dimethyl- and diethylmagnesium were prepared by stirring a mixture of dimethyl- or diethylmercury with magnesium metal in 1:2 ratio at room temperature for 24 h followed by extraction of the crude reaction mixture with ether or THF. Diisopropylmagnesium was prepared by the dioxane precipitation method using isopropylmagnesium chloride. Dicyclopentadienylmagnesium was prepared by the reaction of excess cyclopentadiene with $(CH_3)_2Mg$ in diethyl ether.

Lithium aluminum hydride was obtained from Ventron, Metal Hydrides Division. A solution was prepared by refluxing $LiAlH_4$ in ether or THF overnight followed by filtration through a glass-fritted funnel (medium) using predried Celite analytical filter air (Johns-Mansville). The clear solution was standardized by aluminum analysis.

Reaction of $LiAlH_4$ with $(CH_3)_2Mg$ in THF in 1:4 Ratio. When $LiAlH_4$ (4.0 mmol) in THF was added dropwise at room temperature to a well-stirred solution of $(CH_3)_2Mg$ (16.0 mmol) in THF a clear solution resulted. This reaction mixture was stirred for 15 min. The infrared spectrum of the clear solution showed no band due to Al–H stretching in the region 1600–1800 cm^{-1}: IR (THF) 2780 (m), 1410 (m), 1250–1270 (m br), 1140 (m), 695 (vs), 550 (s), 410 (w); NMR: singlet at −1.74 ppm and sextet at −1.32 ppm, ratio singlet:sextet 1:1.

Reaction of $LiAlH_4$ with Ph_2Mg in THF in 1:4 Ratio. Lithium aluminum hydride (3.5 mmol) in THF was allowed to react with a well-stirred THF solution of Ph_2Mg (14.0 mmol) at room temperature. The reaction was exothermic and no precipitate resulted at any stage. The reaction mixture was stirred for 30 min, and the clear colorless solution was analyzed. Anal. Calcd for $4PhMgH + LiAlPh_4$ (Li:Mg:Al:H:Ph): 1.00:4.00:1.00:4.00:8.00. Found: 1.03:4.05:0.98:3.97:8.07. IR: no Al–H stretching in the region 1600–1800 cm^{-1} and bands at 460, 425, and 400 cm^{-1} due to Mg–C, and Al–C stretching modes; NMR: three multiplets were observed by NMR, the internal chemical separation between the upper and the two lower multiplets δ int = 0.60 and 0.69 ppm.

In an attempt to isolate PhMgH from the mixture containing $4PhMgH + LiAlPh_4$ in THF, benzene was added slowly until precipitation began. The mixture was kept overnight and the insoluble solid filtered and dried under vacuum. Anal. Calcd for PhMgH (Li:Mg:Al:H:Ph): 0.00:1.00:0.00:1.00:1.00. Found: 0.07:1.00:0.05:1.03:1.11. X-ray powder pattern $PhMgH \cdot THF$ 8.05 (s), 6.60 (m), 5.40 (w), 4.80 (m), 4.60 (m), 4.21 (vs), 3 85 (w), 3.60 (w), 3.40 (w), 3.30 (w), 3.05 (v), 2.80 (w), 2.40 (w); x-ray of $Ph_2Mg \cdot 2THF$ same as above.

Preparation of MgH_2 Slurry in THF. When $LiAlH_4$ in diethyl ether was added dropwise to an equimolar amount of a well-stirred solution of diethyl- or diphenylmagnesium in diethyl ether at room temperature, an exothermic reaction took place and an insoluble white solid appeared immediately. The reaction mixture was stirred for 30 min, and the insoluble solid was separated from the supernatant solution by centrifugation and by removing the supernatant solution using a syringe. This solid was washed with diethyl ether several times and finally made into a slurry in THF. Anal. Calcd for MgH_2 (Mg:H): 1.00:2.00. Found: 1.00:1.98.

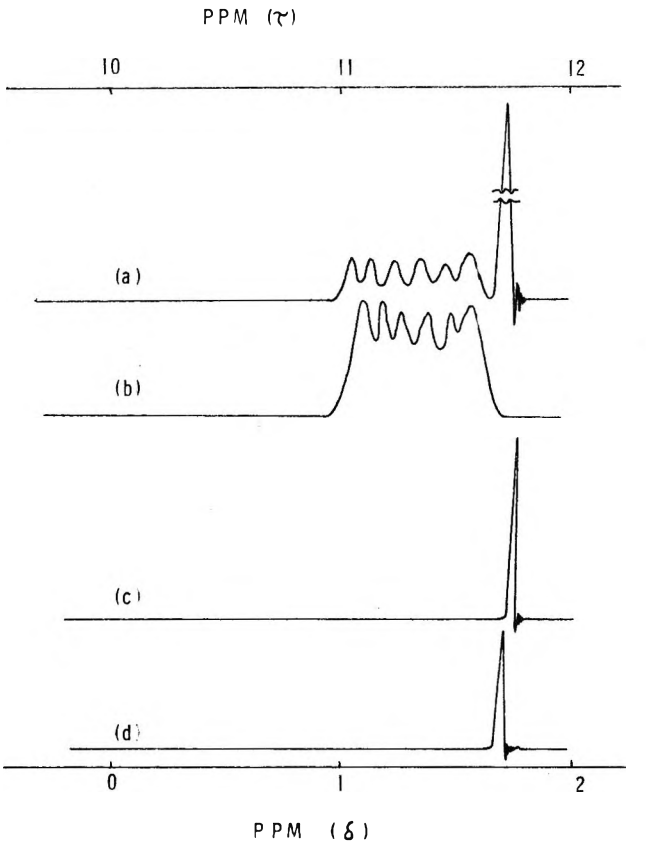

Figure 1. 60-MHz NMR of:

(a) $4(CH_3)_2Mg + LiAlH_4 \xrightarrow{THF} 4CH_3MgH$ + $LiAl(CH_3)_4$ (1.05 M in CH_3MgH),

(b) $LiAl(CH_3)_4$ in THF (0.95 M),

(c) $(CH_3)_2Mg$ in THF (0.65 M),

(d) $(CH_3)_2Mg + MgH_2 \xrightarrow{THF} 2CH_3MgH$ (0.70 M in CH_3MgH).

Preparation of CH_3MgH. To a well-stirred slurry of MgH_2 (4.40 mmol) in THF was added dropwise a THF solution of $(CH_3)_2Mg$ (4.40 mmol) at room temperature. The reaction mixture was stirred for 30 min during which time all the magnesium hydride dissolved. The resulting clear solution was analyzed, and infrared and NMR spectra were recorded. Anal. Calcd for CH_3MgH (Mg:H:CH_4): 1.00:1.00:1.00. Found: 1.00:0.97:1.04.

A THF solution of CH_3MgH was kept overnight at room temperature and analyzed the next day. It contained Mg and H in the ratio 1.00:1.93. When the solvent was removed under vacuum, an amorphous solid formed which did not give an x-ray powder pattern.

Preparation of $CH_3Mg_2H_3$. A THF solution of $(CH_3)_2Mg$ (3.15 mmol) was added dropwise to a well-stirred slurry of magnesium hydride (9.40 mmol) in THF at room temperature. The reaction mixture was stirred at room temperature for 1 h and gave a small amount of a white precipitate. The insoluble solid was filtered and both solid and filtrate were analyzed.

Insoluble solid Anal. Calcd for MgH_2 (Mg:H): 1.00:2.00. Found: 1.00:1.94. The solid contained about 10% of the starting magnesium as magnesium hydride.

Filtrate Anal. Calcd for $CH_3Mg_2H_3$ (Mg:H:CH_4): 2.00:3.00:1.00. Found: 2.00:2.96:1.11. When the THF was removed under reduced pressure, it resulted in a white solid. The x-ray powder pattern showed diffuse lines at 3.20 (m), 2.51 (m), 2.26 (m), and 1.68 (m) which corresponds to MgH_2.

Table I. Infrared Data (in THF) of RMgH and RMg_2H_3 Compounds[a]

MeMgH	MeMgD	EtMgH	*i*-PrMgH	CpMgH	PhMgH
2800 (s)	2795 (m)	2760 (m)	2780 (m)	1500 (sh)	1480 (w)
1430 (w)	1425 (w)	1408 (m)	1380 (m)	1450 (s)	1412 (m)
1375 (m)	1350 (w)	1300 (m)	1345 (m)	1005 (s)	1300 (m)
1280–1300 (m br)	1162 (w)	1260 (m br)	1290 (m br)	955–960 (s br)	1250–70 (s br)
1170 (m)	940 (s)	1120 (m br)	1250 (m br)	750 (vs)	1225 (s)
1025 (s)	825 (sh)	970 (m)	1110 (m)	720 (sh)	1120 (m br)
855 (s)	750 (s)	760 (s br)	980 (s)	652 (s)	1000 (s)
650–720 (s br)	500–550 (s br)	700 (s br)	800 (sh)	550 (m br)	820 (sh)
525 (s)	420 (s)	620 (s)	770 (s)		805 (vs)
		505 (vs)	680–700 (s br)		680 (s)
		405 (s)	605 (s)		630 (sh)
			565 (m)		470 (s)
			490 (m)		375 (s)
			420 (m)		

PhMgD	$MeMg_2H_3$	$MeMg_2D_3$	$PhMg_2H_3$	$PhMg_2D_3$	Ph_3Mg_2H
1482 (w)	1480 (m)	1480 (w)	1480 (w)	1480 (w)	1410 (s)
1410 (m)	1410 (s)	1412 (s)	1410 (w)	1408 (w)	1270–1290 (m br)
1300 (w)	1380 (vs)	1380 (s)	1375 (w)	1375 (w)	1220 (m)
1225 (m)	1300 (vs)	1107 (w)	1260–1300 (s br)	1120 (m)	1010 (m)
1120 (m)	1105 (w)	970 (m)	1120 (m)	990 (m)	850 (m)
997 (m)	965 (s)	940 (s)	990 (m)	940 (vs)	700 (vs)
935 (s)	800 (sh)	800 (sh)	800 (sh)	800 (sh)	675 (sh)
820 (sh)	600–720 (vs br)	600–700 (vs br)	730 (s)	730 (s)	635 (sh)
705 (vs)	520 (s)	520 (s)	700 (vs)	700 (vs)	620 (sh)
600–680 (s br)		420 (m br)	670 (s)	670 (s)	465 (m)
470 (s)			620 (vs br)	620 (m)	428 (s)
380 (m br)			460 (vs)	460 (vs)	370 (s)
				420 (m br)	

[a] Registry no.: MeMgH, 63533-51-7; MeMgD, 63533-525 52-8; EtMgH, 63533-53-9; *i*-PrMgH, 63533-54-0; CpMgH, 63533-55-1; PhMgH, 62086-01-5; PhMgD, 63533-56-2; $MeMg_2H_3$, 63588-48-7; $MeMg_2D_3$, 63588-47-6; $PhMg_2H_3$, 62139-40-6; $PhMg_2D_3$, 63588-49-8; Ph_3MgH, 63588-52-3.

Table II. IR and NMR Data for RMgH Compounds

RMgH, where R =	Me	Et	*i*-Pr	Cp	Ph
IR (ν Mg–C) (cm^{-1})	520 (s)	502 (s)	492 (m)	662 (s)	430 (m)
(in THF)			422 (m)		370 (m)
NMR (ppm)	3.50	0.58 (t)	0.54 (m)	4.07	5.19 (m)
(with respect to THF)		2.53 (8)			5.89 (m)

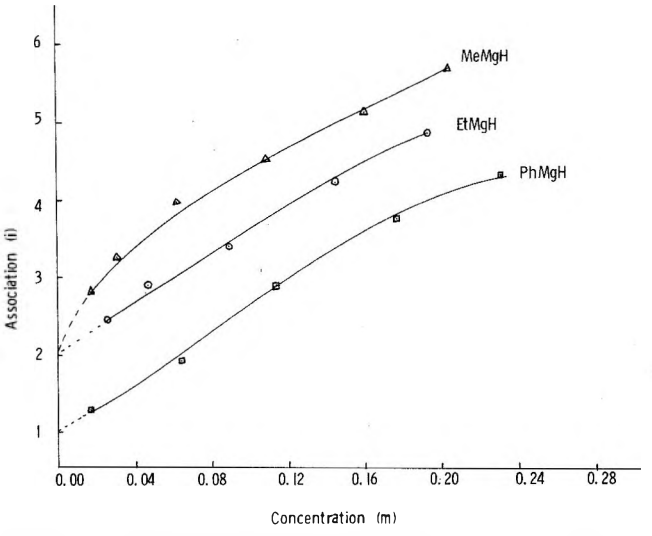

Figure 2. Molecular association of RMgH compounds in THF at reflux temperature (at 260 mmHg).

Preparation of C_2H_5MgH. When $(C_2H_5)_2Mg$ (5.35 mmol) in 10 mL of THF was added dropwise to a THF slurry of MgH_2 (5.30 mmol) and the reaction mixture stirred magnetically at room temperature, a clear solution resulted within 1 h. An elemental analysis of this solution revealed that it contained Mg, H, and C_2H_6 on hydrolysis in molar ratios 1.00:0.98:1.04. Anal. Calcd for C_2H_5MgH: 1.00:1.00:1.00. The THF solution of C_2H_5MgH was stable at room temperature for at least 1 day as shown by the quantitative evolution of hydrogen produced on hydrolysis. When the solvent was removed under vacuum, a highly viscous liquid resulted.

Preparation of *i*-C_3H_7MgH in THF. To a magnetically stirred slurry of MgH_2 (5.0 mmol) in THF was added dropwise a THF solution of $(i\text{-}C_3H_7)_2Mg$. The reaction mixture was stirred at room temperature for 1 h, forming a clear solution. Elemental analysis of this solution showed that it contained Mg and H in the molar ratio 1.00:0.96. This solution was stable at room temperature for at least 1 day as determined by gas-evolution analysis. A highly viscous liquid resulted when the THF was removed under vacuum.

Attempted Preparation of *i*-$C_3H_7Mg_2H_3$. Diisopropylmagnesium (4.0 mmol) in THF was added to a 12.0 mmol of a MgH_2 slurry in THF. The mixture was stirred at room temperature overnight and filtered. The filtrate showed a Mg:H ratio of 1.00:1.07. The solid exhibited a Mg:H ratio of 1.00:1.92. The solid contained about 7.8 mmol of unreacted MgH_2.

Preparation of CpMgH in THF. Dicyclopentadienylmagnesium (6.0 mmol) in THF was added to 6.0 mmol of a slurry of MgH_2 in THF, and the mixture was stirred at room temperature for 1 h, resulting in a clear solution. Anal. Calcd for CpMgH (Mg:Cp): 1.00:1.00. Found: 1.00:0.99. The solution was very air sensitive and turned yellowish brown when kept for some time at room temperature. A crystalline solid CpMgH·1.0THF resulted when the solvent was removed under reduced pressure. The x-ray powder diffraction pattern of the solid showed lines at 9.80 (w), 8.65 (w), 6.50 (w), 4.85 (vs), 4.25 (w), and 3.60 (m). X-ray lines due to Cp_2Mg·2THF 7.50 (m), 7.05 (s), 6.21 (m), 5.83 (m), 5.00 (m), 4.65 (s), 4.40 (m), 4.20 (w), 3.82 (w), 3.70 (m), 3.25 (m), 3.15, 2.85 (vw), 2.47 (vw).

Preparation of PhMgH in THF.[9] To 8.45 mmol of a MgH_2 slurry in THF was added dropwise 8.5 mmol of Ph_2Mg in THF. A clear so-

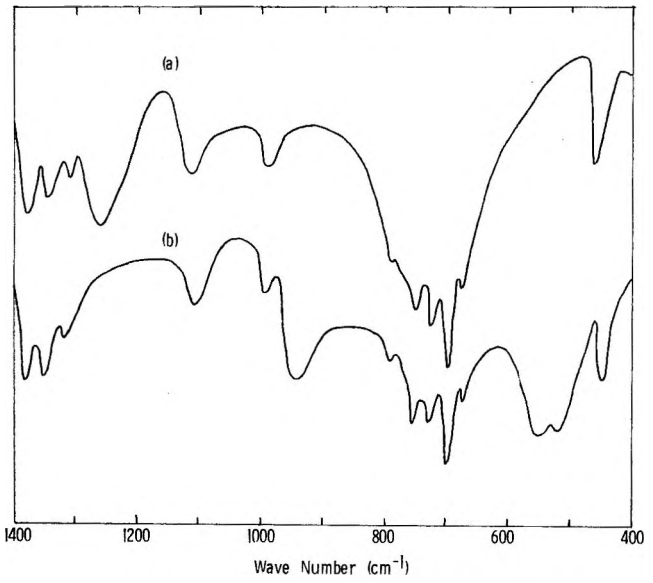

Figure 3. Infrared bands due to Mg–H: (a) $PhMg_2H_3$, and (b) $PhMg_2D_3$.

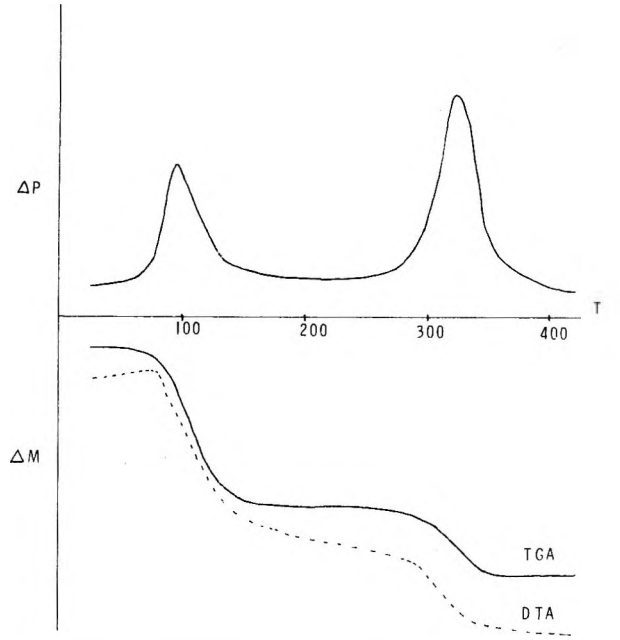

Figure 4. Vacuum DTA–TGA of MeMgH·THF.

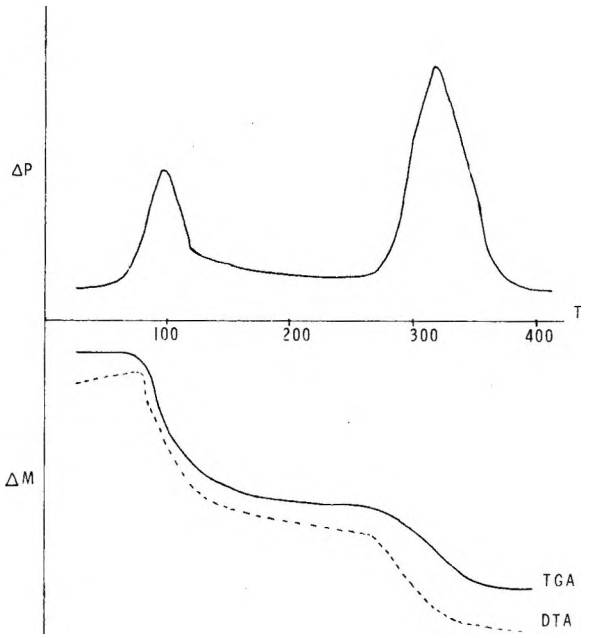

Figure 5. Vacuum DTA–TGA of $MeMg_2H_3$·THF.

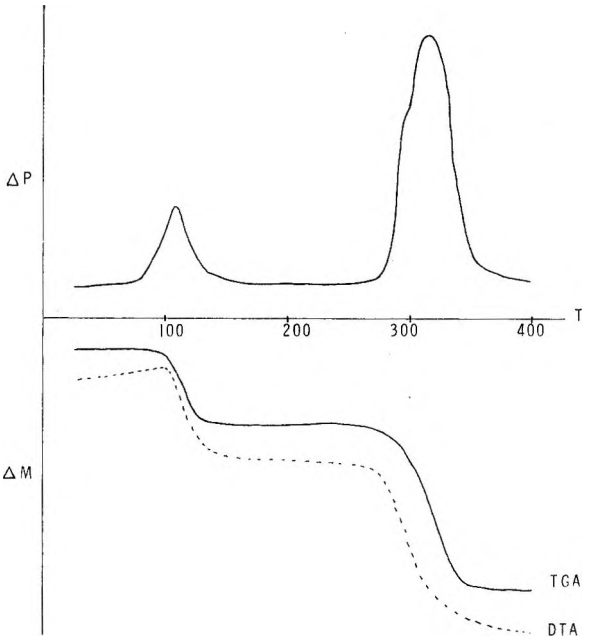

Figure 6. Vacuum DTA–TGA of $PhMg_2H_3$·Et_2O.

lution resulted within a few minutes after stirring at room temperature. Anal. Calcd for PhMgH (Mg:H:Ph): 1.00:1.00:1.00. Found: 1.00:0.97:1.05. This solution was stable for over a 1-month period at 0 °C as determined by gas-evolution analysis. When the solvent was removed under reduced pressure, an amorphous white solid resulted which did not give any x-ray powder pattern. However, when benzene was added to a THF solution an insoluble solid formed which was filtered and analyzed. Anal. Calcd for PhMgH·1THF (Mg:H:Ph:THF): 1.00:1.00:1.00:1.00. Found: 1.00:0.98:1.03:1.05. X-ray powder diffraction pattern 8.05 (s), 6.60 (m), 5.40 (w), 4.80 (m), 4.60 (w), 4.21 (vs), 3.85 (w), 3.60 (w), 3.40 (w), 3.30 (w), 3.05 (vw), 2.80 (vw), 2.43 (vw), 2.40 (w); x-ray pattern of Ph_2Mg·2THF 8.06 (s), 6.61 (m), 5.40 (w), 4.80 (m), 4.60 (w), 4.21 (vs), 3.88 (w), 3.61 (w), 3.40 (w), 3.31 (w), 3.05 (vw), 2.80 (vw), 2.43 (vw), 2.40.

Preparation of $PhMg_2H_3$ in THF.[9] When Ph_2Mg (3.50 mmol) in THF was added dropwise to a stirred slurry of MgH_2 (10.5 mmol) in THF, a clear solution resulted within 30 min. Anal. Calcd for $PhMg_2H_3$ (Mg:H:Ph): 1.00:3.00:1.00. Found: 1.00:2.94:1.07. This solution was dried under vacuum to give a white solid. The solid was placed in diethyl ether, stirred for 1 h, and filtered. The filtrate did not contain magnesium, and analysis of the insoluble solid showed that it contained Mg, H, and benzene on hydrolysis in the ratio 1.00:2.97:1.02. The solid redissolved in THF; however, the THF was cleaved slowly at room temperature and when refluxed in THF an insoluble white solid resulted which on hydrolysis contained Mg, benzene, and *n*-BuOH in ratios 1.00:1.03:3.02.

Dissociation of PhMgH·1THF in Diethyl Ether. To 4.0 mmol of PhMgH·THF was added 5 mL of diethyl ether, and the resulting mixture was stirred for 1 h at room temperature and filtered. The filtrate on hydrolysis showed that it contained Mg and benzene in the ratio 1.00:1.97. The insoluble solid on hydrolysis exhibited Mg, H, and benzene in the ratio of 1.00:1.47:0.52. Anal. Calcd for $PhMg_2H_3$: 1.00:1.50:0.50. The solid contained about 65% of the total magnesium.

Attempted Preparation of Ph_3Mg_2H in THF. When 10.5 mmol of Ph_2Mg in THF was added dropwise to a stirred slurry of MgH_2 (3.5 mmol) in THF, a clear solution resulted within minutes. When this solution was concentrated by removing THF under vacuum, and kept overnight at room temperature, a white solid crystallized. These crystals were separated, washed with THF, and dried under vacuum. Anal. Calcd for Ph_2Mg (Mg:Ph): 1.00:2.00. Found: 1.00:2.03. The x-ray powder diffraction pattern showed that this solid contained lines due to Ph_2Mg·2THF.

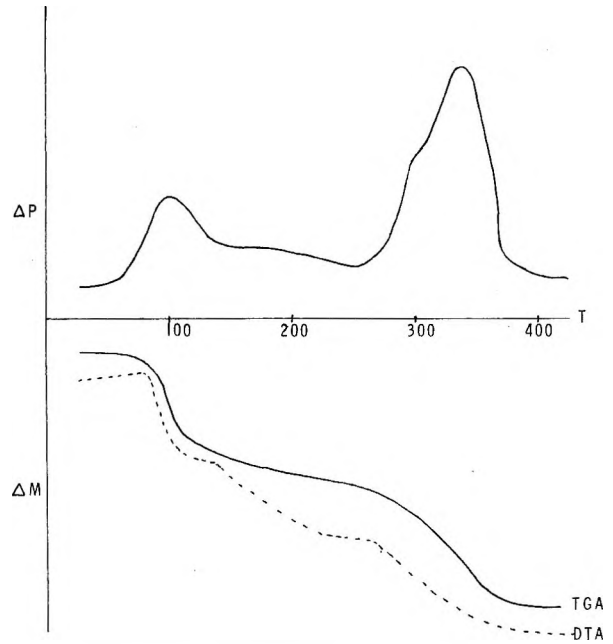

Figure 7. Vacuum DTA-TGA of $PhMg_2H_3$·THF.

Results and Discussion

The first evidence obtained concerning the existence of an RMgH compound came from the reaction of $LiAlH_4$ with $(CH_3)_2Mg$ in 1:4 ratio in THF. When $LiAlH_4$ in THF was allowed to react slowly with a THF solution of $(CH_3)_2Mg$ in a 1:4 ratio, no precipitate resulted at any stage and the reaction mixture remained clear. However, if $LiAlH_4$ was added rapidly to the $(CH_3)_2Mg$ solution in THF, a precipitate did appear which redissolved when stirred for a few minutes. Since MgH_2 is very insoluble in THF, the reaction course observed in ether (eq 4) is undoubtedly not involved here.

$$4(CH_3)_2Mg + LiAlH_4 \xrightarrow{Et_2O} 2MgH_2 + 2(CH_3)_2Mg + LiAl(CH_3)_4 \quad (4)$$

An infrared spectrum of the reaction mixture in THF showed bands at 530 and 695 cm^{-1} characteristic of $MgCH_3$[10] and $LiAl(CH_3)_4$, respectively, and also established the absence of any Al–H stretching bands in the region 1600–1800 cm^{-1}. The infrared data favor the reaction pathway (eq 5) in THF.

$$4(CH_3)_2Mg + LiAlH_4 \xrightarrow{THF} 4CH_3MgH + LiAl(CH_3)_4 \quad (5)$$

A proton NMR spectrum of the reaction solution showed a sharp singlet at τ 11.74 (3.53 ppm upfield from the THF multiplet) and a sextet centered at τ 11.32 (Figure 1). The upfield singlet at τ 11.74 was almost at the position of $(CH_3)_2Mg$, and the sextet corresponded to that observed for $LiAl(CH_3)_4$ in THF.[11] The 1:1 ratio of the upfield singlet to the sextet suggested that the number of methyl groups attached to magnesium are the same as those attached to aluminum, which again supports the proposed reaction course (eq 5). Unfortunately, CH_3MgH could not be isolated from the above reaction mixture in a pure state.

Similarly, when lithium aluminum hydride in THF was added to a THF solution of Ph_2Mg in 1:4 molar ratio, a clear solution resulted. The infrared spectrum of the solution showed the absence of any Al–H stretching band in the region 1600–1800 cm^{-1}; instead, a band due to Mg–Ph stretching at 420 cm^{-1} was observed, suggesting the presence of Mg–Ph bands. When the solvent from this reaction mixture was removed under vacuum, the resulting solid showed x-ray powder diffraction lines due to $LiAlPh_4$.[12] These results support the following reaction route:

$$4Ph_2Mg + LiAlH_4 \xrightarrow{THF} 4PhMgH + LiAlPh_4 \quad (6)$$

When benzene was added to the THF solution of this reaction mixture, an insoluble white solid precipitated which corresponded to PhMgH on analysis. However, the x-ray powder diffraction pattern of this solid corresponded to Ph_2Mg·2THF, indicating disproportionation of the PhMgH to MgH_2 and Ph_2Mg when the solvent is removed.

Interestingly, alkyl- or arylmagnesium hydrides, RMgH (where R = Me, Et, *i*-Pr, Cp, and Ph), have been prepared in a pure state simply by the reaction of a dialkyl- or diarylmagnesium compound with an active form of MgH_2 in THF at room temperature (eq 7).

$$MgH_2 + R_2Mg \xrightarrow{THF} 2RMgH \quad (7)$$

The MgH_2 reacts exothermically with the R_2Mg compound producing a clear solution within minutes. The R:Mg:H ratio of the reaction product is 1:1:1 within experimental error. Solutons of the alkyl- or arylmagnesium hydrides are quite stable at room temperature with no apparent THF cleavage. The active form of magnesium hydride was prepared by the reaction of $LiAlH_4$ with $(C_2H_5)_2Mg$ in 1:1 ratic in ether (eq 8).

$$(C_2H_5)_2Mg + LiAlH_4 \xrightarrow{Et_2O} MgH_2 + LiAlH_2Et_2 \quad (8)$$

The infrared spectra of RMgH compounds in THF solution showed bands due to Mg–R groups (Table I) and broad bands in the region 1250–1300 cm^{-1} due to Mg–H stretching. The band in the region 1250–1300 cm^{-1} is assigned to the bridging Mg–H stretching[13] on the basis of the fact that it shifts to 940 cm^{-1} in the deuterio analogues, RMgD. Coates[14] has shown by infrared studies of RBeH compounds that the strong band at 1330 cm^{-1} is the bridging beryllium–hydrogen stretching (BeH_2Be) vibration, since the band shifted to 970 cm^{-1} in the RBeD compound. We have prepared RMgD compounds in THF by the reaction of R_2Mg with MgD_2. By analogy to the RBeH compound, it is suggested that the broad band present

Table III. Thermal Decomposition of RMgH and RMg_2H_3 Compounds

Compd (wt of sample)	Thermicity	Decomposition range (peak)	% wt loss
$MeMgH$·0.85THF (57.16)	endo	70–110 (85)	56.11
	endo	296–340 (320)	16.35
$PhMgH$·1.06THF (78.54)	endo	75–120 (90)	40.07
	endo	290–369 (348)	44.27
$MeMg_2H_3$·0.38THF (65.85)	endo	70–118 (90)	23.79
	endo	295–340 (318)	12.17
$PhMg_2H_3$·0.89THF (71.72)	endo	75–116 (96)	30.11
	endo	150–280	12.21
	endo	290–365 (336)	32.32
$PhMg_2H_3$·0.37Et_2O (64.35)	endo	90–130 (110)	22.43
	endo	290–339 (315)	50.17

in the region 1250–1300 cm^{-1} in RMgH is due to bridging magnesium–hydrogen (MgH_2Mg) stretching.

The NMR spectra of RMgH compounds in THF showed signals due to alkyl groups attached to magnesium (Table II). Unfortunately, the Mg–H signal was not observed, probably due to its masking by the THF solvent. Molecular-association studies in THF showed CH_3MgH and C_2H_5MgH to be dimeric at low concentration and increasing in association with an increase in concentration. However, molecular weight data of PhMgH showed it to be monomeric in infinitely dilute solution (Figure 2).

When $(CH_3)_2Mg$ in THF was added to an active MgH_2 slurry in THF in a 1:3 ratio, about 90% of the initial MgH_2 dissolved. The infrared spectrum of the solution showed a band at 1290 cm^{-1} which shifted to 940 cm^{-1} in the deuterio analogue $CH_3Mg_2D_3$, suggesting that the absorption band is due to the bridging magnesium–hydrogen (MgH_2Mg) band.

$$Me_2Mg + 3MgH_2 \xrightarrow{THF} 2MeMg_2H_3 \quad (9)$$

When the solvent was removed under vacuum, the resulting solid exhibited x-ray lines due to MgH_2, indicating the disproportion of $CH_3Mg_2H_3$ into CH_3MgH and MgH_2 (eq 10).

$$CH_3Mg_2H_3 \rightarrow CH_3MgH + MgH_2 \quad (10)$$

When diphenylmagnesium in THF was added to 3 mol equiv of magnesium hydride a clear solution resulted. The elemental analysis of this solution corresponded well to $PhMg_2H_3$. The infrared spectrum (Figure 3) gave a strong band at 1290 cm^{-1} which shifted to 935 cm^{-1} in the deuterio analogue $PhMg_2D_3$, suggesting that the absorption band is due to the bridging magnesium–hydrogen (MgH_2Mg) bond. The molecular weight of $PhMg_2H_3$ could not be determined because it cleaved THF under refluxing conditions producing a THF-insoluble product of emperical formula $PhMg_2(OBu^n)_3$.

The results of vacuum DTA–TGA studies on CH_3MgH, $CH_3Mg_2H_3$, PhMgH, and $PhMg_2H_3$ are given in Table III and Figures 4–7. The product RMgH decomposes at 300 °C with gas evolution. The steps involved in the decomposition of RMgH are shown below.

$$1.\ RMgH\cdot THF \rightarrow RMgH + THF \quad (11)$$

$$2.\ RMgH \rightarrow Mg + RH \quad (12)$$

The RMg_2H_3 compounds decompose over a wide temperature range centered at 300 °C.

$$RMg_2H_3 \rightarrow Mg + RH + H_2 \quad (13)$$

Acknowledgment. We are indebted to the Office of Naval Research Contract no. N00014-67-A-0419-005AD, and contract authority no. 093-050/7-11-69(473) for support of this work.

Registry No.—$(CH_3)_2Mg$, 2999-74-8; Ph_2Mg, 555-54-4; MgH_2, 7693-27-8; $(C_2H_5)_2Mg$, 557-18-6; $(i\text{-}C_3H_7)_2Mg$, 3536-97-8; Dicyclopentadienylmagnesium, 1284-72-6.

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Oxidative Cyclodehydrogenation of Aromatic Bis(*o*-aminoanils)

Neil J. Coville and Eberhard W. Neuse*

Department of Chemistry, University of the Witwatersrand, Johannesburg, South Africa

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The two bis-Schiff bases, *N,N'*-terephthalidenebis(o-aminoaniline) (1) and *N,N'*-dibenzylidene-3,3'-diaminobenzidine (8), prepared from the respective aldehyde and amine reactants by low-temperature solution condensation, are converted by molecular oxygen in solution to the benzimidazoles 2 and 9. The oxidative heteroaromatization, especially when catalyzed with ferric chloride, proceeds readily at temperatures as low as 20–60 °C. The unusually mild conditions required for the oxidative ring closure suggest this experimental approach to be well applicable to the polyconversion of analogous polymeric Schiff bases to the corresponding polybenzimidazoles.

A recent note from this laboratory[1] dealt with the copolymerization of aromatic bis(o-diamines) with aromatic dialdehydes and the subsequent cyclodehydrogenation of the resultant polyazomethines, to give polybenzimidazoles. Initial observations in that work led us to conclude that the final aromatization step proceeded in the presence of air, as well as in its absence, in the latter case presumably with elimination of molecular hydrogen. Because of the technological implications of this convenient two-step polycondensation process, it was of prime interest to elaborate more favorable experimental conditions by conducting a study of model reactions leading to well-defined nonpolymeric intermediates and products, in which the progress of the aromatization reaction could be monitored by conventional analytical techniques. It was a particular objective to search for experimental conditions that would favor the primary cyclodehydrogenation step and so would lead to highest possible conversion to benzimidazole structures without concurrently promoting degradation of the amine reactants through oxidative and/or thermal change, or outright elimination, of the sensitive amino groups.

In this communication we present the results of a study

Table I. ^{1}H NMR Resonances of Bisazomethines 1, 8, 3, and 4[a]

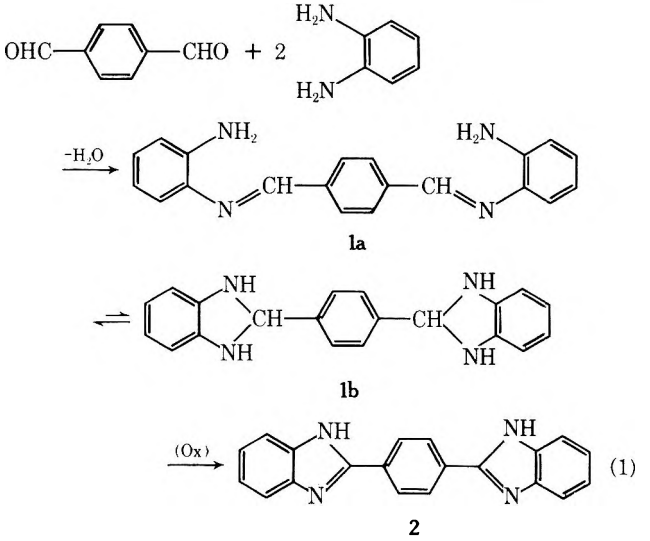
Compd	H (azomethine)	H (amino)	H [ortho, aldehyde ring(s)]	H (all other aromatics)
1	8.59 s (2 H)	5.0 s[b] (4 H)	7.99 s (4 H)	6.3–8.2 m (8 H)
	8.54 s[c]	4.2 s[c]	7.95 s[c]	6.5–7.7 m[c]
	9.1–9.3 m	*d*	8.4 s	7.7 s[e]
8	8.59 s (2 H)	5.2 s (4 H)	7.8–8.0 m (4 H)	6.7–7.5 m (12 H)
	8.57 s (2 H)	4.2 s[f] (4 H)	7.8–7.95 m (4 H)	6.85–7.6 m (12 H)
	9.1–9.3 m	*d*	7.0–8.4 m	
3	8.57 s (2 H)		7.95 s (4 H)	7.1–7.4 m[g] 10 H)
	8.4 s (2 H)		7.9 s (4 H)	7.0–7.4 m[g] (10 H)
	9.4–9.5 s		8.55 s	7.4–7.9 m
4	8.58 s (2 H)		7.7–8.0 m (4 H)	7.3–7.6 m (10 H)
	8.4 s (2 H)		7.7–7.9 m (4 H)	7.1–7.5 m (10 H)
	9.3–9.4 s		7.5–8.3 m	

[a] Chemical shifts δ, in parts per million relative to internal Me_4Si. Solvents: Me_2SO-d_6 (first line), $CDCl_3$ (second line), CF_3COOH (third line, not integrated). [b] Strongly broadened. [c] Insufficiently soluble for meaningful integration. [d] Exchange with solvent. [e] Emerging from 7.3–7.9-ppm range. [f] At 3.8 ppm in acetonitrile. [g] Singlet emerging at 7.3 ppm.

which involved as model compounds the two related bisazomethines 1 and 8 and their respective heteroaromatization products.

Results and Discussion

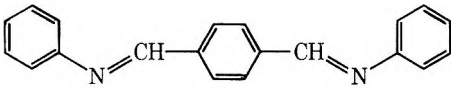
1. Cyclodehydrogenation of *N,N'*-Terephthalidenebis(o-aminoaniline) (1). The bis-Schiff base 1 was prepared by solution condensation of *o*-phenylenediamine with terephthalaldehyde in the absence of moisture and air (eq 1). In



(1)

an effort to minimize involvement in the condensation process of more than one amino group per diamine molecule, the condensation was performed by adding the highly diluted solution of the aldehyde very slowly to the dissolved amine at low temperatures.[2] Suitable solvents included *N,N*-dimethylacetamide (DMAC), dimethyl sulfoxide (Me_2SO), *N*-methylpyrrolidone, and ethanol.

Aromatic Schiff bases possessing an amino group in the ortho position of the aniline ring are capable of tautomerizing to the corresponding closed-ring imidazoline structures, although the basicity of the ortho substituent disfavors ring closure[3] and thus generally renders the "open-chain", trans-configurated azomethine form the more stable one.[4] For **1**, when dissolved in neutral solvents, the azomethine structure **a** is confirmed by spectroscopic data. The IR spectrum ($CHCl_3$) features the moderately strong band of the amino groups' N–H bending mode at 1607 cm^{-1} and the C=N stretching band at 1626 cm^{-1}, the latter in an intensity exceeding that of the benzene bands at 1580–1600 cm^{-1} as similarly observed in the spectrum of the parent compound, terephthalidenedianiline (**3**). The NMR spectrum (Table I), taken on Me_2SO-d_6 solutions, shows the azomethine 2-proton signal at the position (δ 8.59 ppm) expected for aromatic Schiff bases; both **3** and its isomer **4**, *N,N'*-dibenzylidene-*p*-phenylenediamine, give resonances at 8.57–8.58 ppm in this solvent, and signals near this position have been reported for related azomethines.[5] The 4-proton signal of the amino groups emerges at 5.0 ppm (4.6 ppm in the Me_2SO-d_6 spectrum of aniline). The 8-proton resonances of the two outer benzene rings appear as a broad and complex absorption range instead of forming the simple A_2B_2 pattern expected for structure **b**. Solutions in $CDCl_3$ produce very similar shifts, indicating that the reduced solvent polarity has no significant effect, if any, on the ring–chain tautomerism in this system;[6] because of poor solubility in this solvent, however, the spectrum could not be properly integrated. The electronic spectra in various neutral solvents show a band in the vicinity of 300 nm and a slightly more intense one in the range of 415–445 nm (Table II). On the basis of El-Bayoumi's analysis of the benzylideneaniline spectrum[7] and a consequent evaluation of the spectrum of **3**, we interpret the 300-nm absorption as resulting from a ($\pi \rightarrow \pi^*$) transition in the planar conjugated N=CC_6H_4C=N part of the molecule (at about 260 nm in benzylideneaniline),[8] whereas the high-wavelength band may be assigned to an essentially localized ($\pi \rightarrow \pi^*$) excitation in the molecule's noncoplanar[9] anil chromophore (inflection near 310 nm in benzylideneaniline) corresponding to the transition $^1A_{1g} \rightarrow {}^1B_{2u}$ in benzene. In the tautomeric imidazoline structure **b** lacking the conjugated N=CC_6H_4C=N segment, the 300-nm absorption should be replaced by the only slightly perturbed $^1B_{2u}$ band of the benzene system as shown, for example, by *p*-xylene [λ_{max} (Me_2SO) 270, 276 nm].



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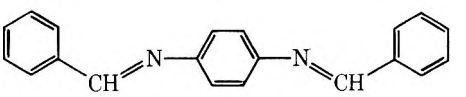


4

In the solid state, when isolated by slow and controlled crystallization, the compound likewise exists as the azomethine form **a**. Thus, the electronic spectrum (KBr matrix) exhibits two bands in approximately the same regions (yet as multicomponent systems) as in the solution spectra, and the IR spectrum (KBr), in addition to the nonbonded and bonded N–H stretching bands at 3475 and 3370 cm^{-1}, shows the C=N stretching peak at 1616 cm^{-1}, although now, just as in the

Table II. Electronic Absorption Maxima ($\pi \rightarrow \pi^*$ Transitions) of Bisazomethines 1, 8, 3, and 4 in the 270–500-nm Region[a]

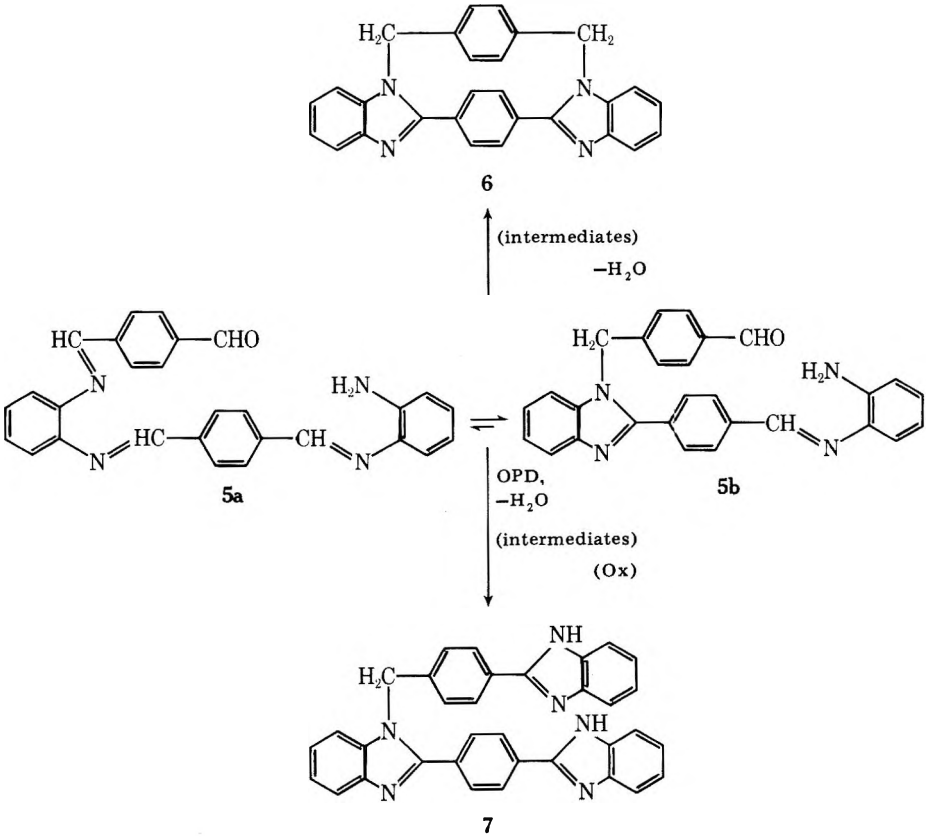
Compd	λ_{max}, nm	$\epsilon \times 10^{-4}$ [b]	λ_{max}, nm	$\epsilon \times 10^{-4}$ [c]
1	300	2.4	445	2.3
	298	2.2	444	2.1
	292	1.8	416[d]	1.7
8	277[e]	3.5[e]	424	2.2
	276[e]	3.5[e]	420	2.4
	265	2.4	402[f]	1.1
3	301	2.4	350	2.4_5
	300	2.2	349	2.3
	298	2.2	348	2.2
4	279	1.9_5	359	2.2_5
	277[e]	2.0	359	2.3
	275	1.9	357	2.0

[a] Solvents: Me_2SO (first line), DMAC (second line), dichloromethane (third line); at ambient temperature. [b] $\pi \rightarrow \pi^*$ transition in N=CC_6H_4C=N (1, 3) and C_6H_5C=N (8, 4) segments. [c] $\pi \rightarrow \pi^*$ transition in amine ring system. [d] At 450 nm in KBr matrix; shoulders at 425 and 490 nm. [e] Value approximate; maximum partly merging with edge absorption of solvent. [f] At 415 nm in KBr matrix; shoulder at 480 nm.

solid-state spectrum of 3 (1617 cm^{-1}), slightly weaker than the adjacent benzene bands.[10]

As a purity check, the 70-eV mass spectra of several crude samples of 1 were examined in the mass number range above the molecular ion peak (*m/e* 314) for the emergence of any peaks due to condensation products involving both amino groups of the phenylenediamine reactant. Indeed, at temperatures of 300 °C and higher, peaks were found invariably at *m/e* 412 and 516 in intensities of 1–5% relative to *m/e* 310 [P^+ (2); see subsequent discussion]. These almost certainly represent the cyclophane 6 (no steric preference implied in the structure shown) and the benzyl derivative 7, both generated from the tris-Schiff base 5a and its ring tautomer 5b (eq 2, OPD = o-phenylenediamine).[11] From our failure to observe the mass peak of 5 (at inlet temperatures ranging from 150 to 380 °C) or detect aldehydic carbonyl absorption in the IR spectra of the samples investigated, we conclude that tautomers 5, formed as by-products in the preparation of 1, under our experimental conditions immediately underwent further reaction involving the formyl function. Self-condensation resulted in the bisimidazole 6 via a macrocyclic pair of Schiff base tautomers (not shown in the scheme), whereas intermolecular condensation (with additional OPD) afforded tautomeric bis- and tetrakis-Schiff bases (not shown; peak at *m/e* 520 not significant because of insufficient volatility below 300 °C), which in turn, at the high inlet temperatures, cyclodehydrogenated spontaneously in the spectrometer to give the trisimidazole 7. The appearance of the two peaks due to P^+ (6) and P^+ (7) in the spectra of crude 1 (yet not of rigorously purified compound) shows that the steric accessibility of the primary amino groups in 1 is not sufficiently reduced by the ortho substituent to prevent a minor extent of further condensation even under the strict controls employed in our experiments.

The cyclodehydrogenation of 1 to give the heteroaromatic 2, 1,4-di(benzimidazol-2-yl)benzene (eq 1), was found to proceed under anaerobic conditions in the melt and, more readily, in the gas phase of the mass spectrometer. Thus,



(2)

Table III. Oxidative Cyclodehydration Reactions (1 → 2; 8 → 9)

Expt[a] no.	Substrate	Substrate concn, mol L^{-1}	Solvent[b]	Temp, °C	Time, h	Method of oxidn[c]
1	1	6.4×10^{-2}	DMAC	60	3[d]	A
2	1	6.4×10^{-2}	DMAC	60	4[d]	B
3[e]	1	6.4×10^{-2}	DMAC[g]	20	50	A
4	1	6.4×10^{-2}	Me_2SO[f]	60	2	B
5	2	5.1×10^{-2}	DMAC[g]	60	3[d]	A
6	2	5.1×10^{-2}	Me_2SO[f]	36	3	A

[a] Crude yields of 2 (expt 1–4) or 9 (expt 5, 6), 89–95%. All experiments conducted in diffuse daylight; no significant changes in yield when conducted either in the dark or under illumination with medium- or high-pressure mercury lamps (quartz vessels). [b] DMAC = *N,N*-dimethylacetamide; Me_2SO = dimethyl sulfoxide. [c] Method A, agitation in air by means of excentrally tumbling stirring bar; method B, air introduced at rate of 120 L/h. [d] Same results after 0.3 h in presence of $FeCl_3$ (6.4×10^{-4} mol L^{-1}). [e] Reaction partially heterogeneous at this temperature. [f] Similar results in absolute ethanolic solution. [g] Similar results in *N*-methylpyrrolidone or tetramethylurea solutions.

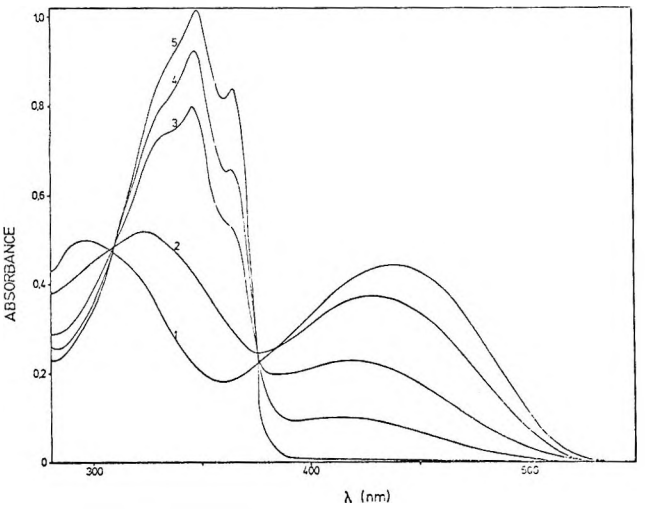


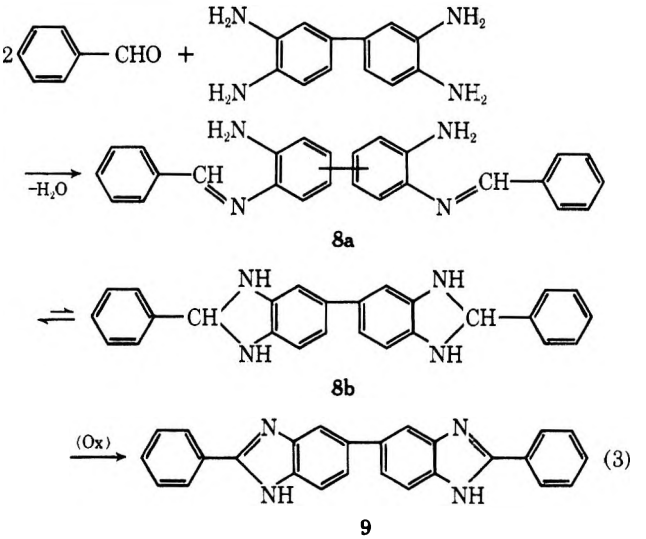
Figure 1. Electronic absorption spectra taken in time intervals on 2.4×10^{-5} M solution of 1 in DMAC during cyclodehydrogenation experiment conducted at 60 °C with excentral stirring (400 rpm) in air. Curve 1, start of experiment; curves 2–5, after respectively 15, 60, 105, and 150 min.

heating the compound above the melting range for 3 h under argon afforded 2 in 40–50% yield (in addition to several degradation products), and a sample volatilized from the probe of the mass spectrometer at inlet temperatures of 250 °C and higher featured the molecular ion peak of **2**, whereas that of **1** predominated at temperatures up to about 200 °C (I_{310}/I_{314} = 4.0 at 260 °C, 0.03 at 170 °C). Surprisingly, however, all attempts to achieve a reasonable extent of cyclodehydrogenation by heating the compound in the dissolved state (60–135 °C) under perfectly anaerobic conditions over periods of time as long as 3 days remained unsuccessful, nor was it possible to accomplish this reaction through photocatalysis by means of medium- or high-pressure mercury lamps as used for the conversion of benzylidene-o-aminoaniline to 2-phenylbenzimidazole.[3] In the presence of molecular oxygen, on the other hand, the reaction proceeded smoothly in a number of solvents. For example, the vigorous agitation in air of (or, alternatively, the copious bubbling of air into) a 6.4×10^{-2} M solution in DMAC for 3 h at 60 °C led to more than 90% conversion, and in ethanolic or Me_2SO solutions the same conversion resulted at even lower temperatures. Solute concentration, mode of agitation, and/or rate of air introduction all proved critical variables in these cyclization reactions and had to be controlled carefully for meaningful comparisons of conversion rates. The oxidative ring closure could also be accomplished with ferric chloride or similar oxidants.[12] Catalytic quantities of $FeCl_3$ in the presence of oxygen, preferably in ethanol or Me_2SO media, proved especially efficacious. For example, a low-concentration (6.3×10^{-4} M) run conducted in Me_2SO at 20 ± 2 °C in the presence of $FeCl_3$ (4×10^{-6} M), with air introduced at a rate of 10 L h^{-1}, proceeded to 50% conversion (UV) within 1.5 h, whereas some 48 h was required for the same result in the absence of the iron salt.

The progress of cyclodehydrogenation under the various conditions was conveniently monitored by UV spectroscopy as previously demonstrated by Grellmann and Tauer[3] for similar systems. The multiple-scan electronic absorption spectrum for a typical experiment conducted in DMAC solution is reproduced in Figure 1. Curve 5 practically superimposes upon the spectrum of pure bisimidazole 2[13] recorded at the same molar concentration. Characteristically, as the heteroaromatization proceeds, the 300- and the 445-nm maxima collapse, to be replaced by the typical multicomponent benzazole band with λ_{max} (DMAC) at 348 nm (ϵ 4.1 × 10^4). The latter, because of the substantially extended chromophore in 2 as compared to the simple 2-phenylbenzimidazole, experiences both hyper- and bathochromic shifts relative to the monoazole, which shows λ_{max} (DMAC) at 306 nm (ϵ 2.7 × 10^4).

Exemplifying cyclodehydrogenation experiments conducted in DMAC or Me_2SO solutions are summarized in Table III.

2. Cyclodehydrogenation of *N,N'*-Dibenzylidene(3,3'-diaminobenzidine) (8). The solution condensation of 3,3'-diaminobenzidine with benzaldehyde under conditions similar to those leading to 1 afforded the bis-Schiff base 8 (eq 3). For



(3)

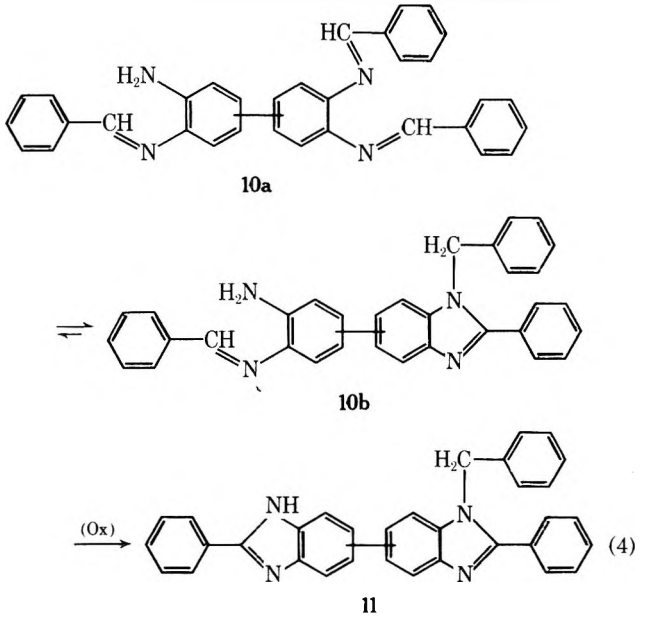
the compound in the dissolved state, the open-chain tautomeric (transoid) structure a[14] follows from spectroscopic data, and similar arguments hold as in the case of 1. The IR solution

spectrum ($CHCl_3$) shows δ_{N-H} of the amino groups at 1606 cm^{-1}, and $\nu_{C=N}$ appears at 1625 cm^{-1} (1626 cm^{-1} in 4). In the NMR spectrum (Me_2SO-d_6), the 2-proton peak of the azomethine links is found near 8.6 ppm, the 4-proton resonance of the amino groups appears at 5.2 ppm, and the ortho protons of the two terminal rings, residing in the C=N systems' deshielding zones, give a 4-proton signal at the same position (7.9 ppm) as shown by **3** and **4**, rather than at an upfield position near 7–7.5 ppm expected for a phenyl group in the 2 position of an imidazoline ring. Again, as in **1**, analogous shifts are observed in the $CDCl_3$ and CF_3COOH spectra (Table I).

In the electronic spectrum (Me_2SO) we find the ($\pi \rightarrow \pi^*$) band of the two benzylideneimino segments (each one of these twisted out of the plane of the biphenyl segment) at about 275 nm, and the strong ($\pi \rightarrow \pi^*$) absorption of the two diamine rings emerges with a maximum at about 420 nm. More allowed because of increased perturbation, the last-named band, just as in **1**, possesses a molar extinction coefficient more than five times as large as twice the value of the coefficient of the corresponding perturbed $^1B_{2u}$ band in aniline.[15]

For **8** in the solid state, the IR spectrum (KBr) fails to present conclusive evidence in support of the open-chain structure **a** as the sole constituent. While all samples investigated were found to show the C=N stretching absorption near 1619 cm^{-1}, the intensity of this band varied appreciably depending on the mode of crystallization, and so did the intensities of the NH stretching absorptions at 3300–3460 cm^{-1}. The electronic spectra (KBr), however, invariably resembled those obtained on solutions. We conclude that crystalline **8** predominantly exists as the azomethine isomer mixture **a**, with **b** possibly admixed to a minor and variable extent.[16]

A mass spectrometric check conducted on crude samples of **8** in the high mass number region revealed the molecular ion peak of the tris-Schiff base **10a** and its tautomer **10b**, as well as that of the *N*-benzyl-substituted bibenzimidazolyl **11** generated from **10** through thermal dehydrogenation in the mass spectrometer (eq 4). While, at inlet temperatures of



(4)

11

200–250 °C, the peak due to **10** [*m/e* 478, 3–5% of P^+ (**8**)] predominates over that of **11** [*m/e* 476, ca. 1% of P^+ (**8**)], the latter peak gains intensity and becomes prevalent as the temperature exceeds 300 °C. The appearance of the two peaks in the mass spectra of crude (but not of pure) **8** indicates that the compound, just like **1**, offers sufficient accessibility of the two primary amino groups to allow some trisubstitution despite the rigorous experimental control exercised in our work. The implications of this finding for analogous polymerization studies are obvious.

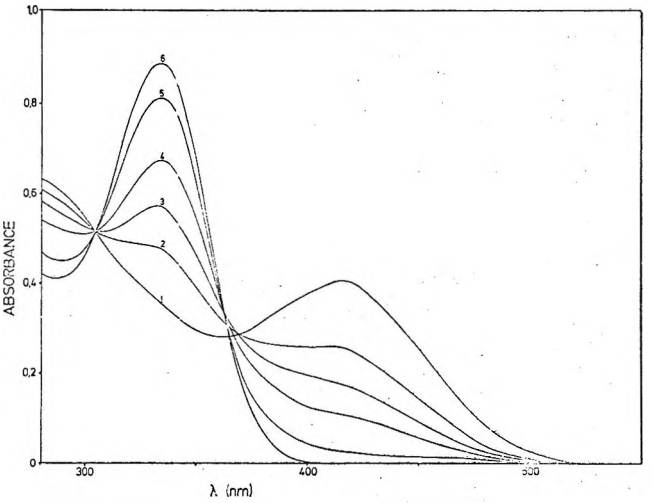


Figure 2. Electronic absorption spectra taken in time intervals on 2.0×10^{-5} M solution of **8** in Me_2SO during cyclodehydrogenation experiment conducted at ambient temperature with excentral stirring (400 rpm) in air. Curve 1, start of experiment; curves 2–6, after respectively 30, 45, 60, 90, and 120 min.

The formation of bisimidazole **9** by cyclodehydrogenation of **8** (eq 3) under anaerobic conditions was brought about both in the melt and in the gas phase of the mass spectrometer at temperatures above 300 °C. On the other hand, just as in the case of **1**, only minimal anaerobic dehydrogenation was observable in the dissolved state within reasonable periods of time, whereas reaction with O_2 proceeded smoothly in ethanolic solution as well as in aprotic solvents. Representative cyclodehydrogenation experiments are summarized in Table III. Progress of the reaction, as before, was monitored by UV spectroscopy (Figure 2); the absorption pattern progressively approached that of authentic[13,17] 2,2′-diphenyl-5,5′-bibenzimidazolyl (**9**),[18] which shows a maximum (DMAC) at 338 nm (ϵ 4.2×10^4). In none of the experiments, conducted either with **1** or with **8**, were we able to isolate and/or identify any by-products that could have resulted from oxidative removal (or involvement in other oxidative side reactions) of the reactants' primary amino groups.

The results of this investigation demonstrate that polynuclear aromatic azomethines derived from *o*-aminoanilines undergo smooth and practically quantitative oxidative cyclodehydrogenation in solution at low temperatures, the experimental conditions being mild enough to preclude thermooxidative degradation or elimination of the reactants' primary amino groups in the course of heteroaromatization. In addition, the aprotic media used in this work belong to the class of neutral solvents most frequently employed in heterocyclic polymer chemistry. The study thus provides conditions suitable for polycyclodehydrogenation of polymeric azomethines comprising a combination of segmental structures of both **1** and **8**, although the observed side reactions involving the tris-Schiff bases and other products require attention. Further work on such macromolecular aspects of the cyclodehydrogenation reaction will be reported elsewhere.

Experimental Section[19]

Solvents and Reagents. All solvents, predried with molecular sieves, type 4A (5A for ethanol), were distilled from suitable dehydrating agents (reduced pressure for DMAC and *N*-methylpyrrolidone). Me_2SO, dried with molecular sieves, was used without redistillation. For use in the preparation of Schiff bases or anaerobic cyclodehydrogenation experiments, solvents were thoroughly degassed and saturated with deoxygenated argon. Benzaldehyde was freshly distilled prior to use. o-Phenylenediamine, mp 101 °C, and tere-

phthaldehyde, mp 115–116 °C, were recrystallized from 96% ethanol. 3,3′-Diaminobenzidine (Burdick & Jackson) was purified by repeated recrystallization under Ar from degassed water (pinch of sodium dithionite added) and, ultimately, methanol, mp 176–178 °C. *N,N′*-Terephthalidenedianiline (**3**) and *N,N′*-dibenzylidene-*p*-phenylenediamine (**4**), both obtained in ca. 90% yield by condensation of the respective aldehydic and amine reactants in boiling absolute ethanol (1 h) under N_2 and solvent removal under reduced pressure, were recrystallized twice from degassed absolute ethanol, mp 157–159 °C (lit.[20] 166 °C) and 137–138 °C (lit.[21] 138 °C), respectively. 2-Phenylbenzimidazole was prepared by low-temperature condensation of benzaldehyde (0.1 M) with *o*-phenylenediamine (0.1 M) (5 h at −10 °C, 12 h at 20 °C) in degassed absolute ethanol and cyclodehydrogenation of the intermediary *N*-benzylidene-*o*-aminoaniline by stirring the solution for 8 h at 60 °C in the presence of air. Solvent removal and recrystallization from ethanol/benzene furnished the imidazole in 80% yield, mp 291–293 °C (lit.[22] 291, 298–300 °C).

***N,N′*-Terephthalidenebis(*o*-aminoaniline) (1).** To a rapidly stirred and argon-purged solution of o-phenylenediamine (1.08 g, 10 mmol) in 10 mL of DMAC was added dropwise, over a period of 3 H, the solution of terephthalaldehyde (0.67 g, 5 mmol) in 25 mL of DMAC at −15 to −17 °C under Ar. The solution was stirred under Ar in the dark for 12 h at −15 °C, followed by 4 h at 0 °C and 1 h at 22 °C. The Schiff base partially crystallized from the solution during this period. The crystals collected after cooling were washed with benzene (3 × 10 mL). A second fraction of **1** crystallized after partial solvent removal in the absence of air (rotating evaporator, 25 °C), and a small third portion was precipitated on further volume reduction by the addition of excess (80 mL) ice water (rapid washing with ethanol and drying under reduced pressure at 20 °C required to prevent hydrolysis), total crude yield 1.46 g (93%). Recrystallization from DMAC at 40 to −8 °C in the absence of air yielded orange-yellow, TLC-pure (R_f 0.7) crystals, mp 210–212 °C (phase change, no clear melting) (lit.[2] 212–214 °C),[21] mol wt 314 (MS).

Anal. Calcd for $C_{20}H_{18}N_4$: C, 76.41; H, 5.77; N, 17.82. Found: C, 76.11; H, 6.10; N, 17.42.

Experiments conducted as described, yet in other aprotic solvents or ethanol, gave similar yields of **1**. Under less rigorous conditions of oxygen preclusion (e.g., employing standard-grade N_2 for blanketing), use of ethanol solvent resulted in slightly enhanced intensity of the peak at *m/e* 310 in the mass spectra of all crude fractions.

In several experiments conducted in DMAC, the mother liquor remaining after removal of the second fraction of **1** was evaporated to dryness (rotating evaporator, 25 °C, absence of air). The residual crystalline solids gave mass spectra substantially identical with those of the spontaneously crystallizing fractions except for a slightly increased ratio of I_{310}/I_{314}.

***N,N′*-Dibenzylidene(3,3′-diaminobenzidine) (8).** Under the conditions described for the preparation of **1**, a solution of benzaldehyde (1.06 g, 10 mmol) in 25 mL of DMAC was added to 3,3′-diaminobenzidine (1.07 g, 5 mmol) dissolved in 10 mL of MDAC, and the mixture was treated as before. Cooling the red solution to −15 °C produced a minor crystalline fraction of **8** (0.40 g). The main portion of the base, 1.43 g, precipitated upon volume reduction to 15 mL (rotating evaporator, 25 °C) and addition of ice water (100 mL), bringing the total crude yield to 94%. Rapid filtration, washing (ethanol, hexane), and drying (reduced pressure, 20 °C) of the precipitated portion was required to avoid hydrolysis. Recrystallization from DMAC as described for **1** afforded yellow, TLC-pure (R_f 0.7) crystals, mp 164–166 °C (phase change, no clear melting), mol wt 390 (MS).

Anal. Calcd for $C_{26}H_{22}N_4$: C, 79.97; H, 5.68; N, 14.35. Found: C, 79.79; H, 5.70; N, 14.31.

Similar yields of **8** resulted from use of other aprotic reaction media or ethanol in place of DMAC. A slight increase in abundance of the peaks at *m/e* 386, 476, and 478 was observed in experiments conducted in ethanol, and the final fractions of product isolated in such experiments tended to be contained with minute quantities of several unknown compounds (TLC).

1,4-Di(benzimidazol-2-yl)benzene (2) from 1. In a typical oxidative cyclodehydrogenation experiment (Table III, expt 1), the solution of **1** (0.200 g, 0.64 mmol) in 10 mL of DMAC was vigorously agitated in air for 3 h at 60 °C by means of an excentrally tumbling (400 rpm) magnetic stirring bar (method A). Predried glassware was used, and the exit neck was fitted with a drying tube. The solution was allowed to stand for 15 h at −15 °C, whereupon 0.07 g of **2** crystallized. Another 0.06 g of crystalline product separated after volume reduction to 5 mL and cooling to −5 °C. A third portion of **2** was precipitated from the filtrate by the addition of water (50 mL), bringing the total crude yield to 0.185 g (93%). The cream-colored compound was recrystallized from DMAC, to give almost colorless fine crystals, TLC pure (R_f 0.2), infusible up to 300 °C (lit.[13] 472 °C), mol wt 310 (MS).

Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55; N, 18.05. Found: C, 77.35; H, 4.76; N, 17.98.

In a similar manner, reactions were conducted in other aprotic solvents, as well as in absolute ethanol (Table III). In ferric chloride catalyzed experiments, $FeCl_3$ (1.0 mol % of **1**) was added from a 0.05 M stock solution in the same solvent in which the reactions were performed. In a number of experiments, oxidation was accomplished by introducing a rapid stream of predried air (120 L/h) into the solutions of **1** (method B) under otherwise unchanged conditions. In several runs conducted in DMAC or ethanol, the final mother liquors were evaporated to dryness under reduced pressure. The residues, 5–10 mg, constituted **2** contaminated with 4-(benzimidazol-2-yl)-benzaldehyde (R_f 0.4, *m/e* 222);[23] no TLC spots or mass peaks were found that would indicate the presence of compounds resulting either from elimination of NH_2 or from oxidative coupling (formation of –N=N–).

2,2′-Diphenyl-5,5′-bibenzimidazolyl (9) from 8. The following procedure, describing expt 5, Table III, exemplifies the oxidative cyclodehydrogenation of **8**. The solution of **8** (0.200 g, 0.51 mmol) in 10 mL of DMAC was agitated in air for 3 h at 60 °C as described for expt 1. The clear solution was reduced in volume to 5 mL, and water (80 mL) was added. The precipitated, grayish-white product, washed with water and dried (0.175 g, 89%), was recrystallized from ethanol/water. The TLC-pure (R_f 0.3) **9** was infusible up to 300 °C (lit. typically[13] 337 °C), mol wt 386 (MS).

Anal. Calcd for $C_{26}H_{18}N_4$: C, 80.81; H, 4.69; N, 14.50. Found: C, 80.40; H, 4.91; N., 14.25.

Other experiments were conducted as summarized in Table III. As before, the use of method B involved passing dry air through the solution at a rate of 120 L/h, and in the ferric chloride catalyzed reactions the catalyst was added from a 0.05 M stock solution.

Acknowledgment. This work was generously supported by the C. S. I. R., the South African Chemical Foundation, and the Shell Chemical South Africa (Pty) Ltd. Thanks are due also to Dr. R. G. Copperthwaite, National Chemical Research Laboratory, for his kind cooperation in recording the photoelectron spectra, and to Mr. D. Bylinsky for scanning the IR spectra.

Registry No.—**1a**, 61990-56-5; **2**, 1047-63-8; **3**, 61990-57-6; **4**, 61990-58-7; **8a**, 62045-63-0; **9**, 15179-41-6; *o*-phenylenediamine, 95-54-5; terephthaldehyde, 623-27-8; benzaldehyde, 100-52-7; 3,3′-diaminobenzidine, 91-95-2.

References and Notes

(1) E. W. Neuse, *Chem. Ind. (London)*, 315 (1975).
(2) (a) The compound was first prepared[2b] from the two components in boiling ethanol (95% yield). In our hands, this procedure afforded the base appreciably contaminated with cyclodehydrogenated material in addition to trisubstituted products **5** and successor species. See text. (b) F. F. Stephens and J. D. Bower, *J. Chem. Soc.*, 1722 (1950).
(3) K. H. Grellmann and E. Tauer, *J. Am. Chem. Soc.*, **95**, 3104 (1973); *Tetrahedron Lett.*, 1909 (1967).
(4) (a) Contrasting with the *o*-aminoanils, the corresponding anils possessing the more acidic mercapto group as an ortho substituent generally exist as the ring-tautomeric thiazoline isomers.[3,4b–e] (b) R. G. Charles and H. Freiser, *J. Org. Chem.*, **18**, 422 (1953). (c) P. E. Miller, G. L. Oliver, J. R. Dann, and J. W. Gates, Jr., *ibid.*, **22**, 664 (1957). (d) L. F. Lindoy and S. E. Livingstone, *Inorg. Chim. Acta*, **1**, 365 (1967). (e) F. J. Goetz, *J. Heterocycl. Chem.*, **5**, 509 (1968).
(5) (a) A. F. McDonagh and H. E. Smith, *Chem. Commun.*, 374 (1966); (b) A. van Putten and J. W. Pavlik, *Tetrahedron*, **27**, 3007 (1971).
(6) (a) In CF_3COOH solution, the azomethine proton signals of both **1** and **8**, as expected,[6b] emerge at a position shifted downfield by some 0.7 ppm (Table I), yet in intensities 20–30% lower than calculated for structures **a**. Although much of this signal attenuation probably results from hydrolysis (peak intensity slowly decreasing with time), the possibility of partial tautomerization to structures **b**, prompted by the amino nitrogen atom's decreased basicity upon protonation, cannot be ignored. Yet the spectra of both compounds lack conclusive evidence for the presence of **b**, as the signals of the rapidly exchanging protons of the NH_2 (forms **a**) and NH (forms **b**) groups both are expected to vanish in this acidic medium, and the tertiary CH protons in **b**, which should resonate at 7–7.5 ppm, may well give signals submerged in the aromatic resonances in this region. (b) M. Kurihara, H. Saito, K. Nukada, and N. Yoda, *J. Polym. Sci. Part A-1*, **7**, 2897 (1969).
(7) M. A. El-Bayoumi, M. El-Aasser, and F. Abdel-Halim, *J. Am. Chem. Soc.*, **93**, 586 (1971); M. El-Aasser, F. Abdel-Halim, and M. A. El-Bayoumi, *ibid.*, **93**, 590 (1971).
(8) El-Bayoumi et al.[7] assigned the 260-nm band in benzylideneaniline to a transition to a charge-transfer state in which the C=N system acts as the electron acceptor and the benzal ring as the donor. LCAO–MO calculations[9d] indicate, however, that negative charge is accumulated on the benzal ring in the excited state; moreover, the banc undergoes a pro-

nounced red shift on para substitution of that ring by the withdrawing NO_2 group.[9b] Both findings, coupled with the band's comparative intensitivity to solvent effects observed both in benzylideneaniline[7] and in **1** (Table II), render a charge transfer of the type proposed[7] rather unlikely as the cause of this absorption. We prefer to assign the band to a $\pi \rightarrow \pi^*$ transition originating from the highest occupied π level of the N=CC_6H_4C=N unit. Such assignment accords with the band's bathochromic (and hyperchromic) shift on achieving coplanarity of the molecule by protonation or ring closure to the imidazole system.[9c]

(9) (a) With respect to noncoplanarity of the outer ("aniline") rings with the N=CHC_6H_4CH=N segment, the same arguments (conjugation of the aniline rings' π systems with the lone-pair electrons on N)[7,9b] hold as in the case of *N*-benzylideneaniline, in which rotation of the *N*-phenyl ring out of the plane of the benzalimino chromophore has been established.[5b,7,9c-e] It is only on heteroaromatization (process **1** → **2**) that an approximate coplanarity of the molecule's benzene rings can result. (b) V. A. Ismailski and E. A. Smirnov, *Zh. Obshch. Khim.*, **26**, 3389 (1956). (c) P. Brocklehurst, *Tetrahedron*, **18**, 299 (1962). (d) W. F. Smith, *ibid.*, **19**, 445 (1963). (e) H. B. Bürgi and J. D. Dunitz, *Chem. Commun.*, 472 (1969); *Helv. Chim. Acta*, **54**, 1255 (1971).

(10) In the KBr spectra of several crude or too rapidly recrystallized products we found the C=N band in reduced intensity; at the same time, two new nonbonded and bonded N–H stretching peaks appeared at 3440 and 3350 cm^{-1} in addition to the aforementioned two bands of these origins. This suggests that product separating from solution under nonequilibrium conditions may indeed contain some imidazoline tautomers.

(11) The facile formation of *N*-benzyl substituted benzimidazoles (aldehydines) from bis-Schiff bases of aromatic *o*-diamines is on record: J. B. Wright, *Chem. Rev.*, **48**, 397 (19651).

(12) (a) The oxidative heteroaromatization of *o*-aminoanils to benzimidazoles has been achieved in the presence of cupric salts,[12b] lead tetraacetate,[12c] and active MnO_2,[12d] and some mechanistic implications have been discussed.[12e] These methods, however, requiring large quantities of oxidants and inefficient separation techniques for the imidazole products, give inferior yields and are not adaptable to polymerization chemistry. (b) R. Weidenhagen, *Chem. Ber.*, **69**, 2263 (1936); R. Weidenhagen and U. Weedon, *ibid.*, **71**, 2347 (1938); R. Weidenhagen and G. Train, *ibid.*, **75**, 1936 (1942). (c) F. F. Stephens and J. D. Bower, *J. Chem. Soc.*, 2971 (1949). (d) I. Bhatnagar and M. V. George, *Tetrahedron*, **24**, 1293 (1968). (e) W. G. Nigh in "Oxidation in Organic Chemistry", W. S. Trahanovsky, Ed., Academic Press, New York, N.Y., 1973, p 59.

(13) R. A. Gaudiana and R. T. Conley, *Polym. Lett.*, **7**, 793 (1969).

(14) (a) The product most likely is a mixture of two positional isomers. Electron density determinations by MO calculations[14b] show the two *m*-amino groups in the tetramine starting compound to be somewhat more basic than the two *p*-amino groups. The calculated difference in electronic charge (1.862 vs. 1.856) is, however, not significant enough to justify a prediction of predominance of the 3,3′-di(benzylideneimino) compound over the 4,4′ isomer. (b) D. A. Bochvar, I. V. Stankevich, V. V. Korshak, and A. L. Rusanov, *Dokl. Akad. Nauk SSSR*, **184**, 95 (1969).

(15) A. L. Sklar, *J. Chem. Phys.*, **7**, 984 (1939).

(16) An attempt to differentiate between solid a and **b** by N(1s) x-ray photoelectron spectroscopy failed, only a single, albeit broad (width at half-height 3.0–3.5 eV) band (E_b = 399.5 ± 0.5 eV) being shown by both **1** and **8**. The binding energies of NH_2 and NH, on the one hand, and of CH=N, on the other, in these compounds obviously are within the experimental error limits of the method. Accordingly, E_b values of 398.9, 399.5, and 399.2 eV were found respectively for **3**, **4**, and *o*-phenylenediamine. 2-Phenylbenzimidazole gave a peak corresponding to E_b = 400.0 eV.

(17) (a) H. Vogel and C. S. Marvel, *J. Polym. Sci.*, **50**, 511 (1961); (b) Y. Iwakura, K. Uno, and Y. Imai, *J. Polym. Sci., Part A-2*, 2605 (1964); (c) D. N. Gray, G. P. Shulman, and R. T. Conley, *J. Macromol. Sci., Chem.*, **1**, 395 (1967).

(18) (a) Although conventionally[13,17] represented by structure **9** comprising a 5,5′ linkage between the two benzimidazole units, the compound in the solid state almost certainly is a mixture of tautomers in which the benzazole groups are connected via 5,5′, 6,6′, and **5**,6′ bonds. In (neutral) solutions, however, the NH protons of benzimidazoles are known[18b] to undergo rapid 1,3-exchange, rendering such distinctions meaningless. (b) H. A. Staab and A. Mannschreck, *Tetrahedron Lett.*, 913 (1962).

(19) Melting points, uncorrected, were taken in sealed capillaries. IR spectra were taken on a Perkin-Elmer 521 spectrophotometer. ^1H NMR spectra were obtained with a Hitachi Perkin-Elmer R20 NMR spectrometer operating at 60 MHz; chemical shifts, δ, are in parts per million relative to internal Me_4Si. Electronic absorption spectra were recorded on a Unicam SP1800 spectrophotometer. Mass spectra (MS) were scanned with a Varian-MAT CH5 mass spectrometer at 70 eV ionizing voltage. N(1s) x-ray photoelectron spectra (Mg Kα radiation) were obtained at −100 °C with the aid of an AEI Scientific ES200 electron spectrometer; peaks were calibrated by reference against internal NH_4NO_3 [$E_{b(NH_4)}$ = 402.3 eV]: precision, ±0.2 eV. Thin layer chromatography (TLC) was performed on precoated SiO_2 plates, Merck silica gel 60 F_{254}, in 4:5 acetone/hexane. Microanalyses were by Robertson Laboratory, Florham Park, N.J.

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(21) G. Smets and A. Delvaux, *Bull. Soc. Chim. Belg.*, **56**, 106 (1947).

(22) (a) H. Franzen, *Chem. Ber.*, **40**, 903 (1907); (b) W. Wrasidlo and H. H. Levine, *J. Polym. Sci., Part A-2*, 4795 (1954).

(23) A sample isolated from large-scale runs by column chromatography (0.5%) had mp 255–260 °C dec; ν_{CO} (KBr) 1703 cm^{-1}; λ_{max} (DMAC) 341 nm; *m/e* 222 (P^+), 193 ($P^+ - H - CO$). The aldehyde probably resulted from partial hydrolysis of **1** and subsequent cyclodehydrogenation.

Palladium-Catalyzed Reductions of Halo- and Nitroaromatic Compounds with Triethylammonium Formate

Nicholas A. Cortese and Richard F. Heck*

Department of Chemistry, University of Delaware, Newark, Delaware 19711

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Aromatic halides and nitro compounds are readily reduced at 50–100 °C to hydrocarbons and amines, respectively, with triethylammonium formate in the presence of either palladium on charcoal or a soluble triarylphosphine–palladium acetate catalyst. Aryl halides are reduced to deuterio derivatives with dideuterioformic acid.

The reducing ability of alkylammonium formates in the palladium-catalyzed reductive dimerization of conjugated dienes has been noted by Roffia et al.[1] In subsequent studies we also became interested in this reducing system[2] and now report applications of it to the reduction of aromatic halides and nitro compounds.

Results and Discussion

Aryl Halides. We initially employed a soluble catalyst, a combination of palladium acetate with a triarylphosphine, for the reductions with triethylammonium formate. We later found that palladium on charcoal was often as useful and, of course, had the advantage of being easily removable from the reaction mixture. The results of these experiments with organic halides are shown in Table I.

It appears that aromatic halide groups may be removed with extreme ease by the palladium-catalyzed reduction with triethylammonium formate at 50–100 °C. The other products of the reaction are the triethylamine hydrohalide and carbon dioxide. Other reducible groups such as nitrile and nitro are not reduced as readily as the halo substituent. Double bonds are apparently reduced at rates comparable to those with the chloro group, and mixtures resulted from the reduction of

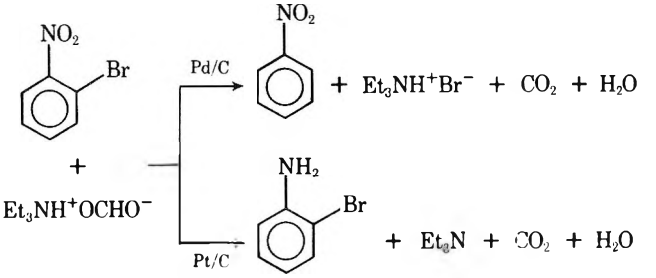


Table I. Reduction of Aromatic Halides of Triethylammonium Formate[a]

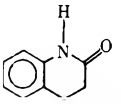
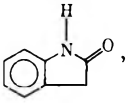
Registry no.	Substituted benzene	Registry no.	Catalyst	Mol % Pd based on organic halide	Temp, °C	Reaction time, h	Product, % yield[b]
623-03-0	1-CN, 4-Cl	7440-05-3	5% Pd/C	0.2	100	23.5	C_6H_5CN, 80
1126-46-1	1-CO_2CH_3, 4-Cl		5% Pd/C	0.2	100	42	$C_6H_5CO_2CH_3$, 93
7560-44-3	1-CH=$CHCO_2CH_3$, 4-Cl		5% Pd/C	0.2	100	1.5	C_6H_5CH=$CHCO_2CH_3$, 22 $C_6H_5CH_2CH_2CO_2CH_3$, 55
100-00-5	1-NO_2, 4-Cl		5% Pd/C	0.2	100	1	$C_6H_5NO_2$, 91
						6	$C_6H_5NO_2$, 83 $C_6H_5NH_2$, 3
						48	$C_6H_5NH_2$, 85[e]
106-47-8	1-NH_2, 4-Cl		5% Pd/C	0.2	100	<1	$C_6H_5NH_2$, 87[e]
	1-CO_2CH_3, 4-Cl		5% Pd/C	0.2	100	29	1-CO_2CH_3, 4-D, 90[e]
108-86-1	Br	3375-31-3	$Pd(OAc)_2$ + 2P(*o*-tol)$_3$[f]	1	50	4.5	C_6H_6, 92
623-00-7	1-CN, 4-Br		$Pd(OAc)_2$ + 2P(*o*-tol)$_3$	1	50	20	C_6H_5CN, 83
3650-78-0	1-CN, 4-Br		5% $Pd/BaSO_4$	1	50	20	C_6H_5CN, 53
2859-78-1	1-CH=$CHCO_2CH_3$, 4-Br[c]		5% Pd/C	0.2	100	7	C_6H_5CH=$CHCO_2CH_3$, 93[e]
585-79-5	1,2-$(OCH_3)_2$, 4-Br		5% Pd/C + 4P(*o*-tol)$_3$	1	50	15	1,2-$(CH_3O)_2C_6H_4$, 68
	1-NO_2, 3-Br[d]		$Pd(OAc)_2$ − 2P(*o*-tol)$_3$	1	50	1.5	$C_6H_5NO_2$, 81 $C_6H_5NH_2$, 2
	1-NO_2, 3-Br[d]		$Pd(OAc)_2$ − $2PPh_3$	1	50	23	$C_6H_5NO_2$, 55 $C_6H_5NH_2$, 12
	1-NO_2, 3-Br[d]		$Pd(OAc)_2$ + 2P(2,5-*i*-$pr_2C_6H_3$)$_3$	1	50	23	$C_6H_5NO_2$, 54 $C_6H_5NH_2$, 25
	1-NO_2, 3-Br[d]		5% Pd/C	1	50	1.5	$C_6H_5NO_2$, 46 $C_6H_5NH_2$, 15
	1-NO_2, 3-Br[d]		5% Pd/C + 2P(*o*-tol)$_3$	1	50	20	$C_6H_5NO_2$, 44 $C_6H_5NH_2$, 16
577-19-5	1-NO_2, 2-Br[d]		5% Pd/C	1	50	48	$C_6H_5NO_2$, 78 $C_6H_5NH_2$, 8
106-40-1	1-NH_2, 4-Br		$Pd(OAc)_2$ + 2P(*o*-tol)$_3$	1	50	1	$C_6H_5NH_2$, 69[e]
615-57-6	1-NH_2, 2,4-Br_2		5% Pd/C	1	50	0.5	$C_6H_5NH_2$, 50 2-$BrC_6H_4NH_2$, 10 4-$BrC_6H_4NH_2$, 4
6630-33-7	1-CHO, 2-Br		$Pd(OAc)_2$ + 2P(*o*-tol)$_3$	1	50	2	C_6H_5CHO, 43 $C_6H_5CH_2OH$, 10 $C_6H_5CH_3$, 10
	1-CHO, 2-Br		5% Pd/C	1	50	20	C_6H_5CHO, 44 $C_6H_5CH_2OH$, 8
103-64-0	CH=$CHBr$[d]		$Pd(OAc)_2$ + 2P(*o*-tol)$_3$	1	50	1.5	C_6H_5CH=CH_2, 32 $C_6H_5CH_2CH_3$, 9
			5% Pd/C		50	19.5	C_6H_5CH=CH_2, 34 $C_6H_5CH_2CH_3$, 31
2687-12-9	CH=$CHCH_2Cl$		$Pd(OAc)_2$ + 4P(*o*-tol)$_3$	1	50	24	(*E*)-C_6H_5CH=$CHCH_3$, 34 (*Z*)-C_6H_5CH=$CHCH_3$, 3 $C_6H_5CH_2CH$=CH_2, 23 C_6H_5CH=$CHCH_2OCHO$, 28
389-87-7	1-Br, 4-I		5% Pd/C	0.2	100	1.5	C_6H_5Br, 58
619-44-3	1-CO_2CH_3, 4-I		5% Pd/C	0.2	100	48	$C_6H_5CO_2CH_3$, 91

[a] Reactions were carried out with 20 mmol of organic halide, 22 mmol of HCO_2H, and 28.5 mmol of Et_3N, except as indicated. [b] GLC yield except where indicated. [c] Reaction was carried out with 50 mmol of organic halide, 220 mmol of HCO_2H, and 285 mmol of Et_3N. [d] Reactions were carried out with 10 mmol of organic halide, 22 mmol of HCO_2H, and 28.5 mL of Et_3N. [e] Isolated yield. [f] P(o-tol)$_3$ = tri-*o*-tolylphosphine.

methyl 4-chlorocinnamate. Methyl 4-bromocinnamate could be reduced selectively in 93% yield, however. When compared under identical conditions, 4-chlorobenzonitrile reduced considerably more rapidly than 4-bromobenzonitrile. Reduction with the soluble catalysts was somewhat dependent upon the phosphine groups present in the catalyst. At 50 °C, *m*-bromonitrobenzene in 1.5 h gave an 81% yield of nitrobenzene with only 2% aniline formed, employing 1 mol % of 2:1 tris(o-tolylphosphine)–palladium acetate as catalyst. Less selectivity was seen with either triphenylphosphine or tris-(2,5-diisopropylphenylphosphine) catalysts or with 5% palladium on charcoal alone. *o*-Bromonitrobenzene reduced in 78% yield to nitrobenzene even with the 5% palladium on charcoal catalyst. The use of 5% platinum on charcoal led to the exclusive formation of *o*-bromoaniline in 94% yield.

Methyl 4-chlorobenzoate was reduced with dideuterioformic acid to give a 90% yield of pure methyl 4-deuteriobenzoate. A related deuteration has been reported by Bcsin,[3] but stoi-

Table II. Reductions of Aromatic Nitro Compounds with Triethylammonium Formate[a]

Registry no.	Substituted Benzene (50 mmol)	Catalyst, 0.2 mol %	Mol of Et_3N	Mol of HCO_2H	Time, h	Product (substituted benzene), % yield
98-95-3	NO_2	5% Pd/C[b]	0.214	0.165	2.3	NH_2, 100
619-50-1	1-CO_2CH_3, 4-NO_2	5% Pd/C[b]	0.214	0.165	2	1-CO_2CH_3, 4NH_2, 97[c]
91-23-6	1-OCH_3, 2-NO_2	5% Pd/C	0.214	0.165	4	1-OCH_3, 2-NH_2, 94[c]
100-17-4	1-OCH_3, 4-NO_2	5% Pd/C	0.214	0.165	4	1-OCH_3, 4-NH_2, 89
104-04-1	1-$NHCOCH_3$, 4-NO_2	5% Pd/C	0.214	0.165	4.5	1-$NHCOCH_3$, 4-NH_2, 85[c]
	1-NO_2, 2-Br[d]	5% Pt/C	0.039	0.033	1.3	1-NH_2, 2-Br, 94[c]
612-41-9	1-CH=$CHCO_2H$, 2-NO_2	5% Pd/C	0.285	0.220	5.3	 , 72[c]
555-68-0	1-CH=$CHCO_2CH_3$, 3-NO_2	5% Pd/C	0.194	0.150	3.5	1-CH=$CHCO_2CH_3$, 3-NH_2 1-$(CH_2)_2CO_2CH_3$ } ~75
3740-52-1	1-CO_2H, 2-NO_2	5% Pd/C	0.214	0.165	23	 , 75[e]
577-59-3	1-$COCH_3$, 2-NO_2	5% Pd/C	0.357	0.275	25	1-CH_2CH_3, 2-NH_2, 50

[a] Carried out at reflux temperature. [b] 0.1 mol % catalyst used. [c] Yield of pure isolated product. [d] 10 mmol used. [e] After sublimation.

chiometric quantities of palladium chloride and sodium borodeuteride in methanol-d_1 were required.

4-Bromo- and 2,4-dibromoaniline reduced readily also. Attempts to selectively reduce the dibromoaniline were not promising. There was a slight preference for reduction of the 4-bromo group rather than the 2-, but the difference was not large enough to be preparatively useful.

2-Bromobenzaldehyde does not reduce selectively. A mixture of benzaldehyde (43%), benzyl alcohol (10%), and toluene (10%) was obtained with 1 equiv of reducing agent. Both β-bromostyrene and cinnamyl chloride gave mixtures of products under the usual conditions. The bromostyrene gave styrene and ethylbenzene, while the cinnamyl chloride produced three isomeric phenylpropenes and cinnamyl formate. The reaction has been applied to allyl derivatives previously in the absence of amine.[4] Cyclohexyl chloride did not reduce in 26 h at 100 °C with the palladium on charcoal catalyst. Aryl iodides also were reduced by the reagent. 4-Nitroiodobenzene reacted very slowly, but 4-bromoiodobenzene gave bromobenzene in 58% yield and methyl 4-iodobenzoate gave methyl benzoate.

No reduction of nitrobenzene or bromobenzene takes place with formic acid and the catalyst without the addition of excess tertiary amine.

The reduced products were easily isolated from these reaction mixtures by diluting with ether to precipitate the triethylamine hydrohalide, filtering, and distilling the filtrate.

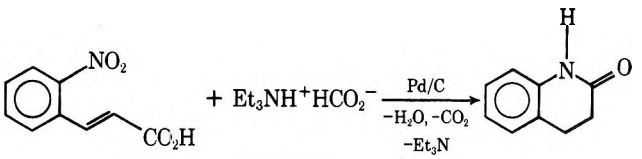
The results suggest a mechanism of reaction involving oxidative addition of the aryl halide to a palladium(0)–phosphine catalyst followed by displacement of halide on the metal by formate ion. Decomposition of the formate group by a deinsertion of carbon dioxide and reductive elimination of the hydrocarbon would explain the reaction.

$$(Pd(PR_3)_2(OAc)_2 + HCO_2H \longrightarrow Pd(PR_3)_2 + CO_2 + 2HOAc)$$

$$Pd(PR_3)_2 + ArX \longrightarrow ArPd(PR_3)_2X \overset{HCO_2^-}{\rightleftharpoons} ArPd(PR_3)_2OCH \overset{-CO_2}{\longrightarrow} Ar\text{-}Pd\text{-}H \longrightarrow ArH + Pd(PR_3)_2$$

The fact that chlorobenzene does not react with tetrakis(triphenylphosphinepalladium(0)) below about ~120 °C[5] is evidence against this mechanism. However, the triphenylphosphine present no doubt strongly inhibits the oxidative addition of chlorobenzene in that reaction compared with the reduction reactions in the absence of the phosphine or with only 2 equiv per palladium.

Aromatic Nitro Compounds. The nitro group is readily reduced in very good yields with 3 mol of triethylammonium formate with palladium on charcoal as catalyst at the boiling temperature of the reaction mixture (~90–100 °C). Results are summarized in Table II. We have generally used about a 10% excess of formic acid and a 30% excess of triethylamine. The reduction is very slow or does not proceed at all without a large excess of the amine. The best procedure is to add the formic acid slowly to a boiling solution of the nitro compound in the amine. The excess amine formate remains as a separate lower phase at the end of the reaction. The products are easily isolated by adding methylene chloride to dissolve the amine salt and then filtering from the catalyst and concentrating the filtrate. The triethylamine salt is readily removed by distillation under reduced pressure and the crude product remaining can be purified by distillation or recrystallization. We have used 0.2 mol % of 5% palladium on charcoal as catalyst generally, but, of course, the reaction rates can be increased if more catalyst is used. The triethylammonium formate–palladium reducing system does not reduce methyl cinnamate significantly under the usual reaction conditions. However, *o*-nitrocinnamic acid is reduced by the reagent to the saturated lactam in 72% yield. Reduction of *o*-nitrophenylacetic acid by the reagent yields a 1:1 mixture of the lactam and *o*-



aminophenylacetic acid. Sublimation of the product mixture produces the lactam in 75% yield. With sufficient reducing agent *o*-nitroacetophenone produces o-ethylaniline in 50% yield. Presumably, condensation reactions are also occurring to reduce the yield in the last reaction. Azobenzene was not reduced under our usual conditions.

The palladium–amine formate reagent is a very convenient combination for selective laboratory reductions of aryl halides and nitro compounds.[6] Attempts to reduce other functional groups with various catalysts using the amine formate reagent

were generally not successful, however. Cyclohexanone did reduce slowly with 5% ruthenium on carbon to cyclohexanol but the reaction did not appear to be fast enough to be useful.

Experimental Section

Reagents. Triethylamine (Aldrich) was distilled prior to use. The formic acid (97%) was obtained from Aldrich. The platinum and palladium on charcoal catalysts were products of Matheson Coleman and Bell. The halides and nitro compounds were commercial products and purified if they had low melting points or were darkly colored.

General Procedure for Reduction of Organic Halides. In a heavy-walled 170-mL "Pyrex" bottle was placed 10 mmol of the halide, the appropriate quantity of either the palladium acetate–phosphine catalyst or 5% palladium on charcoal. The triethylamine was then added. The bottle was flushed with a stream of argon and capped with a rubber-lined cap. The formic acid was then added by syringe through the rubber liner of the cap. The mixture was heated at the appropriate reaction temperature. The progress of the reaction could be followed by noting the increase of pressure (CO_2) in the bottle. For this purpose a small pressure gauge was connected to the bottle through a syringe needle through the rubber-lined cap. The reactions were also monitored by GLC. Products could be isolated by adding sufficient methylene chloride to the product solution to dissolve the unreacted lower layer of amine formate and then filtering and distilling.

Methyl 4-Deuteriobenzoate. A mixture of 3.41 g (20 mmol) of methyl *p*-chlorobenzoate, 4 mL (28.5 mmol) of triethylamine, and 0.085 g (0.04 mmol) of 5% Pd/C was prepared in a 170-mL heavy-walled "Pyrex" bottle. The air was blown from the bottle with a stream of argon and the bottle was capped with a rubber-lined cap. The formic acid-d_2 was then injected (1.056 g, 22 mmol) by syringe through the liner and the mixture was heated in a steam bath for 29 h. Analyses by GLC now showed the chloride had all reacted. The cooled reaction mixture was diluted with ether and filtered through Celite. After rinsing the amine salt with ether, the combined filtrates were concentrated and distilled. There was obtained 2.45 g (90%) of methyl 4-deuteriobenzoate, bp 92–94 °C (20 mm). The mass spectrum of the sample showed it to be 91% monodeuterated. The NMR spectrum was as follows in $CDCl_3$: 3.95 ppm (s, 3 H), 7.62 (d, 2 H, J = 8 Hz), and 8.27 (d, 2 H, J = 8 Hz).

General Procedure for the Reduction of Nitro Compounds. In a 100-mL three-necked round-bottomed flask equipped with a condenser and dropping funnel was placed the nitro compound, the 5% palladium on charcoal, and the triethylamine. The mixture was stirred magnetically and heated on the steam bath while the 97% formic acid was added dropwise. Two layers were formed. The mixture was then heated until GLC analyses showed the absence of the nitro compound in the upper phase. Products were isolated by addition of methylene chloride, filtration, and concentration. The product was either distilled under reduced pressure, recrystallized, or, in one case, sublimed.

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Registry No.—Triethylammonium formate, 585-29-5; methyl 4-deuteriobenzoate, 13122-30-0.

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Reductive Deamination of Arylamines by Alkyl Nitrites in *N,N*-Dimethylformamide. A Direct Conversion of Arylamines to Aromatic Hydrocarbons

Michael P. Doyle,* [1] Joseph F. Dellaria, Jr., Bernard Siegfried, and Stephen W. Bishop

Department of Chemistry, Hope College, Holland, Michigan 49423

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Rapid deamination of arylamines by alkyl nitrites occurs in *N,N*-dimethylformamide and results in the replacement of the primary amino group by hydrogen. Consistently moderate to high yields of aromatic hydrocarbons are reported for nitrosation reactions of *tert*-butyl, benzyl, and isopentyl nitrites with 17 representative aromatic amines. *o*-Alkyl substituted aromatic amines are reductively deaminated by this method with only minor interference from indazole formation. Competing reactions that result in the production of phenols, biphenyls, or azobenzenes are minor processes in reactions that are performed in dimethylformamide. Deuterium labeling studies indicate that dimethylformamide is the sole hydrogen donor in these reductive deamination reactions. Comparative reductive deamination reactions of *p*-nitroaniline in commonly employed aprotic solvents demonstrate that dimethylformamide is superior to tetramethylurea, dioxane, tetrahydrofuran, chloroform, acetonitrile, and hexamethylphosphoramide as a hydrogen donor. The results obtained in this study are interpreted as involving aryl radicals in the formation of aromatic hydrocarbons.

Common procedures for the replacement of an aromatic primary amino group by hydrogen involve preliminary diazotization of the aromatic amine followed by reductive substitution by a hydrogen donor.[2] Although first in the extensive list of reducing agents to be thoroughly investigated,[3] primary alcohols are recognized as unsatisfactory for reductive deamination of a great variety of arylamines primarily because of competing ether formation.[3] Alkaline solutions of formaldehyde have also been used for reductive deamination of arylamines and are advantageous for reductions of diazonium ions that could not be effected by primary alcohols;[4] however, this reductive method has been restricted to a narrow range of aromatic amines, since diazo oxides are formed from ortho- and para-substituted diazonium salts by hydrolytic cleavage

Table I. Product Yields from Reactions of Arylamines with Alkyl Nitrites in Dimethylformamide at 65 °C[a]

$ArNH_2$	Registry no.	ArH	Product yield[b] from reaction of $ArNH_2$ with $(CH_3)_3CONO$ % ArH[c]	$C_6H_5CH_2ONO$ % ArH	$C_6H_5CH_2ONO$ % C_6H_5CHO[d]
2,4-Dinitro-5-fluoroaniline	367-81-7	2,4-$(NO_2)_2C_6H_3F$	63	52	27
2,4-Dinitroaniline	97-02-9	*m*-$C_6H_4(NO_2)_2$	(68)		
4,5-Dichloro-2-nitroaniline	6641-64-1	4-NO_2-1,2-$C_6H_3Cl_2$	(68)		
4-Methyl-2-nitroaniline	89-62-3	*m*-$NO_2C_6H_4CH_3$	(58)		
p-Nitroaniline	100-01-6	$C_6H_5NO_2$	82 (69)	83	33
m-Nitroaniline	99-09-2	$C_6H_5NO_2$	60		
o-Nitroaniline	88-74-4	$C_6H_5NO_2$	72		
2,4,6-Trichloroaniline	634-93-5	1,3,5-$C_6H_3Cl_3$	85	87	16
2,5-Dichloroaniline	95-82-9	*p*-$C_6H_4Cl_2$	80 (72)		
p-Aminoacetophenone	99-92-3	$C_6H_5COCH_3$	65		
p-Aminobenzophenone	1137-41-3	$(C_6H_5)_2CO$	76		
o-Aminobenzophenone	2835-77-0	$(C_6H_5)_2CO$	69	61	24
p-Anisidine	104-94-9	$C_6H_5OCH_3$	75	70	16
4-Nitro-1-aminonaphthalene	776-34-1	1-$C_{10}H_7NO_2$	72[e]		
4-Chloro-1-aminonaphthalene	4684-12-2	1-$C_{10}H_7Cl$	44		
2,4,6-Trimethylaniline	88-05-1	1,3,5-$C_6H_3(CH_3)_3$		44[f]	9
2-Methyl-6-Chloroaniline	87-63-8	*m*-$ClC_6H_4CH_3$	41 (35)		

[a] Unless indicated otherwise, reactions were performed by adding 10.0 mmol of the amine in DMF to 15.0 mmol of the alkyl nitrite in DMF at 65 °C. The total volume of DMF was 50 mL. [b] Absolute yield of the aromatic hydrocarbon after extraction; yields were generally determined by GLC analysis through comparison to an internal standard. From duplicate runs experimentally determined percentage yields were accurate to within ±3% of the reported values. [c] Isolated yields of the purified (distillation or recrystallization) aromatic hydrocarbon from reactions that employed between 0.01 and 0.10 mol of the reactant amine are given in parentheses. [d] Yield of benzaldehyde was determined by GLC and ^1H NMR analyses. Benzyl alcohol was the only other product derived from benzyl nitrite; % C_6H_5CHO + % $C_6H_5CH_2OH$ = 95 ± 3% of reacted benzyl nitrite. [e] Reaction with isopentyl nitrite. [f] 39% yield from reaction with isopentyl nitrite in DMF.

in alkaline media.[2] Hypophosphorus acid, as a result of extensive investigations by Kornblum,[2,5] has proven to be a conveniently employed and generally effective reducing agent for diazonium salts. Although other reduction methods and reducing agents for replacement of an aromatic primary amino group by hydrogen have been promoted in recent years,[6-9] hypophosphorus acid remains the standard reagent for reductions of diazonium salts.

In contrast to procedures that utilize or require a sequential two-step amino-group replacement by hydrogen (diazotization-hydrogen transfer), Cadogan and Molina have recently reported the successful use of pentyl nitrite in boiling tetrahydrofuran for direct reductive deamination of primary aromatic amines.[10] In their in situ reductive deamination procedure Cadogan and Molina rely on the efficiency of hydrogen abstraction from a carbon position that is adjacent to an ether oxygen.[11] Although their results do not generally compare favorably with those from reductive deaminations that employ hypophosphorus acid, particularly in reactions with *o*-alkyl substituted arylamines, the convenience of their in situ method and their use of anhydrous media are attractive.

Our investigations of copper(II) halide promoted reactions of alkyl nitrites with arylamines prompted this investigation of a reaction process that is potentially competitive with substitutive deamination and related reactions.[12,13] In this paper, we report that treatment of arylamines with alkyl nitrites in *N,N*-dimethylformamide results in reductive deamination and that this procedure compares favorably with Kornblum's hypophosphorus acid procedure as a generally effective method for the replacement of an aromatic primary amino group by hydrogen.[14] The use of *N,N*-dimethylformamide as the hydrogen donor effectively minimizes those side reactions that accompany similar reactions that occur in tetrahydrofuran or dioxane.

Results and Discussion

We have reported that *tert*-butyl nitrite reacts slowly with *p*-nitroaniline in acetonitrile at 65 °C to produce nitrobenzene.[12a] However, the yield of nitrobenzene is less than 50%, which indicates that this procedure is unsuitable as a general method for reductive deamination. Surprisingly, when this same reaction is performed in *N,N*-dimethylformamide (DMF) at 65 °C, gas evolution is rapid and nitrobenzene is formed in 82% yield. Compared to reactions in acetonitrile at 65 °C, which are generally complete only after 1 h, those in DMF are immediate and are complete within 10 min following complete addition of the amine. Table I presents the yields of aromatic compounds that are obtained from reactions of representative arylamines with *tert*-butyl nitrite in DMF (eq 1).

$$ArNH_2 + RONO \xrightarrow{DMF} ArH + ROH + N_2 + H_2O \quad (1)$$

Consistently moderate to high yields of the reductive deamination product are observed in nitrosation reactions that occur in DMF with the varied selection of aromatic amines. Indeed, even *o*-alkyl substituted arylamines are effectively deaminated by this procedure. In tetrahydrofuran, 2-methyl-6-chloroaniline does not form *m*-chlorotoluene, but, instead, yields 7-chloroindazole;[10] in DMF, 7-chloroindazole is formed as a minor side product (10% yield). Comparison of the product yields from nitrosative deamination of structurally similar arylamines in THF[10] and in DMF (Table I) indicates that dimethylformamide is a more effective hydrogen donor than is tetrahydrofuran. Side reactions that lead to the production of phenols, biphenyls, and azobenzenes are minor competing processes in DMF.[15] However, a dark resinous material is formed in these reactions in amounts that reflect the difference between 100% and the percentage yields of arenes that are reported in Table I; similar red or red-brown residues have been reported to result from nitrosative deamination by other reductive procedures.[5,8] Although no attempt was made in this study to optimize the yields of individual products, the yields of purified arenes that were obtained by reductive deamination in DMF were similar to those obtained by the hypophosphorus acid reduction of diazonium salts.[2,5]

Isopentyl nitrite and benzyl nitrite were reacted with a se-

Table II. Deuterium Content of Aromatic Hydrocarbons Formed by Nitrosative Deamination of Arylamines[a]

Amine	Nitrite	Solvent	Arene[b] d_0, %	Arene[b] d_1, %
$2,4,6\text{-}Cl_3C_6H_2NH_2$	$C_6H_5CD_2ONO$	DMF	100	
$2,4,6\text{-}Cl_3C_6H_2ND_2$	$(CH_3)_3CONO$	DMF[c]	100	
$2,4,6\text{-}Cl_3C_6H_2NH_2$	$(CH_3)_3CONO$	DMF + 1.0 equiv of D_2O[d]	100	
$2,4,6\text{-}Cl_3C_6H_2NH_2$	$C_6H_5CD_2ONO$	CH_3CN	70	30
$2,4,6\text{-}Cl_3C_6H_2NH_2$	$C_6H_5CH_2ONO$	CD_3CN[e,f]	83	17
$2,4,6\text{-}Cl_3C_6H_2NH_2$	$(CH_3)_3CONO$	CD_3CN[f,g]	43	57
$4,5\text{-}Cl_2\text{-}2\text{-}(NO_2)C_6H_2NH_2$	$(CH_3)_3CONO$	CD_3CN[g]	59	41

[a] Reactions were performed at 65 °C. [b] Determined by mass spectral analysis of the arene isolated by GLC collection. Percentage deuterium content was averaged from at least two separate determinations. [c] 84% yield of 1,3,5-trichlorobenzene. [d] 85% yield of 1,3,5-trichlorobenzene. [e] 64% yield of 1,3,5-trichlorobenzene + 63% benzaldehyde. [f] Reactions were run with 2 mmol of the amine in 3.0 mL of the deuterated acetonitrile. [g] 55% yield of 1,3,5-trichlorobenzene.

Table III. Reductive Deamination of *p*-Nitroaniline in Aprotic Solvents[a]

Solvent	RONO	Registry no.	$C_6H_5NO_2$, %[b]
Dimethylformamide	*t*-BuONO		82
Tetramethylurea[c]	*t*-BuONO		75
Dioxane	*t*-BuONO		65
Tetrahydrofuran	PentONO	463-04-7	65[d]
Chloroform[e]	*t*-BuONO		52[f]
Chloroform + 2 eq DMF[e]	*t*-BuONO		51[g]
Acetonitrile	*t*-BuONO	540-80-7	50
Hexamethylphosphoramide	*i*-PentONO	110-46-3	30

[a] Reactions were performed by adding 10.0 mmol of the amine in the indicated solvent to 15.0 mmol of the alkyl nitrite in the same solvent at 65 °C or at reflux (THF and $CHCl_3$). Unless indicated otherwise, the total volume of the solvent was 50 mL. [b] Absolute yield of nitrobenzene determined by GLC analysis after extraction. [c] Total volume was 30 mL. [d] Ref 10. [e] Amine was added in portions as a solid. [f] +34% *p*-Nitro-α,α,α-trichlorotoluene. [g] +36% *p*-Nitro-α,α,α-trichlorotoluene.

ries of arylamines in DMF at 65 °C to determine whether the structure of the alkyl nitrite had a pronounced effect on the extent of reductive deamination. Isopentyl nitrite gave results that were nearly identical to those obtained with *tert*-butyl nitrite under the same reaction conditions. Product yields from reactions with benzyl nitrite are given in Table I and similarly indicate no dependence of the reductive deamination process on the structure of the alkyl nitrite. Benzaldehyde was formed together with benzyl alcohol as the only identifiable products emanating from benzyl nitrite. The combined yields of benzaldehyde (Table I) and benzyl alcohol were nearly quantitative.

The formation of benzaldehyde in aromatic amine reactions with benzyl nitrite suggested that this nitrite may be a hydrogen donor in reductive deamination reactions. In order to determine the nature of benzaldehyde production and to identify the probable source of the hydrogen that is transferred in these reactions, α,α-dideuteriobenzyl nitrite was prepared and reacted with 2,4,6-trichloroaniline in dimethylformamide. The reduced product 1,3,5-trichlorobenzene was isolated by GLC separation and its deuterium content was determined by mass spectral analysis. Similarly, *N,N*-dideuterio-2,4,6-trichloroaniline was prepared and subjected to reductive deamination by *tert*-butyl nitrite in DMF. In a third experiment, 1.0 molar equiv of D_2O (based on the amine) was employed with undeuterated reactants. Within the limits of our detection, only 1,3,5-trichlorobenzene that did not contain deuterium was formed (Table II). These results strongly suggest that *N,N*-dimethylformamide is the sole hydrogen donor in deamination reactions that are performed in that aprotic solvent. Benzaldehyde formation is independent of the reductive deamination process. Indeed, in control experiments in which benzyl nitrite was heated at 65 °C in DMF for 1 h and then isolated by the usual workup procedure, benzaldehyde (21%) and benzyl alcohol (47%) were formed, and benzyl nitrite (32%) was recovered.[16]

Similar deuteration studies were performed for nitrosative deamination reactions that employed acetonitrile as the solvent and potential hydrogen donor, and their results are reported in Table II. Benzyl nitrite is a surprisingly effective hydrogen donor in acetonitrile; acetonitrile is surprisingly ineffective as a hydrogen donor. Use of α,α-dideuteriobenzyl nitrite in the reaction with 2,4,6-trichloroaniline leads to 30% deuteration in 1,3,5-trichlorobenzene. However, in a separate experiment with acetonitrile-d_3 only 17% of monodeuterated 1,3,5-trichlorobenzene is formed. In view of the relatively low yield of deuterated arene in acetonitrile-d_3 for reactions of arylamines with *tert*-butyl nitrite, the results with benzyl nitrite may be explained as a consequence of the isotope effect for hydrogen (and deuterium) transfer from the benzylic position.[17] Due to the complex nature of hydrogen transfer and the relatively low yield of products from reductive deamination in acetonitrile, however, no definitive conclusion other than that related to the effectiveness of DMF and acetonitrile as hydrogen donors can be drawn from these investigations.

An increasing number of solvents, including tetramethylurea,[8] dioxane,[6] and tetrahydrofuran,[10] have been promoted in recent years as effective hydrogen donors for the reduction of diazonium compounds. However, only tetrahydrofuran has been employed in a direct reductive deamination process.[10] To compare hydrogen-donor capabilities, *p*-nitroaniline was subjected to nitrosative deamination in a representative series of solvents under reaction conditions identical to those that are reported for reactions in DMF. The results of this investigation are described in Table III. Although results from reductive deamination of only one amine are reported, DMF is clearly the superior hydrogen donor among the aprotic solvents employed in this study.

Tetramethylurea approaches DMF in its effectiveness as a hydrogen donor, and this similarity suggests that reduction occurs primarily by hydrogen transfer from the *N*-methyl group rather than solely from the formyl position. This explanation also accounts for the relative absence of carbon dioxide in the gaseous products. Deamination of *p*-nitroaniline by *tert*-butyl nitrite in DMF at 65 °C yields a mixture of gaseous products that is composed of nitrogen (93%), nitrous oxide (2%),[18] and carbon dioxide (5%). We have been unable, however, to isolate product(s) that are formed from DMF following hydrogen transfer.

The results obtained in this study of reductive deamination

Scheme I

$$ArNH_2 + RONO \rightarrow ArN{=}N{-}OR + H_2O \quad (2)$$

$$ArN{=}N{-}OR \rightarrow ArN_2\cdot + RO\cdot \quad (3)$$

$$ArN_2\cdot \rightarrow Ar\cdot + N_2 \quad (4)$$

$$Ar\cdot + SolH \rightarrow ArH + Sol\cdot \quad (5)$$

of aromatic amines are consistent with the involvement of aryl radicals (Scheme I).[20] Additional evidence for the operation of the radical pathway was obtained through trapping experiments in which equal volumes of acrylonitrile and acetonitrile were employed as the solvent for the reaction between *p*-nitroaniline and *tert*-butyl nitrite; only a trace amount of nitrobenzene was formed and polymerization of acrylonitrile was observed. The amount of gaseous products was only two-thirds of that obtained from reactions without added acrylonitrile, suggesting that the aryldiazo radical is an intermediate in this reaction process. Furthermore, the observation of *p*-nitro-α,α,α-trichlorotoluene from reactions in chloroform (Table III) suggests a radical coupling mechanism for the formation of this unusual product.[21]

Our results do not distinguish the mechanism proposed in Scheme I from one that involves the intermediacy of aryldiazenes (Scheme II). Hydrocarbons are the predominant products from bimolecular decomposition of aryldiazenes.[22] However, if aryldiazenes are reaction intermediates in reductive nitrosation reactions of arylamines, they cannot be solely responsible for hydrocarbon formation. Nitro substituents inhibit aryldiazene decomposition to the corresponding aromatic hydrocarbon,[22] whereas nitro substituents do not measurably affect the yield of the reduced product in nitrosation reactions (Table I).

Several attempts were made to convert primary alkylamines to their corresponding hydrocarbons through reactions with *tert*-butyl nitrite in DMF at 65 °C. However, as expected from prior investigations of aprotic diazotization of aliphatic amines,[19] low product yields were obtained. For example, adamantane was formed from 1-adamantamine in only 5% yield, and 1-amino-4-phenylbutane produced 1-phenylbutane and tetrahydronaphthalene in 6 and 2% yield, respectively.[23]

Reductive deamination by alkyl nitrites in DMF is not limited to primary aromatic amines. Preliminary results in our laboratory have demonstrated that arylhydrazines are reduced to the corresponding aromatic hydrocarbons without competing formation of aryl azides. These and related transformations are presently under investigation.

Experimental Section

General. Instrumentation has been previously described.[12a] Mass spectra were obtained using a Fannigan Model 1015 gas chromatograph–mass spectrometer operated at 70 eV. *tert*-Butyl nitrite was prepared from *tert*-butyl alcohol according to the procedure of Noyes;[24] isopentyl nitrite was obtained commercially. Benzyl nitrite was formed from benzyl alcohol, sodium nitrite, and aluminum sulfate according to the published procedure,[25] and its purity was monitored regularly by ^{1}H NMR spectral analysis.[26] α,α-Dideuteriobenzyl nitrite was similarly prepared from α,α-dideuteriobenzyl alcohol. The amines that were employed in this study were commercially available and, with the exception of *p*-anisidine, were used without prior purification. Reagent grade *N,N*-dimethylformamide, acetonitrile, and hexamethylphosphoramide were distilled from calcium hydride prior to their use as reaction solvents. Dioxane was distilled from lithium aluminum hydride, and chloroform was washed with concentrated sulfuric acid prior to distillation. Tetramethylurea was used without further purification. *N,N*-Dideuterio-2,4,6-trichloroaniline was prepared by hydrogen–deuterium exchange in D_2O catalyzed by sulfuric acid-d_2; ^{1}H NMR analysis verified total exchange. Acetonitrile-d_3 was obtained commercially (99 atom % ^{2}H) and was used without further purification.

Scheme II

$$ArN_2\cdot + SolH \rightarrow ArN{=}NH + Sol\cdot \quad (6)$$

$$ArN{=}NH \rightarrow ArH + N_2 \quad (7)$$

Reductive Deamination of Aromatic Amines. General Procedure. To a rapidly stirred solution of the alkyl nitrite (15.0 mmol) and anhydrous DMF heated at 65 °C in a three-necked round-bottom flask equipped with a reflux condenser, addition funnel, and gas outlet tube was added the aromatic amine (10.0 mmol) dissolved in a minimal amount of DMF. The amine was added slowly to the reaction solution over a 5-min period. Gas evolution was immediate, continued steadily throughout the addition, and was generally complete within 10 min following complete addition of the amine. Total gas evolution was measured on the closed system by water displacement from a calibrated gas buret; with the exception of reactions with *o*-alkyl-substituted aromatic amines and the naphthylamines, the yield of gaseous products was 220 ± 20 mL (based on 10 mmol of the amine). After complete gas evolution, the reaction solution that had turned deep red from the initial yellow was cooled and then poured into 200 mL of 20% aqueous hydrochloric acid and extracted with 200 mL of ether, and the organic layer was washed once with 200 mL of aqueous hydrochloric acid. The resulting ether solution was dried over anhydrous magnesium sulfate and the ether was removed under reduced pressure. Ether solutions containing volatile products were distilled at atmospheric pressure through a 12.5-cm Vigreux column.

A similar procedure was employed for reactions of *p*-nitroaniline in those solvents that are described in Table III.

Product Analyses. Structural assignments for the aromatic hydrocarbons produced in reactions of arylamines with alkyl nitrites were made following extraction by ^{1}H NMR spectral comparisons and/or by GLC retention time and peak enhancement with authentic samples. *p*-Nitro-α,α,α-trichlorotoluene was identified by ^{1}H NMR, IR, and mass spectral analysis following isolation of this compound from the reaction mixture (see Table III) by GLC separation. The gaseous products from the reaction of *p*-nitroaniline with *tert*-butyl nitrite in dimethylformamide were analyzed by GLC retention times on a 5-ft silica gel column and by infrared spectral analysis.

Product yields were determined by GLC analyses for the vast majority of reactions reported in this study. Prior to workup a weighed amount of dibenzyl ether was added to the reaction solution as an internal standard. The average integrated area ratio from at least two GLC traces was employed in each yield determination. Absolute yields were calculated with the use of experimentally determined thermal conductivities for each of the aromatic hydrocarbons examined by this method. Thermal conductivity ratios were determined immediately prior to product analyses to ensure accuracy in these calculations. Yields also determined by ^{1}H NMR spectral analysis were in substantial agreement (±2%) with those obtained by the GLC method.

The absolute yields of benzaldehyde and benzyl alcohol were obtained by ^{1}H NMR spectral analysis of the reaction solutions following extraction. The average values of at least five integrations were utilized in the calculation of absolute yields. Yields obtained by the GLC method confirmed those determined by ^{1}H NMR spectral analysis.

Determination of the deuterium content in aromatic hydrocarbons was made by mass spectral comparisons of the molecular ion peaks of an authentic sample with those peaks observed from the reaction product. No difference in relative peak intensity was observed from analyses at 70 and 20 eV. For each analysis the aromatic hydrocarbon was isolated from the reaction mixture by GLC separation and this sample was inserted into the ionization chamber through the use of a solid probe. A minimum of two mass spectral traces was employed in the calculation of deuterium content for each reaction.

1,2-Dichloro-4-nitrobenzene. The procedure employed for reductive deamination of 4,5-dichloro-2-nitroaniline exemplifies those used for the preparative scale reactions that are reported in Table I (yield of distilled or recrystallized product given in parentheses). To a rapidly stirred solution of *tert*-butyl nitrite (5.47 g, 0.0530 mol) and anhydrous DMF (80 mL) heated at 50 °C in a 250-mL three-necked round-bottom flask equipped with a reflux condenser and addition funnel was added 4,5-dichloro-2-nitroaniline (7.28 g, 0.0352 mol) dissolved in 70 mL of DMF. The reaction temperature was maintained at 50 °C to minimize the loss of *tert*-butyl nitrite. The amine solution was added dropwise to the nitrite solution over a 25-min period. Gas evolution was immediate and continued steadily throughout the addition. After addition was complete, no further gas evolution was observed and the reaction solution was allowed to cool to room temperature. The resulting burnt orange reaction solution was diluted

with 300 mL of ether and then poured into 300 mL of 20% aqueous hydrochloric acid. After separation, the ether solution was washed with an additional 300 mL of 20% aqueous hydrochloric acid and was dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and the residue was distilled at 0.6 Torr to give 4.56 g of a light yellow liquid (bp 107–110 °C at 0.6 Torr; lit.[27] bp 254–257 °C) that crystallized on standing (mp 40.5–41.0 °C; lit.[27] mp 43 °C): 0.0238 mol, 68% yield.

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Registry No.—Dimethylformamide, 68-12-2; $C_6H_5CH_2ONO$, 935-05-7.

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1,2,4-Triazine 1- and 2-Oxides. Reactivities toward Some Electrophiles and Nucleophiles

Brian T. Keen, Robert J. Radel, and William W. Paudler*

Department of Chemistry, The University of Alabama, University, Alabama 35486

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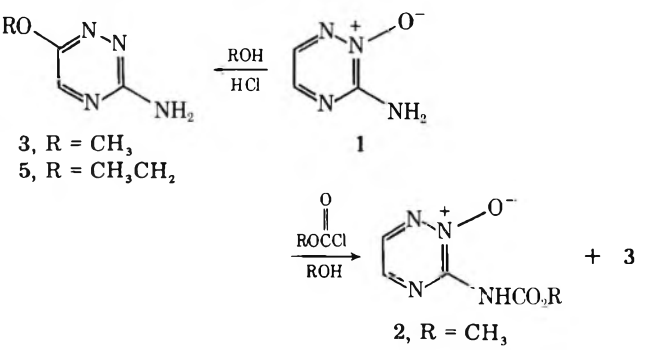
The 3-amino- (**1**), 3-methylamino- (**6**), 3-dimethylamino- (**7**), and methylthio- (**10**) 1,2,4-triazine 2-oxides undergo an addition–elimination reaction with methanol, ethanol, or 2-propanol to give the corresponding 6-alkoxy-1,2,4-triazines. The 1,2,4-triazine 1-oxides do not react with methanol under similar reaction conditions. Reaction of 3-amino-1,2,4-triazine 1-oxide (**14**) with nitrous acid in the presence of hydrobromic acid forms 3-bromo- (**19**) and 3,6-dibromo-1,2,4-triazine 1-oxide (**20**). The 3-methoxy- (**13**), 3-amino- (**14**), 3-methylamino- (**15**), and 3-dimethylamino- (**16**) 1,2,4-triazine 1-oxides react with bromine to give the respective 6-bromo-1,2,4-triazine 1-oxides (**21–24**). Possible reaction paths to account for these transformations are proposed.

1,2,4-Triazines have proven to be rather unusual π-deficient heteroaromatic compounds, as exemplified by their facile covalent hydration across the N_4–C_5 bonds,[1] their propensity for acting as dienes in Diels–Alder reactions,[2] and the tendency for ring contraction of their N-alkylated derivatives.[3]

We have described the selective N-1 and N-2 oxidation of several 1,2,4-triazine derivatives[4,5] and now wish to report some interesting chemical transformations of these compounds.

During studies involving the condensation of 3-amino-1,2,4-triazine 2-oxide (**1**) with methanolic methyl chloroformate, the expected urethane (**2**) was the minor product; the



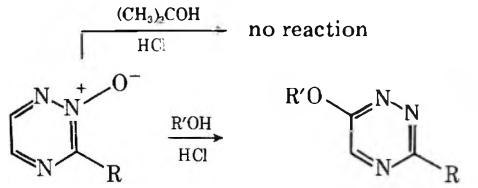
3, R = CH_3
5, R = CH_3CH_2

1

2, R = CH_3
4, R = CH_3CH_2

major one is a compound $C_4H_6N_4O$ whose ^1H NMR spectrum shows three singlets (δ 7.94, 5.30 and 4.05 (ppm)), with relative area ratios of 1:2:3. The broad two-proton singlet at δ 5.30 is subject to facile H → D exchange. Thus, we are dealing with either 5- or 6-methoxy-3-amino-1,2,4-triazine (**3**).

Since 5-ethoxy-3-amino-1,2,4-triazine[6] is known, the reaction was repeated with ethyl chloroformate in ethanol. The resulting ethoxy-3-amino-1,2,4-triazine formed as the major product, along with compound **4**, was compared with an authentic sample of the 3-amino-5-ethoxy-1,2,4-triazine. The latter compound (mp 166–168 °C) is different from the material obtained in this reaction (mp 110–112 °C). Thus, the 3-amino-6-alkoxy-1,2,4-triazines (**3** and **5**) are the major products in these reactions. Since this transformation, does *not* occur upon treatment of 3-amino-1,2,4-triazine or its 1-oxide with methanol and methyl chloroformate, the presence of the 2-oxide function is clearly required. When 3-amino-1,2,4-triazine 2-oxide (**1**) is treated with methanol containing only anhydrous hydrochloric acid, rather than methyl chloroformate, 6-methoxy-3-amino-1,2,4-triazine (**3**) is the only product.



1, R = NH_2
6, R = $NHCH_3$
7, R = $N(CH_3)_2$
10, R = SCH_3

3, R = NH_2; R' = CH_3
5, R = NH_2; R' = CH_3CH_2
8, R = $NHCH_3$; R' = CH_3
9, R = $N(CH_3)_2$; R' = CH_3
11, R = SCH_3; R' = CH_3
12, R = NH_2; R' = $(CH_3)_2CH$

The deoxygenated 6-methxy derivatives (**8, 9**) of 3-methylamino- (**6**) and 3-dimethylamino- (**7**) 1,2,4-triazine 2-oxides are obtained when these compounds are treated with methanolic hydrochloric acid.

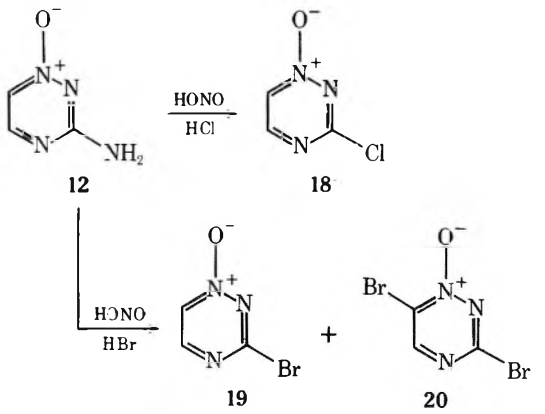
It clearly remains to establish whether a 3-amino substituent is required for this reaction to proceed. When 3-methylthio-1,2,4-triazine 2-oxide (**10**) was reacted with methanolic HCl, the 6-methoxy-3-methylthio-1,2,4-triazine (**11**) was readily obtained (cf. Table I for structure proof).

When either ethyl or isopropyl alcohol is used in place of methanol, the corresponding 6-ethoxy and 6-isopropoxy derivatives (**5, 12**) are formed. *tert*-Butyl alcohol, on the other hand, does not react with these 3-amino-1,2,4-triazine 2-oxides under the same reaction conditions.

It now became of interest to investigate the reactivity of the corresponding 3-substituted 1,2,4-triazine 1-oxides under similar reaction conditions. The necessary compounds **14–16** were prepared by nucleophilic displacement of the 3-methoxy group in 3-methoxy-1,2,4-triazine 1-oxide (**13**) (cf. Experimental Section). 3-Dimethylamino-1,2,4-triazine 1-oxide (**16**) can also be prepared by direct N-oxidation of 3-dimethylamino-1,2,4-triazine (**17**).[7]

None of these 1-oxides react with methanolic HCl under the conditions which yield the 6-alkoxy compounds in the 2-oxides.

As previously reported,[5] diazotization of 3-amino-1,2,4-triazine 2-oxide affords the 3-halo derivatives. When this reaction was applied to 3-amino-1,2,4-triazine 1-oxide, the corresponding 3-halo (chloro or bromo) derivatives (**18, 19**) were obtained. In addition to the formation of the 3-bromo derivative, a dibromo compound ($C_3HN_3OBr_2$) was also formed. The structure of this material is readily established by comparison of the ^1H NMR spectrum of compound **19** with that of the dibromo derivative. The chemical-shift assign-

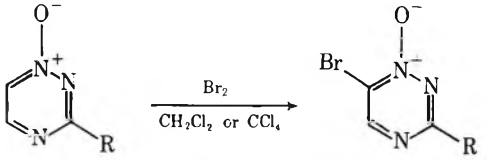


12 **18** **19** **20**

ments for H_5 (δ 8.50) and H_6 (τ 8.11) of the protons in compound **19** are consistent with our results described earlier.[4] Since it is well known that replacement of a hydrogen by bromine on an aromatic ring has only a small effect on the chemical shift of a proton on the ortho carbon, the singlet (δ 8.63) observed in the ^1H NMR spectrum of the dibromo compound **20** must be due to H_5. Thus, we are dealing with 3,6-dibromo-1,2,4-triazine 1-oxide (**20**).

An obvious extension of this dibromination reaction led us to examine the bromination of several 3-substituted 1,2,4-triazine 1-oxides.

When the 1-oxides of 3-amino- (**14**), 3-methylamino- (**15**), 3-dimethylamino- (**16**), or 3-methoxy- (**13**) 1,2,4-triazines are

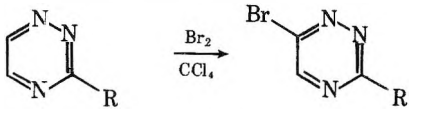


13, R = OCH_3
14, R = NH_2
15, R = $NHCH_3$
16, R = $N(CH_3)_2$

21, R = OCH_3
22, R = NH_2
23, R = $NHCH_3$
24, R = $N(CH_3)_2$

treated with bromine in carbon tetrachloride or methylene chloride, in the presence of triethylamine, the corresponding monobromo derivatives **21–24** are obtained in excellent yields. The question as to whether we are again dealing with 6-bromo derivatives or not is readily answered by a comparison of the ^1H NMR chemical shifts of these bromo derivatives with those of their precursors (cf. Table I). Since the chemical shifts of the aromatic protons in these bromo compounds are in the region δ 8.10–8.30, these compounds are the 6-bromo derivatives (**21–24**). Further confirmation of these assignments is found in a comparison of the ^{13}C chemical shifts of 3-methoxy-1,2,4-triazine 1-oxide (**13**) (δ_c (ppm): C_3, 166.5; C_5, 154; C_6, 124.5) with those of the 6-bromo derivative 21 (δ_c (ppm): C_3, 164; C_5, 156; C_6, 119).[8]

These facile bromination reactions prompted us to examine two non-N-oxidized 1,2,4-triazines, the 3-methoxy (**25**) and 3-dimethylamino (**17**) derivatives. In the former instance, no



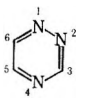
17, R = $N(CH_3)_2$
25, R = OCH_3

26, R = $N(CH_3)_2$
No reaction

ring bromination occurred, while, in the latter one, a monobromo derivative **26** was obtained. The structure of this compound was readily established by a comparison of its ^1H NMR spectrum with that of the starting material (cf. Table I).

Mechanistic Considerations. The unique deoxygenative 6-alkoxylation of the 3-substituted 1,2,4-triazine 2-oxides

Table I. ^{1}H NMR and Analytical Data for Some 1,2,4-Triazines[a]



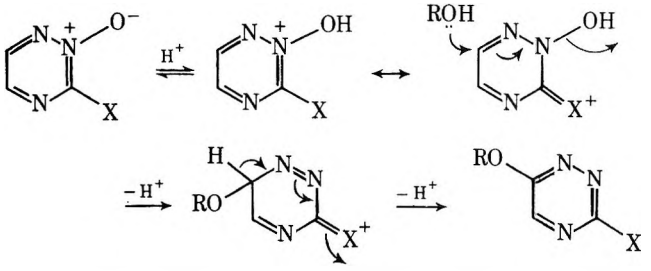
Compd no.	Mol Formula	Substituents[c] R_3	R_6	Registry no.	Chemical Shifts[a] R_3	R_5	R_6	mp, °C
2[b]	$C_5H_6N_4O_3$	$NHCO_2CH_3$	H	63196-97-4	3.85 9.30	8.00	8.15	136–138
3	$C_4H_6N_4O$	NH_2	OCH_3	63196-98-5	5.30	7.94	4.05	119–120
5	$C_5H_8N_4O$	NH_2	OCH_2CH_3	63196-99-6	5.24	7.99	4.46	110–112
6[b]	$C_4H_6N_4O$	$NHCH_3$	H	63197-00-2	3.20 3.25	7.80	7.80	130–131
8	$C_5H_8N_4O$	$NHCH_3$	OCH_3	63197-01-3	3.02 3.08	7.96	4.02	99–101
9	$C_6H_{10}N_4O$	$N(CH_3)_2$	OCH_3	63197-02-4	3.20	7.96	4.02	10–12
10[b]	$C_4H_5N_3OS$	SCH_3	H	63197-03-5	2.70	8.03	8.26	94–96
11	$C_5H_7N_3OS$	SCH_3	OCH_3	63197-04-6	2.78	8.18	4.16	5–6
12[c]	$C_6H_{10}N_4O$	NH_2	$OCH(CH_3)_2$	63197-05-7	5.11	7.96	5.36 1.38	102–104
15[c]	$C_4H_6N_4O$	$NHCH_3$	H	63197-06-8	3.03 5.90	8.14	7.55	164–165.5
18[c]	$C_3H_2N_3OCl$	Cl	H	63197-07-9		8.55	8.09	40–41
19[c]	$C_3H_2N_3OBr$	Br	H	63197-08-0		8.50	8.11	64–66
20[c]	$C_3HN_3OBr_2$	Br	Br	63197-09-1		8.63		113–115
21[c]	$C_4H_4N_3O_2Br$	OCH_3	Br	63197-10-4	4.08	8.61		133–135
22[c]	$C_3H_3N_4OBr$	NH_2	Br	63197-11-5	7.90	9.00		130 dec
23[c]	$C_4H_5N_4OBr$	$NHCH_3$	Br	63197-12-6	3.03 5.68	8.34		185–187
24[c]	$C_5H_7N_4OBr$	$N(CH_3)_2$	Br	63197-13-7	4.21	8.33		176–177
26[c]	$C_5H_7N_4Br$	$N(CH_3)_2$	Br	63197-14-8	3.28	8.14		66–67.5

[a] δ (ppm), $CDCl_3$, [b] N_2-oxide. [c] N_1-oxide. [d] R_5 = H. [e] Satisfactory analytical values (±0.3% for C, H. N) were reported for all compounds in table.

Table II. Experimental Variables for the Syntheses of Various 6-Alkoxy 3-Substituted 1,2,4-Triazines

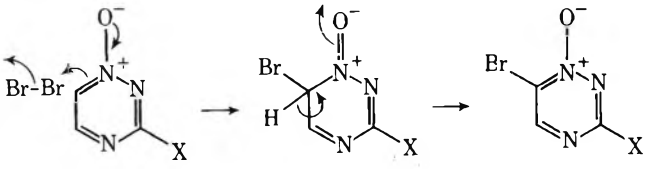
Compd	Reaction time (h)	Temp, °C	% yield	mp, °C
3	0.5	64.5	71	119–120
5	0.5	78.4	64	110–112
8	0.2	64.5	50	99–101
9	0.2	64.5	51	10–12
11	4	64.5	90	5–6
12	36	82.4	65	102–104

warrants some mechanistic speculation. Since the reaction does not depend upon possible amine–imine tautomerization, and since the 3-dimethylamino as well as 3-methylthio 2-oxides react, any mechanistic considerations involving this phenomenon can be eliminated. Furthermore, since all of the functional groups situated at C_3 are electron donating, and because an acidic medium as well as the presence of a 2-rather than 1-oxide group is required for this transformation to occur, the following reaction path can be reasonably proposed:

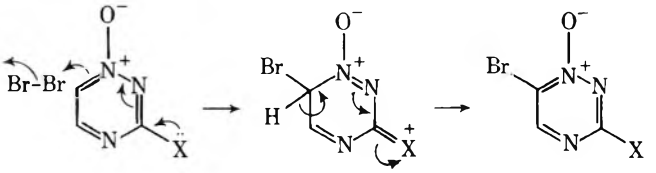


The formation of the 3-substituted 6-halo-1,2,4-triazine 1-oxides from the corresponding 3-substituted 1-oxides, in conjunction with the observation that the same transformation does not take place on the 3-methoxy-1,2,4-triazine, while it occurs in the 3-dimethylamino 1,2,4-triazine, might well be accounted for by either one or both of the following two paths:

Path a



Path b



In view of the observation that 3-methoxy-1,2,4-triazine does not react with bromine under these conditions, while the 3-dimethylamino derivative does, this may simply reflect the greater contribution of path b in the latter instance. The N-1 oxide would simply facilitate electrophilic substitution of C-6, beyond the activation possible by a 3-methoxy substituent.

These new substitution and addition–deoxygenation reactions on the 1,2,4-triazine ring system offer facile routes to functionally substituted 3,6- and 6-substituted 1,2,4-triazines, compounds needed for the syntheses of various potential antibiotics. Further studies of these *N*-oxides and their synthetic utility are in progress.

Experimental Section

Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6M instrument on all new compounds. Their molecular ions and frag-

mentation patterns are consistent with the indicated structures. A Varian HA-100 instrument was used to record the ^1H NMR and a Perkin-Elmer R-26 instrument to record ^{13}C NMR spectra. Melting points are corrected. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia, and the Analytical Services Laboratory, Department of Chemistry, The University of Alabama.

Reaction of 3-Amino-1,2,4-triazine 2-Oxide (1) with Methyl Chloroformate in Methanol. To a solution of 500 mg (4.46 mmol) of 3-amino-1,2,4-triazine 2-oxide (1) in 150 mL of dry CH_3OH was added 843 mg (8.9 mmol) of methyl chloroformate. The solution was refluxed for 4 h, after which time an excess of $NaHCO_3$ was added and refluxing was continued overnight. The solution was evaporated to dryness and the residue was sublimed to give a pale-yellow solid. This solid was chromatographed on grade III silica gel with $CHCl_3$ as eluant to give 337 mg (60%) of 6-methoxy-3-amino-1,2,4-triazine (**3**) and 157 mg (2) of 3-methoxycarbonylamino-1,2,4-triazine 2-oxide (**2**).

A similar procedure using ethyl chloroformate and dry CH_3CH_2OH gave 406 mg (65%) of 6-ethoxy-3-amino-1,2,4-triazine (**5**), along with 123 mg (15%) of 3-ethoxycarbonylamino-1,2,4-triazine 2-oxide (**4**).

3-Methylamino-1,2,4-triazine 2-Oxide (6). Into a solution of 350 mg (3.0 mmol) of 3-bromo-1,2,4-triazine 2-oxide in 50 mL of dry tetrahydrofuran (THF) was bubbled gaseous methylamine. The solution, which immediately became yellow, was stirred for an additional 10 min. Evaporation to dryness gave a yellow solid which was crystallized from 50% petroleum ether/THF to give 190 mg (75%) of 3-methylamino-1,2,4-triazine 2-oxide (**6**).

3-Methylthio-1,2,4-triazine 2-Oxide (10). Into a solution of 500 mg (2.8 mmol) of 3-bromo-1,2,4-triazine 2-oxide in 250 mL of anhydrous ether was bubbled gaseous methyl mercaptan. The solution was stirred overnight. Excess Na_2CO_3 was added and stirring was continued for an additional hour. The solution was filtered and the solvent evaporated. The residue was triturated with 50 mL of hexane, filtered, and sublimed at 100 °C/0.05 Torr to give 350 mg (87%) of 3-methythio-1,2,4-triazine 2-oxide (**10**).

6-Alkoxy 3-Substituted 1,2,4-Triazines from 3-Substituted 1,2,4-Triazine 2-Oxides. (General procedure, cf. Table II for experimental variables.) In a typical experiment, a solution of 500 mg (4.5 mmol) of 3-amino-1,2,4-triazine 2-oxide in 50 mL of dry MeOH saturated with HCl was refluxed for 30 min. Excess sodium carbonate was added and refluxing was continued for 30 min. The mixture was filtered and the filtrate was evaporated to dryness. The residue was sublimed at 90 °C/0.05 Torr to give 400 mg (71%) of 6-methoxy-3-amino-1,2,4-triazine (**3**).

3-Amino-1,2,4-triazine 1-Oxide (14). To 2.54 g (0.02 mol) of 3-methoxy-1,2,4-triazine 1-oxide (**13**) was added to 40 mL of methanolic NH_3. The mixture was heated in a sealed tube at 100 °C for 4–5 h. After allowing the mixture to come to room temperature, 1.75 g of product (**14**) was collected by filtration. An additional 0.48 g of **12** could be obtained by evaporating the mother liquor and extracting the residue with 20 mL of $CHCl_3$; total yield 98%.

3-Methylamino-1,2,4-triazine 1-Oxide (15). A mixture of 3-methoxy-1,2,4-triazine 1-oxide (**13**) (650 mg, 5.0 mmol) and 10 mL of 5% $MeNH_2$ in MeOH was heated in a sealed tube at 90 °C for 1 h. After cooling, 500 mg of **15** was collected by filtration. Additional product (150 mg) could be obtained by evaporating the mother liquor and extracting the residue with 10 mL of $CHCl_3$. An analytical sample was prepared by sublimation at 105–110 °C/0.01 Torr.

3-Chloro-1,2,4-triazine 1-Oxide (18). To 6 mL (30 mmol) of warm 5 N HCl was added 330 mg (2.9 mmol) of 3-amino-1,2,4-triazine 1-oxide (**14**). The stirred reaction mixture was cooled to 5 °C and 414 mg (6.0 mmol) of $NaNO_2$ dissolved in 2 mL of H_2O was added dropwise (5 min). After 5 min of additional stirring, 10 mL of $CHCl_3$ was added and the mixture was allowed to come to room temperature. The layers were separated and the aqueous portion was extracted with additional $CHCl_3$ (3 × 10 mL). The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was chromatographed on alumina (grade III) with $CHCl_3$ to give 90 mg of **18** (24%). An analytical sample was prepared by sublimation at 30–40 °C/0.01 Torr.

Reaction of 3-Amino-1,2,4-triazine 1-Oxide (14) with HNO_2/HBr. To 448 mg (4.0 mmol) of **14** was added 6 mL (27 mmol) of 4.5 N HBr. The clear solution was cooled to 5 °C and 552 mg (8.0 mmol) of $NaNO_2$ in 2 mL of H_2O was added dropwise (5 min). After 5 min of stirring, 10 mL of $CHCl_3$ was added. The reaction was worked up as above to give 120 mg of **19** (17%) and 50 mg of **20** (5%). Both **19** and **20** were further purified by vacuum sublimation.

3-Methoxy-6-bromo-1,2,4-triazine 1-Oxide (21). To 127 mg (1.0 mmol) of 3-methoxy-1,2,4-triazine 1-oxide (**13**) dissolved in 40 mL of CH_2Cl_2 was added 2 mL of 2.2 M Br_2 in CCl_4 and 140 mg (1.0 mmol) of annydrous K_2CO_3. The mixture was stirred at room temperature overnight and then heated at 40–50 °C for 1.0 h. The mixture was filtered and the filtrate evaporated in vacuo. The residue was chromatographed on neutral alumina (grade III) with 50% $CHCl_3/C_6H_6$ to give 100–120 mg of **21** (50–60%). An analytical sample was prepared by sublimation at 60 °C/0.01 Torr.

6-Bromo-3-amino-1,2,4-triazine 1-Oxide (22). To 222 mg (2.0 mmol) of 3-amino-1,2,4-triazine 1-oxide (**14**) dissolved in 150 mL of CH_2Cl_2 and 25 mL of reagent grade CH_3CN was added 3 mL of 2.2 M Br_2 (6.6 mmol) in CCl_4. The mixture was stirred at room temperature for 0.5 h and 420 mg (30 mmol) of anhydrous K_2CO_3 was added. After it was stirred for an additional 0.5 h, the mixture was filtered and evaporated in vacuo. The residue was triturated with 10 mL of CH_2Cl_2 and filtered to give 380 mg of **22** (100%). Compound **22** was further purified by sublimation at 130 °C/0.01 Torr.

6-Bromo-3-methylamino-1,2,4-triazine 1-Oxide (23). To 126 mg (1.0 mmol) of 3-methylamino-1,2,4-triazine 1-oxide (**15**) dissolved in 40 mL of 50% CH_2Cl_2/CCl_4 was added 1 mL of 2.2 M Br_2 (2.2 mmol) in CCl_4, followed by 0.2 mL (1.4 mmol) of Et_3N in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature overnight and then evaporated in vacuo, and the residue was chromatographed on alumina (grade III) with $CHCl_3$. Sublimation of the major component at 110 °C/0.01 Torr gave 142 mg of **23** (70%).

6-Bromo-3-dimethylamino-1,2,4-triazine 1-Oxide (24). To 140 mg (1.0 mmol) of 3-dimethylamino-1,2,4-triazine 1-oxide (**16**) in 30 mL of CCl_4 was added 1.5 mL of 2.2 M Br_2 (3.3 mmol) in CCl_4 followed by 0.2 mL (1.4 mmol) of Et_3N in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature for 0.5 h and then evaporated in vacuo. The residue was chromatographed on neutral alumina (grade III) with 50% $C_6H_6/CHCl_3$. The major component was sublimed at 110 °C/0.01 Torr to give 165 mg of **24** (77%).

6-Bromo-3-dimethylamino-1,2,4-triazine (26). To 310 mg (2.5 mmol) of 3-dimethylamino-1,2,4-triazine (**14**) dissolved in 30 mL of CCl_4 was added 2.5 mL of 2 M Br_2 (5.0 mmol) in CCl_4 followed by 0.4 mL (3 mmol) of Et_3N. After stirring overnight, the mixture was evaporated in vacuo. The residue was chromatographed on alumina (grade III) with 50% $C_6H_6/CHCl_3$. The major component was sublimed at 40 °C/0.01 Torr to give 252 mg of **26** (50%).

Acknowledgment. We thank Diamond Shamrock Corp. for partial support of this work.

Registry No.—**1**, 61177-95-5; **7**, 61178-04-9; **13**, 27531-67-5; **14**, 61178-11-8; **16**, 61178-07-2; methyl chloroformate, 79-22-1; ethyl chloroformate, 541-41-3; 3-bromo-1,2,4-triazine 2-oxide, 61178-02-7; methylamine, 74-89-5; methyl mercaptan, 74-93-1; methanol, 67-56-1; ethanol, 64-17-5; 2-propanol, 67-63-0.

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(7) T. K. Chen, Ph.D. Dissertation, Ohio University, 1971 (*Diss. Abstr.*, 156 (1971)).
(8) It should be mentioned that the relaxation time of C_6 in the bromo derivatives is extremely long. All ^{13}C NMR spectra were taken as 1.5 M solutions in $CDCl_3$. A Perkin-Elmer R-26 instrument was used.

2,4-Diaryl-3-dimethylaminothietane 1,1-Dioxides. Synthesis, Configuration, and Stability[1]

Frank S. Abbott,* James E. Coates, and Katsuji Haya

Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, V6T 1W5, Canada

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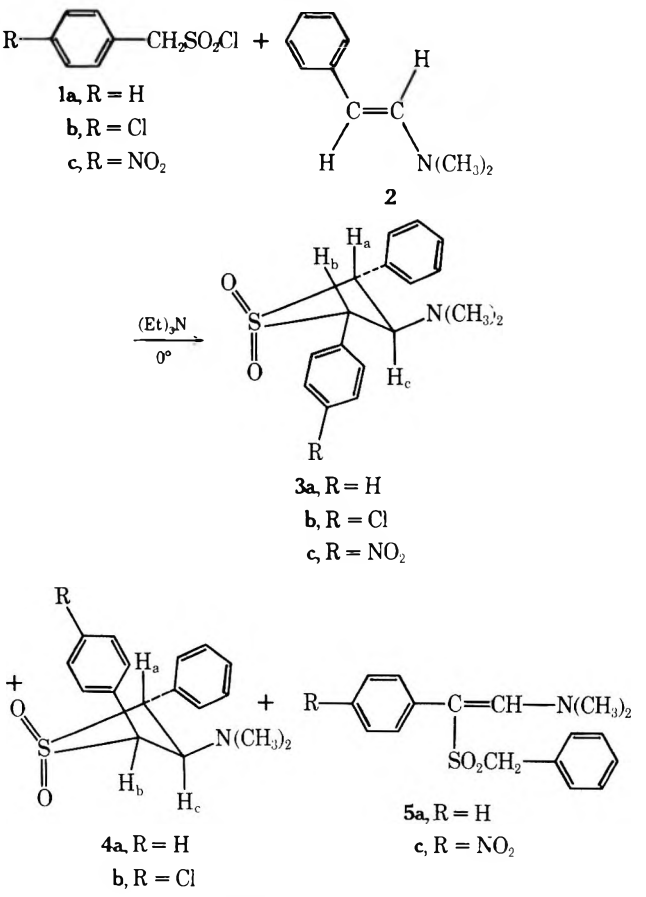
Reaction of *trans*-β-dimethylaminostyrene (**2**) with phenylsulfene gave the thietane 1,1-dioxide isomers **3a** and **4a**, and the acyclic isomer **5a**. Configurations were assigned to **3a** and **4a** on the basis of their NMR spectra and relative stabilities. Isomer **4a** was unstable and isomerized to a mixture of **3a** and **5a** on treatment with triethylamine. When heated in ethanol, **4a** gave a number of decomposition products the nature of which confirmed the reversibility of the cycloaddition reaction. The isomer ratios for cyclic products were sensitive to solvent change and supported a dipolar intermediate for the cyclization. Reaction of **2** with *p*-chlorophenylsulfene gave only two cycloadducts (**3b** and **4b**) which indicated that the configuration of **2** was maintained during cyclization. A substituent effect is evident in the cyclization with *p*-nitrophenylsulfene and in the stability of the cyclic product.

As part of an investigation of thietane 1,1-dioxide derivatives for analgetic activity, certain intermediary 2,4-diaryl-3-dimethylaminothietane 1,1-dioxides (**3** and **4**) were prepared. We now wish to report on the chemistry of these intermediates.

It is well established that sulfenes,[2] generated by base-induced dehydrohalogenation of sulfonyl halides, react with enamines to afford 3-aminothietane 1,1-dioxides and, in some instances, acyclic substitution products.[3] In the present work, the reaction of phenylmethanesulfonyl chloride (**1a**) with *trans*-β-dimethylaminostyrene (**2**) in the presence of triethylamine gave a mixture of the thietane 1,1-dioxide isomers **3a** and **4a**, and the acyclic species **5a** in high yield (Scheme I). The ratio of the three isomers in the crude product was conveniently determined from the integrals for the *N*-methyl protons in the NMR spectrum. Isomer separation was achieved by fractional crystallization.

Scheme I



Isomer **3a** was assigned a cis configuration (phenyls cis to each other and trans to the dimethylamino group) on the basis of its NMR spectrum which showed H_a and H_b as a doublet, and H_c as a triplet (J = 9 Hz). The magnitude of the coupling constant was explicable in terms of a folded thietane 1,1-dioxide ring[5] on which all three ring substituents occupy pseudoequatorial positions and thus axial–axial coupling of vicinal H. That isomer **4a** possessed a trans configuration was evident from the magnetic nonequivalence of H_a and H_b which were seen as a pair of doublets in the 100-MHz spectrum. The doublets were further split as a consequence of ^4J coupling (J_{ab} = 1 Hz).[5e] The shift to lower field (H_b) is consistent with the observation that equatorial protons of 2-halogeno-3-morpholinothietane 1,1-dioxides always appear at lower field than axial protons.[6a] A nonambigous assignment of conformation to **4a** using NMR spectroscopy was not possible because of the equivalency of the vicinal coupling constants $J_{ac} = J_{bc}$ = 9.4 Hz).[5d] However, it is likely that the conformation shown in Scheme I is preferred since inversion gives a species in which both a phenyl ring and the dimethylamino group are pseudoaxial. Models indicate that severe nonbonded interactions between the dimethylamino group and sulfonyl oxygen would ensue in the inverted conformation. The trans phenyl configuration assigned to **4a** was further supported by the upfield shift of the *N*-methyl protons (δ 1.93 vs. δ 2.10 in **3a**) which is attributed to the shielding of these protons by the phenyl ring cis to the dimethylamino group.

The NMR data for the cyclic isomers (**3b, 4b**) obtained from the reaction of *p*-chlorophenylmethanesulfonyl chloride and **2** correlates well with that of **3a** and **4a** and readily allows determination of configuration. That only two cyclic isomers were formed in the reaction of **2** and *p*-chlorophenylsulfene was in agreement with the few reports in the literature to the effect that the configuration of trans acyclic enamines is maintained in the sulfene cycloadducts.[6a,11,12] It followed therefore that the *p*-chlorophenyl group in **4b** was cis to the dimethylamino moiety. Chemical evidence supporting this configurational assignment was obtained by examination of the thiete products obtained from the amine oxide elimination reaction on cyclic isomers **3b** and **4b**.[13]

In the case of *p*-nitrophenylsulfene cyclization with enamine (**2**) where only one cyclic product was obtained, a cis pseudoequatorial arrangement of aromatic groups was assigned. Considering the instability of the trans isomers **4a** and **4b** together with solvent effects on isomer ratios (see below) the most stable isomer **3c** is expected. In the NMR spectrum the *N*-methyl protons of **3c** appear at δ 2.14 in accord with values observed for cis isomers **3a** and **3b**. H_a and H_b in **3c** although formally nonequivalent surprisingly appear as a doublet.

Table I. Effect of Solvent on the Composition of Isomers from the Reaction of *trans*-β-Dimethylaminostyrene with Sulfenes Derived from Sulfonyl Chlorides (1a,b,c)

	Ratio, %							
	(R = H)[a,b]			(R = Cl)			(R = NO_2)[a]	
Solvent	*c*	*t*	Acyclic	*c*	*t*	Acyclic	c	acyclic
Et_2O–THF	15	82	3				98	2
$CHCl_3$	19	74	7	20	70	10	89	11
CH_3CN	35	60	5	40	55	5	72	28
CH_3CN–H_2O[c]	36	47	17				67	33

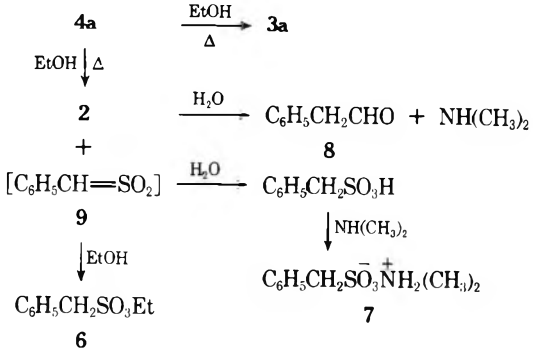
[a] Reactions run under identical conditions using the same quantities of reactants. [b] Essentially identical results were obtained when the reaction was repeated. [c] H_2O at twice the molar equivalent of enamine was added to flask just prior to initiating the addition of sulfonyl chloride.

Acyclic isomer **5a** was readily identified from IR and NMR spectra. Spectroscopic evidence was obtained for an acyclic isomer analogous to **5a** from the reaction of enamine and *p*-chlorophenylsulfene but the compound was not isolated. The corresponding acyclic isomer **5c** is bright yellow. Comparison of the UV spectrum of **5c** (λ_{max} 250 (ε 18 700) and 271 nm (ε 19 700) with that of **5a** (λ_{max} 253 nm (ε 15 800)) indicated that the nitro group was attached to the styryl chromophore in **5c.** This required that **5c** arise from a cycloadduct rather than by direct sulfonylation of **2.**

The observation that considerable decomposition occurred when the crude product was crystallized from hot hexane–ethanol prompted an investigation of the relative stability of **3a** and **4a.** After refluxing a sample of pure cis isomer **3a** in ethanol for 1 h, 81% remained unchanged. When trans isomer **4a** was treated in the same manner, complete decomposition occurred. NMR analysis revealed that approximately 57% of the decomposition products from **4a** consisted of **2** (28%), **3a** (11%), and ethyl phenylmethanesulfonate (**6,** 61%). Part of the remaining 43% was apparently composed of sulfonic acid salts. NMR analysis of the water soluble products obtained by refluxing a sample of **4a** in ethanol for 12 h showed that 67% of the trans isomer had been converted to dimethylammonium phenylmethanesulfonate (**7**). When an ethanol solution of **4a** was analyzed by VPC with the injection port at 280 °C, peaks attributable to **2** and **6** and a peak having the same retention time as phenylacetaldehyde (**8**) were observed. Under the same conditions, **3a** gave only minor, unidentified peaks. These results confirm the reversibility of the cycloaddition reaction. The cycloaddends, **2** and **9,** are regenerated depending on the relative stability of the cycloadduct (Scheme II). Reaction of **9** with ethanol accounted for the sulfonate ester **6,** and reaction with water present in the ethanol to give a sulfonic acid and subsequent protonation of dimethylamine liberated by hydrolysis of **2** explained the formation of **7.** Hamid and Trippett[7] have also presented evidence that the cycloaddition of sulfenes to enamines is, in some cases at least, reversible.

To further study the relative stability of **3a** and **4a,** a solution of crude material in acetonitrile (consisting of 19% **3a,** 74% **4a,** and 7% **5a**) and an equimolar amount of triethylamine hydrochloride was treated with triethylamine at room temperature for 4 days. NMR analysis of the product indicated that 92% of the starting material was accounted for and of this 64% was **3a,** 8% **4a,** and 28% **5a.** The decisive conversion of **4a** to **3a** is somewhat analogous to the base-induced epimerization of *trans*-2,4-diphenylthietane 1,1-dioxide to the cis isomer reported by Dodson and co-workers[5b] and confirms the configurational assignments made for **3a** and **4a.** Truce reported a slow isomerization of the least stable isomer of 2,2-dimethyl-3-dimethylamino-4-phenylthietane 1,1-dioxide in acetonitrile containing triethylamine to the more stable trans isomer (phenyl trans to amino moiety).[6b] It was also apparent from the present results that some cyclic material underwent

Scheme II



ring opening to give **5a.** Alkali hydroxide-catalyzed cleavage of thietane 1,1-dioxides to the corresponding acyclic isomers is known[4,8,9] and certain 2-halogeno-3-morpholinothietane 1,1-dioxides ring cleave to acyclics with refluxing dioxane and triethylamine.[6c]

The relative stabilities of the cyclic isomers of 2-(4-chlorophenyl)-3-dimethylamino-4-phenylthietane 1,1-dioxide are quite evident. The trans (**4b**) decomposed on attempted recrystallizations from hot solvent while cis isomer (**3b**) could be readily crystallized. This apparent substituent effect on stability is even more evident with the single cis *p*-nitro analogue. Pure **3c** dissolved in acetonitrile isomerized spontaneously at room temperature to give **5c.** Adding triethylamine to a solution of **3c** results in the immediate formation of a dark reddish color. In addition to the formation of **5c** some crude water-soluble product could be recovered which from the IR was apparently salts of *p*-nitrophenylsulfonic acid.

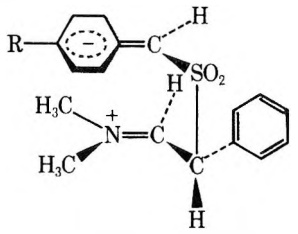
The ratio of isomers in the products from these cyclizations was found to vary with the solvent used and a brief study of these effects was undertaken. In most instances the yields were high (>90%). Isomer compositions of the crude products were determined by NMR. Solvents employed and the results are recorded in Table I.

The predominant formation of the least stable trans isomers in the cyclizations of phenyl- and *p*-chlorophenyl sulfenes is not unusual. Similar findings for sulfene–enamine reactions have been reported.[6a,b] As solvent polarity is increased the more stable cis isomers were formed in increasing amounts suggesting a dipolar intermediate may be involved in these cyclizations.[6d]

Before considering this possibility it was important to determine whether solvent effects were reaction mode related or simply a result of isomerization and ring opening of lesser stable trans products which could increase with rising solvent polarity.[10] In the instance of phenylsulfene cyclization with β-dimethylaminostyrene this is not the case and several experiments illustrated this. Using acetonitrile as solvent the relative composition of isomers **3a, 4a,** and **5a** was the same whether reactants were dumped together with workup in 15

min or if sulfonyl chloride was added during 1 h and the reaction stirred a further 15 h (ice–H_2O conditions). If post-isomerization were operative the longer addition and reaction time should result in greater proportions of cis and perhaps acyclic isomer since trans encounters excess triethylamine. Pure trans isomer was subjected to Et_3N and Et_3N·HCl under the usual reaction conditions in the solvents THF–Et_2O and acetonitrile. Upon workup (98% recoveries) no cis or acyclic isomer could be detected in the NMR of either of the crude products. Finally pure trans isomer (half the molar equivalent of reactants in a typical reaction) was dissolved in CH_3CN–H_2O (see Table I) and the usual cyclization carried out using half the normal quantities of reactants. NMR analysis of the product (18% **3a**, 75% **4a**, 7% **5a**) showed that added trans isomer acted as a simple diluent with no degradation.

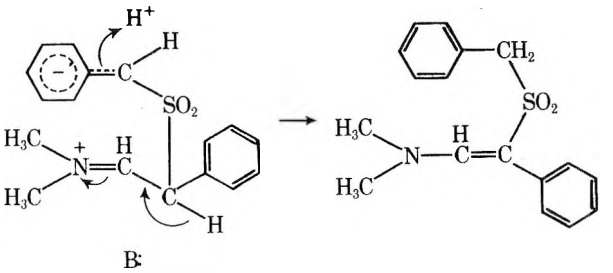
Mechanistic possibilities for the cyclization of a variety of sulfenes to enamines have recently been discussed in the literature.[6b] Both concerted and stepwise processes were considered but experimental data do not as yet provide the answer concerning a definitive mechanism. Our own data tend to support the zwitterionic intermediate concept at least for the sulfene-enamine cyclizations reported here. Electrostatic attractions of the delocalized charges in the intermediate favor the formation of the trans product as observed when R = H



or Cl. As solvent polarity increases a tighter solvation effect on the dipolar species would allow greater product discrimination. Hence the formation of the more thermodynamically stable cis isomer is increased in the polar acetonitrile solvent.

The formation of a single cis isomer when R = NO_2 (*p*-nitrophenyl trans to amino moiety) has similarily been observed by Truce and Rach.[6b] They suggested a possible substituent effect which through greater carbanion stabilization or more efficient charge dispersal, decreasing electrostatic attractions would lead to the more stable cyclic product. Rapid isomerization of least stable isomer under reaction conditions could not be discounted and in our example may well be true considering the low stability of even the cis isomer (**3c**). It is surprising, however, that no trans was detected in the Et_2O–THF reaction (Table I). The yield was high with little formation of acyclic isomer partly because of the low solubility of **3c** which precipitates readily once formed. Considering the physical properties of the trans isomers **4a** and **4b** (decreased solubilities compared to cis isomers) at least some trans isomer corresponding to **3c** was expected particularly if it was the preferred isomer. We therefore tend to interpret the results of the *p*-nitrosulfene reaction as a substituent effect with respect to a zwitterionic mechanism.

The existence of a zwitterionic intermediate in these cycloadditions suggests the possibility of increased formation of acyclic product as solvent polarity increases.[3a] This was not observed (Table I, R = H, Cl) in our study and is consistent with previous reports for sulfene–enamine cycloadditions.[3a] The addition of a small amount of H_2O to acetonitrile was an attempt to trap intermediate by providing a ready proton source. The overall yield of products (**3a, 4a, 5a**) was slightly reduced since the H_2O present can compete for reaction with the sulfene. The proportion of acyclic isomer **5a** was found to be significantly increased (Table I). While apparently successful, this unfortunately represents only one example.



It was thought that *p*-nitrophenylsulfene cyclization should have given further evidence of this nature. A substituent effect, if operative, by stabilizing or prolonging the lifetime of the intermediate would enhance acyclic isomer formation. When the reaction was run in CH_3CN–H_2O no evidence for any acyclic isomer other than **5c** (formed from ring opening of cyclic isomer) could be detected. Adding pure **3c** to CH_3CN–H_2O under the reaction conditions gave the same proportion of acyclic (**5c**) as obtained in the normal cycloaddition reaction.

Experimental Section

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Beckman IR-10 spectrophotometer using potassium bromide wafers unless otherwise stated. Ultraviolet spectra were determined in acetonitrile with a Bausch and Lomb Model 505 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60, T-60 or XL-100 spectrometer, using tetramethylsilane as the internal standard; unless otherwise stated, the solvent was deuteriochloroform and the concentration of solutions was ca. 10%. Vapor phase chromatography was carried out on a Micro-Tek gas chromatograph Model MT-200 with flame ionization detector using a 6 ft × $^5/_{32}$ in. (i.d.) stainless steel column packed with 5% SE-30 on Chromport (70–80 mesh); conditions are specified. Microanalyses were performed by Alfred Bernhardt Mikronanalytisches Laboratorium, 5251 Elbach uber Engelskirchen, Fritz-Pregl-Strasse 14-16, West Germany.

Materials. Commercial anhydrous diethyl ether was dried using sodium wire. Dry acetonitrile was obtained by distilling reagent grade solvent from phosphorus pentoxide. Anhydrous tetrahydrofuran was prepared by distilling solvent of low peroxide content from lithium aluminum hydride. Dry, ethanol-free chloroform was prepared according to the sulfuric acid procedure of Vogel.[14]

The preparation of β-dimethylaminostyrene (**2**) has previously been described.[4] The NMR spectra of solution and neat samples showed the presence of only one geometric isomer which was assigned a trans configuration on the basis of the magnitude of the coupling constant for the vinyl protons (J = 14 Hz). This was in agreement with the assignment made by Caserio and co-workers.[15] VPC analysis of an acetone solution of **2** with the nitrogen flow at 54 mL/min and the injection port, oven, and detector at 255, 150, and 243 °C, respectively, gave one peak, retention time 2.5 min.

Phenylmethanesulfonyl chlorides were prepared according to literature methods.[16,17] Triethylamine was distilled from KOH pellets and stored over the same.

General Procedure for the Reaction of *trans*-β-Dimethylaminostyrene (2) with Arylmethanesulfonyl Chlorides. A stirred solution of 1.0 equiv of **2** and 1.0 equiv of triethylamine in solvent was cooled in ice water. A dry nitrogen atmosphere was provided and the system was protected from moisture. Arylmethanesulfonyl chloride (1.0 equiv) dissolved in solvent was added dropwise over a period of 15 min. After stirring for an additional 45 min the reaction mixture was evaporated under vacuum with the aid of a lukewarm water bath. The resulting residue was dissolved in $CHCl_3$ and extracted with several equal portions of water to remove the triethylamine hydrochloride. Evaporation of the dried (Na_2SO_4) organic layer under reduced pressure gave the crude product.

***cis*-2,4-Diphenyl-3-dimethylaminothietane 1,1-Dioxide (3a).** Under the general conditions of the reaction, using 100 mL of acetonitrile as solvent, **1a** (12.95 g, 0.069 mol) and **2** (10.00 g, 0.068 mol) afforded 20.19 g (98.6%) of crude solid.[18] Crystallization from hexane–ethanol followed by three recrystallizations from hexane–methyl ethyl ketone gave **3a** as transparent plates, mp 137–138 °C dec; IR 1320, 1133 cm^{-1} (sulfone); NMR δ 7.70–7.23 (m, 10, phenyls), 5.28 (d, 2, J = 9 Hz, H_a and H_b), 3.68 (t, 1, J = 9 Hz, H_c), and 2.10 (s, 6, N-methyls).

Anal. Calcd for $C_{17}H_{19}NO_2S$ (301.41): C, 67.74; H, 6.35, N, 4.65. Found: C, 67.91; H, 6.46; N, 4.64.

***trans*-2,4-Diphenyl-3-dimethylaminothietane 1,1-Dioxide (4a).**[4] Under the general conditions, 12.95 g (0.069 mol) of **1a** dissolved in 126 mL of 1:1 THF–Et_2O was reacted with 10.00 g (0.068 mol) of **2** in 100 mL of Et_2O to give 19.80 g (96.7%) of crude yellow solid.[18] Crystallization from hexane–methyl ethyl ketone gave **4a** as white, fluffy needles, mp 112–113 °C dec. After two recrystallizations, the mp was 114.5–115.5 °C dec (lit.[4] 109 °C); IR 1320, 1160 cm^{-1} (sulfone); NMR (agreed with lit.[4]) δ 7.68–7.22 (m, 10, phenyls), 5.43 (broad t, 2, H_a and H_b), 3.68 (t, 1, J = 9 Hz, H_c), and 1.93 (s, 5, N-methyls); NMR (100 MHz) δ 5.494 (m, 1, J_{bc} = 9.4 Hz, J_{ba} = 1 Hz, H_b), 5.304 (m, 1, J_{ac} = 9.4 Hz, J_{ab} = 1 Hz, H_a).

Benzyl 1-Phenyl-2-dimethylaminoethenyl Sulfone (5a). The first mother liquor from the isolation of **3a** was cooled in a dry ice box overnight which caused an off-white solid to precipitate. Evaporation of the supernatant gave a brown oil which was heated with hexane and dissolved with a minimum amount of ethanol. Cooling the solution in a refrigerator gave **5a** as colorless crystals which were recrystallized from methyl ethyl ketone to give transparent plates, mp 130–131 °C; IR 1630 (enamine), 1276, 1125 cm^{-1} (sulfone); NMR δ 7.41 (d, 10, phenyls), 7.00 (s, 1, vinyl), 4.05 (s, 2, benzyl), and 2.60 (s, 6, N-methyls); UV_{max} 253 nm (ϵ 15 800).

Anal. Calcd for $C_{17}H_{19}NO_2S$ (301.41): C, 67.74; H, 6.35; N, 4.65. Found: C, 67.78; H, 6.34; N, 4.76.

Decomposition of *trans*-2,4-Diphenyl-3-dimethylaminothietane 1,1-Dioxide (4a) in Ethanol. A solution of 233 mg of pure **4a** in 50 mL of ethanol was heated at reflux for 1 h. Evaporation under reduced pressure gave a yellow, mobile oil which possessed an odor similar to that of **2**. A strong band at 1640 cm^{-1} in the IR spectrum (neat) supported the presence of **2** and strong bands at 1350, 1170, and 920 cm^{-1} suggested the presence of a sulfonic acid ester. In the NMR spectrum signals attributable to **2**, **3a**, and ethyl phenylmethanesulfonate (**6**) were apparent by comparison with spectra of authentic samples. No absorption due to the starting material **4a** was observed. The three compounds accounted for approximately 57% of the oil of which 28% was **2**, 11% **3a** and 61% **6**. A major peak at δ 2.28 was unassigned.

A solution of 467 mg (1.55 mmol) of pure **4a** in 100 mL of ethanol was heated at reflux for 12 h. Evaporation under reduced pressure gave a viscous oil with an aldehydic odor. The oil was dissolved in 30 mL of $CHCl_3$ and extracted with three 20-mL portions of water. Evaporation of the pooled aqueous extracts in vacuo afforded 300 mg of white, gummy solid. NMR analysis indicated that 75% of this material (225 mg, 1.04 mmol) was dimethylammonium phenylmethanesulfonate (**7**). Three crystallizations from hexane–acetone gave transparent needles, mp 116–118 °C. A mixture melting point with an authentic sample of **7** was not depressed and the IR spectra were superimposable.

VPC analysis of an ethanol solution of pure **4a** with the nitrogen flow at 55 mL/min, and the injection port, oven, and detector at 280, 140, and 250 °C, respectively, gave four peaks excluding that of the solvent. Three of the peaks were identified by coinjection with authentic samples as phenylacetaldehyde 8 (1.4 min), **2** (4.4 min) and **6** (7.8 min).

Ethyl Phenylmethanesulfonate (6).[19] To a refluxed solution of 5.06 g (0.050 mol) of triethylamine in 100 mL of absolute ethanol was added 9.53 g (0.050 mol) of **1a** dissolved in 30 mL of CH_3CN dropwise over a period of 1 h. The system was protected from moisture with a drying tube. After refluxing for another 2 h the reaction was evaporated under reduced pressure. The resulting residue was dissolved in 50 mL of $CHCl_3$ and extracted with three 50-mL portions of water. Evaporation of the dried ($MgSO_4$) organic layer gave 4.29 g (50%) of crude product (**6**) as a pale yellow oil. Double distillation afforded an analytical sample of **6** as a colorless liquid, bp 87 °C (0.02 mm) (lit.[19] 129–130 °C (0.04 mm)); IR (neat) 1350, 1170, 920 cm^{-1} (sulfonic acid ester); NMR δ 7.32 (s, 5, phenyl), 4.32 (s, 2, benzyl), 4.11 (q, 2, J = 7 Hz, methylene), and 1.25 (t, 3, J = 7 Hz, methyl).

Anal. Calcd for $C_9H_{12}O_3S$ (200.26): C, 53.98; H, 6.04; S, 16.01. Found: C, 53.88; H, 6.15; S, 16.16.

Dimethylammonium Phenylmethanesulfonate (7). Phenylmethanesulfonyl chloride (**1a**) (2.0 g, 0.011 mol) was heated in 150 mL of boiling water for 30 min to give a homogeneous solution (acid to indicator paper). The solution was reduced to a volume of about 30 mL by evaporation under vacuum and then treated with excess dimethylamine. The remaining water was evaporated to give a pale yellow oil which solidified when washed with acetone. Three crystallizations from hexane–acetone gave 1.1 g (46%) of **7** as transparent needles, mp 116–118 °C; IR 3180–2820, 2475 (ammonium band), 1210, 1052 cm^{-1} (sulfonic acid); NMR δ 8.37–7.72 (band, 2, NH_2), 7.52–7.20 (m, 5, phenyl), 4.05 (s, 2, benzyl), and 2.26 (t, 6, J = 5.5 Hz, N-methyls).

Anal. Calcd for $C_9H_{15}NO_3S$ (217.28): C, 49.75; H, 6.96; N, 6.45. Found: C, 49.68; H, 7.38; N, 6.39.

Isomerization of *trans*-2,4-Diphenyl-3-dimethylaminothietane 1,1-Dioxide (4a). Crude product which was essentially pure in the three isomers and consisted of 19% **3a**, 74% **4a**, and 7% **5a** (NMR analysis) was used. To a stirred solution of 3.01 g (0.010 mol) of crude product and 1.38 g (0.010 mol) of triethylamine hydrochloride in 20 mL of dry CH_3CN and 10 mL of dry $CHCl_3$ which was protected from moisture were added two drops of triethylamine. The isomerization was followed by removing samples at intervals and observing the increase in intensity of the enamine band (1630 cm^{-1}) of **5a**. The greatest increase occurred during the first day and no change was detectable at the end of the third day. The solution was allowed to sit for another 24 h and then evaporated in vacuo to give a residue which was dissolved in 20 mL of $CHCl_3$ and extracted with three 20-mL portions of water. Evaporation of the dried (Na_2SO_4) organic layer under reduced pressure gave a yellow solid. NMR analysis of this material indicated that 92% was accounted for by the three isomers of which 64% was **3a**, 8% **4a**, and 28% **5a**.

***trans*-2-(4-Chlorophenyl)-3-dimethylamino-4-phenylthietane 1,1-Dioxide (4b).** Under the conditions of the general reaction, 4.50 g (0.020 mol) of **1b** in 38 mL of $CHCl_3$ was added dropwise over a period of 0.5 h to 2.94 g (0.02 mole) of **2** and 2.02 g (0.020 mole) of triethylamine in 30 mL of $CHCl_3$. After 8 h, the white precipitate (**4b**, 3.79 g, 56%) was collected by suction filtration and washed with $CHCl_3$. Extensive decomposition occurred when crystallization of crude **4b** was attempted. Washing several times with $CHCl_3$ gave an analytical sample, mp 154 °C dec;[20] IR 1323, 1164 cm^{-1} (sulfone); NMR (≈2%) δ 7.69–7.40 (m, 9, aromatics), 5.49 (d, 1, J = 9.5 Hz, H_b), 5.31 (d, 1, J = 9.5 Hz, H_a), 3.69 (t, 1, J = 9.5 Hz, H_c), and 1.96 (s, 5, N-methyls).

Anal. Calcd for $C_{17}H_{18}ClNO_2S$ (335.85): C, 60.80; H, 5.40; N, 4.17. Found: C, 60.63; H, 5.20; N, 4.18.

***cis*-2-(4-Chlorophenyl)-3-dimethylamino-4-phenylthietane 1,1-Dioxide (3b).** Evaporation under reduced pressure of the filtrate from the reaction described for **4b** gave a residue which was redissolved in 25 mL of $CHCl_3$ and extracted with four 10-mL portions of water. Evaporation of the dried (Na_2SO_4) organic layer followed by washing of the resulting residue with Et_2O yielded a yellow solid (0.82 g, 12%) which consisted of 35% **3b** and 65% **4b** (NMR analysis[21]). Evaporation of the Et_2O washings followed by washing of the residue with Et_2O afforded 0.30 g (4%) of yellow solid. Crystallization of this latter material from hexane–ethanol gave the cis isomer as white needles, mp 145–146 °C dec; IR 1333, 1164 cm^{-1} (sulfone); NMR δ 7.63–7.26 (m, 9, aromatics), 5.25 (d, 1, J = 9 Hz, H_a[22]), 5.22 (d, 1, J = 9 Hz, H_b), 3.57 (t, 1, J = 9 Hz, H_c), and 2.08 (s, 6, N-methyls).

Anal. Calcd for $C_{17}H_{18}ClNO_2S$ (335.85): C, 60.80; H, 5.40; N, 4.17. Found: C, 60.88; H, 5.34; N, 4.20.

***cis*-2-(4-Nitrophenyl)-3-dimethylamino-4-phenylthietane 1,1-Dioxide (3c).** Under the general reaction conditions *p*-nitrophenylmethanesulfonyl chloride 2.36 g (0.01 M) in 25 mL of CH_3CN was added to 1.47 g (0.01 M) of **2** and 1.01 g (0.01 M) of Et_3N in 25 mL of CH_3CN. Cold ether (200 mL) is added to precipitate Et_3N·HCl. After filtration the filtrate was evaporated to give an orangish residue. Addition of ether causes product to precipitate. Upon filtering and evaporation further product is obtained on treating oily residue with ether and hexane.[18] Crystallization from hexane–methyl ethyl ketone gave **3c** as pale yellow prisms, mp 130–131 °C dec; IR 1524, 1354 (nitro group), 1336, 1324, 1160, 1138 cm^{-1} (sulfone); NMR δ 8.47–8.20 (m, 2, protons ortho to nitro group), 7.87–7.60 (m, 2, protons meta to nitro group), 7.60–7.33 (m, 5, phenyl), 5.36 (d, 2, J = 9 Hz, H_a and H_b), 3.70 (t, 1, J = 9 Hz, H_c), and 2.14 (s, 6, N-methyls).

Anal. Calcd for $C_{17}H_{18}N_2O_4S$ (346.40): C, 58.95; H, 5.24; N, 8.09. Found: C, 60.14; H, 5.12; N, 7.99.

Although the analysis was not satisfactory for carbon, the results of the analyses performed on the thiete 1,1-dioxide derived from **3c** were satisfactory.[13]

With Et_2O–THF as solvent further addition of Et_2O when reaction is complete results in precipitation of most of the product.[18] Et_3N·HCl is removed by triturating solid with H_2O. With $CHCl_3$ as solvent Et_3N·HCl is removed by extracting $CHCl_3$ with H_2O. Evaporation of the dried (Na_2SO_4) $CHCl_3$ leaves a dark orange-red oil which on ether treatment provides solid crude product.[18]

After sitting at room temperature for 2 h, a solution of 100 mg of **3c** in 5 mL of CH_3CN had turned bright orange. NMR analysis of the oil obtained by evaporating the solution under reduced pressure after 43 h indicated that 87% was accounted for by the isomers **3c** and **5c** of which 34% was **3c** and 76% **5c**.

Benzyl 1-(4-Nitrophenyl)-2-dimethylaminoethenyl Sulfone (5c). A reddish-black oil was obtained when the Et_2O filtrate from the synthesis of **3c** was evaporated under reduced pressure. Washing the oil with Et_2O caused 1.7 g (6.5%) of yellow solid to separate which was found to consist of 36% **3c** and 61% **5c** (NMR analysis). Two crystallizations from 1-butanol gave **5c** as bright yellow, flat needles, mp 165.5–166.5°; IR 1625 (enamine), 1530, 1355 (nitro group), 1297, 1135, 1115 cm^{-1} (sulfone); NMR δ 8.30–8.03 (m, 2, protons ortho to nitro group), 7.60–7.30 (m, 7, protons meta to nitro group and phenyl protons), 7.11 (s, 1, vinyl), 4.13 (s, 2, benzyl), and 2.67 (s, 6, N-methyls); UV_{max} 250 (ϵ 18 700) and 271 nm (ϵ 19 700).

Anal. Calcd for $C_{17}H_{18}N_2O_4S$ (346.40): C, 58.95; H, 5.24; N, 8.09. Found: C, 58.99; H, 5.09; N, 8.22.

Acknowledgments. This work was supported in part by Medical Research Council of Canada Grant MA-3044.

Registry No.—**1a**, 1939-99-7; **1b**, 6966-45-6; **1c**, 4025-75-6; **2**, 14846-39-0; **3a**, 63268-45-1; **3b**, 63231-37-8; **3c**, 63231-38-9; **4a**, 63268-46-2; **4b**, 63268-47-3; **5a**, 63231-34-5; **5c**, 63231-35-6; **6**, 42454-54-6; **7**, 63231-36-7.

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2,4-Diarylthiete 1,1-Dioxides. Synthesis, Thermolysis Studies, and Addition Reactions

James E. Coates and Frank S. Abbott*

Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C. V6T 1W5 Canada

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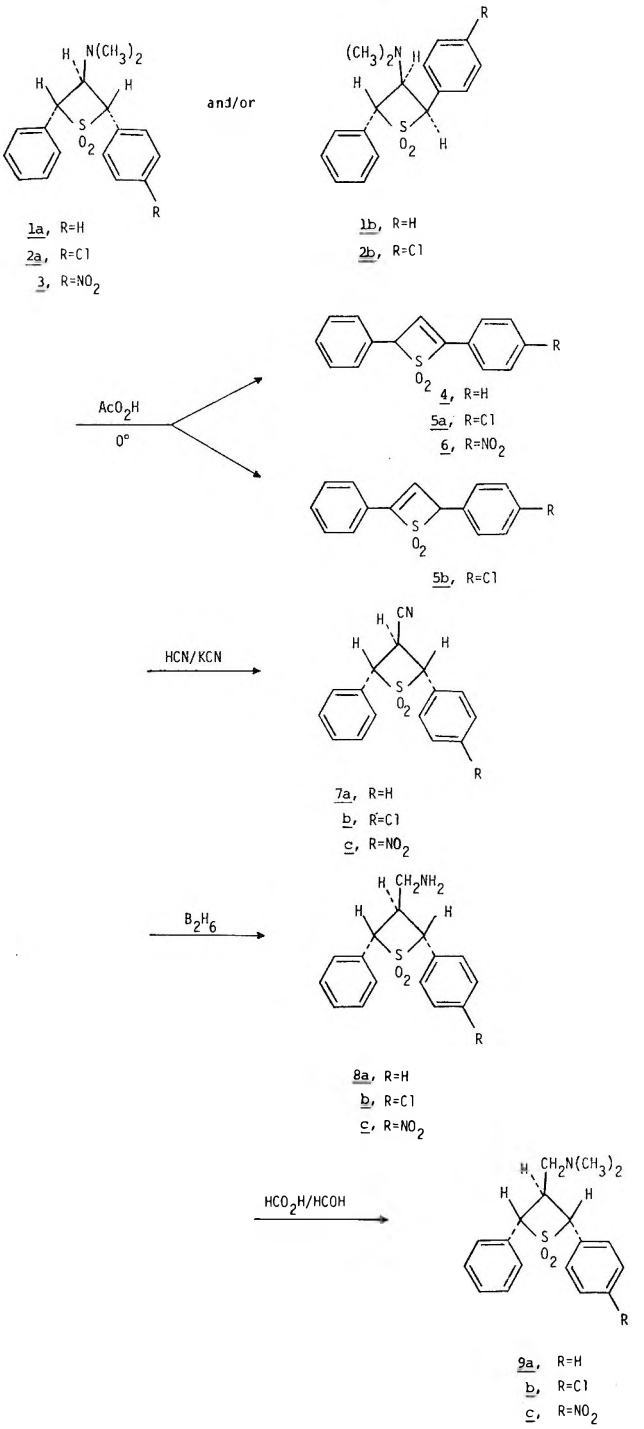
Several 2,4-diarylthiete 1,1-dioxides were prepared by amine oxide elimination of the corresponding 2,4-diaryl-3-dimethylaminothietane 1,1-dioxides. The thiete 1,1-dioxides were readily thermolyzed to chalcones and evidence was obtained which supports the involvement of a vinylsulfene intermediate in the thermolytic transformation. A ketonic sulfone was isolated and identified from thermolytic degradation of **4**. Addition of hydrogen cyanide or nitroethane to the thiete 1,1-dioxides followed by reduction to the primary amines and subsequent dimethylation gave 2,4-diaryl-3-dimethylaminomethylthietane 1,1-dioxides. 3-Cyanothietane 1,1-dioxide (**7c**) on treatment with base eliminates SO_2 to form olefins. The utility of thiete 1,1-dioxides to add HCN provides a synthetic route to a number of 3-substituted thietane 1,1-dioxides.

2-Aryl-3-dimethylaminomethylthietane 1,1-dioxides are of interest as conformationally restricted analogues of diphenylpropylamine-type analgetics. In order to synthesize the title compounds it was felt that appropriate thiete 1,1-dioxides would prove to be ideal intermediates. The reactivity of thiete 1,1-dioxides to nucleophilic addition is known,[1c,d] and it appeared feasible to utilize this property in the preparation of 3-cyano- and 3-nitroalkylthietane 1,1-dioxides which could be reduced to the 3-aminomethyl functional group. During the course of this work the amine oxide elimination reaction proved useful in confirming the conformation of the starting thietane 1,1-dioxides. Thermolysis studies of the thiete 1,1-dioxides were initiated to obtain chemical evidence as to the position of the double bond relative to differing aryl substituents.

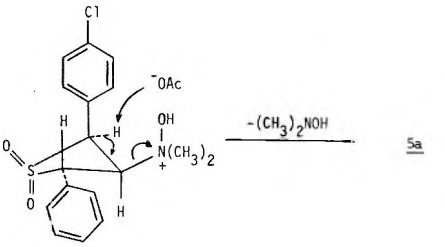
2,4-Diarylthiete 1,1-dioxides (**4, 5, 6**) were obtained by the amine oxide elimination reaction of 3-dimethylaminothietane 1,1-dioxides (**1, 2, 3**)[1b] (Scheme I). Treatment of either a mixture of the cis and trans isomers (**1a, 1b**)[2] or the cis isomer alone with peracetic acid gave 2,4-diphenylthiete 1,1-dioxide (**4**)[3] in good yield. Because of the intramolecular nature of the amine oxide elimination reaction,[5] its application to the isomers **2a** and **b** provided a means of verifying their assigned configurations. In **2a** both H-2 and H-4 are cis to the dimethylamino group and, therefore, according to the intramolecular mechanism of the elimination this isomer should have given a mixture of thiete 1,1-dioxide isomers **5a** and **b**. On the other hand, as only H-4 in **2b** is cis to the basic group, this isomer should have afforded **5b**. When a dilute tetrahydrofuran solution of **2a** was treated with peracetic acid the

Scheme I



product obtained was found by NMR analysis to consist of 65% **5a** and 35% **5b**. The preferential formation of **5a** is attributable, at least in part, to the acidifying effect of the *p*-chloro substituent on H-2. Repeating the reaction in tetrahydrofuran with isomer **2b** gave 18% **5a** and 82% **5b**. Thus, the results were consistent with the configurations previously assigned to **2a** and **b**.[1b] In contrast, the elimination reaction of **2b** in glacial acetic acid gave a product composed of 95% **5a** and 5% **5b**. A plausible explanation for this result is that under acidic conditions, an intermolecular (E2) mechanism is operative. Attack of acetate ion at the pseudoequatorial proton (H-2) which is sterically less hindered (as well as more acidic) than the pseudoaxial proton (H-4) in the protonated *N*-oxide form **10** of **2b** would favor formation of **5a**.

The UV spectrum of **5a** showed a maximum at 262 nm (ε 26 300) and that of **5b** possessed a shoulder at 230 nm (ε



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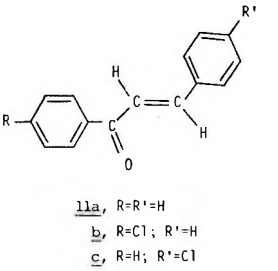
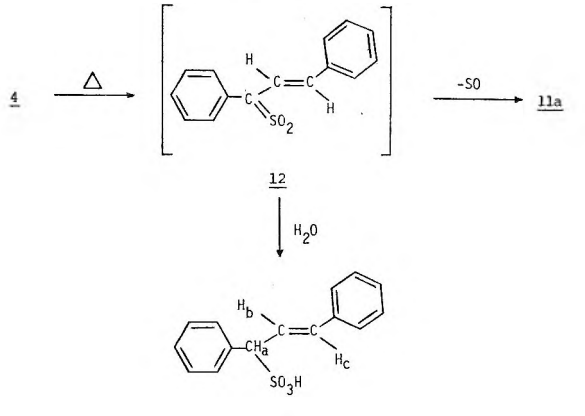
20 300) and a maximum at 256 nm (ε 22 600). The bathochromic shift observed in the spectrum of **5a** was attributed to the conjugation of the *p*-chlorophenyl ring with the heterocyclic double bond. The wavelength maximum in the spectrum of **5b** was similar to that observed in the spectrum of **4** (λ_{max} 255 nm, ε 19 600) and it was reasonable, therefore, that the *p*-chlorophenyl ring in **5b** was unconjugated. These configurational assignments were further supported by the NMR spectra which showed H-4 in **5a** at lower field (λ 5.91) than H-4 in **5b** (δ 5.85). It has been reported that the benzylic proton of 2-phenylthietane occurs at lower field than that of 2-(4-chlorophenyl)thietane.[6]

NMR analysis of the crude product from the reaction of **3** with peracetic acid in glacial acetic revealed the presence of only one thiete 1,1-dioxide, **6**. The bathochromic shift evident in the UV spectrum of **6** (λ_{max} 288 nm, ε 19 000) when compared to the spectrum of **4** indicated that the *p*-nitrophenyl ring in **6** was conjugated with the heterocyclic double bond. The greater acidity of H-2 relative to that of H-4 in **3** probably accounts for the exclusive formation of **6**. Downfield shifts of protons H-3 and H-4 in the NMR of **6** as compared to **4** and **5** were observed and attributed to substituent and solvent effects.

Thermolytic Reactions. It had been observed that 2,4-diphenylthiete 1,1-dioxide (**4**) at its melting point decomposed with vigorous evolution of gas. An IR spectrum of the melt was almost identical with *trans*-benzylideneacetophenone (*trans*-chalcone, **11a**). Heating a sample of **4** at 166 °C for 3



11a, R=R'=H
b, R=Cl; R'=H
c, R=H; R'=Cl



min gave **11a** to the extent of 92% as well as a small, undetermined amount of the cis isomer as measured by GC. King and co-workers have proposed that thermolytic conversion of

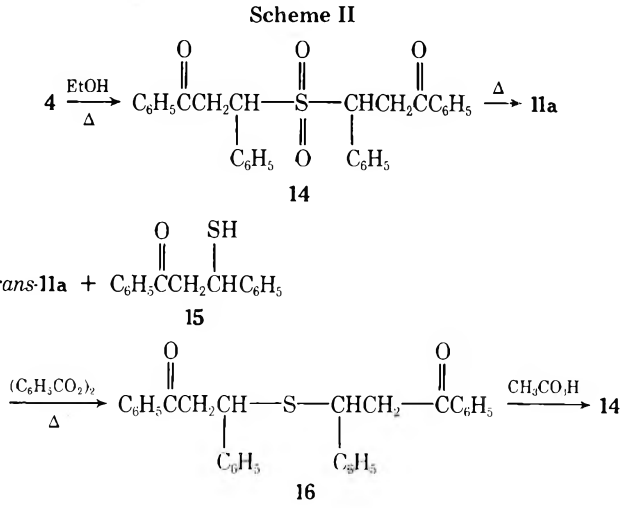
thiete 1,1-dioxides to α,β-unsaturated carbonyl compounds involves electrocyclic opening of the heterocycle to give a vinyl sulfene intermediate which then undergoes desulfinylation.[7] According to this mechanism, the formation of **11a** would occur via the intermediate **12**.[8] A previous attempt to trap the vinyl sulfene intermediate derived from thiete 1,1-dioxide met limited success.[9] It was considered of interest, therefore, to investigate the possible trapping of **12**. Water was used as the trapping agent since it is known that sulfenes react readily with water to give sulfonic acids. Refluxing a solution of **4** in aqueous tetrahydrofuran gave the predicted sulfonic acid **13** in 71% crude yield as well as a small amount of **11a** and a ketonic sulfone, **14**. The UV spectrum of **13** (λ_{max} 253 (ϵ 21 600), 282.5 (ϵ 2740) and 292 nm (ϵ 1450)) was quite similar to that reported[12] for the carboxylic analogue of **13**, 2,4-diphenyl-3-butenoic acid (λ_{max} 252 (ϵ 22 490), 283.5 (ϵ 2080), and 292.5 nm (ϵ 1320)). Although the configuration of the carboxylic acid was not assigned, from a consideration of the procedure whereby the acid was synthesized,[11] it was most certainly trans. The same configuration was, therefore, assigned to **13**.[12] As the free sulfonic acid was unstable, it was further characterized as the stable dimethylamine salt. In the NMR spectrum of the salt, the protons (H_a, H_b, and H_c) appeared as an ABX system with coupling constants J_{bc} = 15.0 Hz, J_{ab} = 9.0 Hz and J_{ac} = −1 Hz. The magnitude of the couplings was in accord with structure **13**.[13]

Thermolysis of **5a** and **b** provided further evidence for the double bond positions in the two isomers. According to the proposed mechanism,[7] isomer **5a** should have given benzylidene-*p*-chloroacetophenone (**11b**) whereas **5b** should have yielded *p*-chlorobenzylideneacetophenone (**11c**). Indeed, heating **5a** at 164 °C for 3 min afforded **11b** in 80% yield and no **11c** (GC analysis). When **5b** was treated in the same manner, an 85% yield of **11c** was obtained and no **11b**. Heating the *p*-nitro derivative **6** at 166 °C for 3 min gave one major product (GC) which possessed characteristic chalcone bands in the infrared, but the predicted product was not isolated.

Some decomposition of **4** occurred upon recrystallization from hot solvents and particularly so when the solvent was ethanol. Mother liquors contained **11a** plus a small amount of white solid which was identified as a ketonic sulfone from IR spectra. Refluxing **4** in ethanol allowed isolation of 17% of the ketonic sulfone **14** (Scheme II). Fractional crystallization of the crude sulfone gave white needles (mp 184–185 °C) and transparent plates (mp 196–197 °C) which are considered to be diastereoisomers of bis(1,3-diphenyl-3-oxopropyl) sulfone (**14**) based on the spectroscopic and synthetic evidence. Besides absorption characteristics of a sulfone, bands at 1683 and 1241 cm^{-1} in the IR spectrum of the low melting isomer indicated the presence of a benzoyl functionality. Comparison of its UV spectrum (λ_{max} 244 nm, ϵ 25 000) with that of acetophenone[13b] (λ_{max} 240 nm, ϵ 13 000) suggested two benzoyl groups per molecule. The NMR spectrum was in agreement with structure **14** and showed the nonaromatic protons as an ABX pattern. From the 100-MHz spectrum, the chemical shift of protons A was calculated[14] to be δ 3.72 (J_{AX} = 2.8 Hz) and that of protons B to be δ 3.93 (J_{BX} = 10.2 Hz) with J_{AB} = 17.5 Hz. The IR spectrum of the high melting isomer was quite similar but not identical with that of the low melting material, whereas the NMR spectra were superimposable.

To confirm the assigned structure, an unequivocal synthesis of **14** was carried out (Scheme II). Heating β-mercapto-β-phenylpropiophenone (**15**) with *trans*-**11a** in the presence of benzoyl peroxide gave the sulfide **16**.[15] The sulfide **16** was not purified but was oxidized directly to give **14**. Fractional crystallization gave white needles, the IR, UV, and NMR spectra of which were identical with those of the low melting ketonic sulfone derived from **4**. A mixture melting point of the two was not depressed. Because of the synthetic procedure

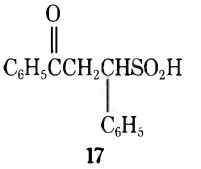
Scheme II



used, both diastereoisomeric forms of **14** (*dl* and *meso*) should have been formed. A second substance was obtained as transparent plates, the melting point and IR spectrum of which were identical with those of the high melting isomer from the decomposition of **4**.

When either diastereoisomeric form of **14** was heated at its melting point it decomposed with vigorous evolution of a gas to give **11a** (IR analysis). The thermolysate from the low melting isomer was found by GC to consist of a mixture of *trans*- and *cis*-**11a**, respectively. A possible mechanism is desulfonylation[17] of **14** followed by loss of a hydrogen atom from each of the intermediate radical fragments to give **11a**.

Compound **14** is formally derived from two molecules of **4** by the loss of sulfur monoxide and the addition of water. Since sulfinic acids are known to readily add to α,β-unsaturated carbonyl compounds to give sulfones[18] and since **11a** is formed along with **14** in the decomposition of **4** in hot ethanol, it is tempting to implicate the sulfinic acid **17** in the formation of

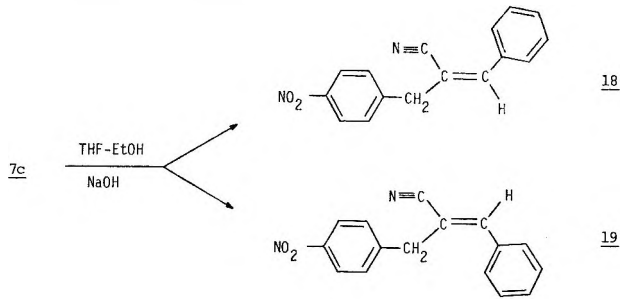


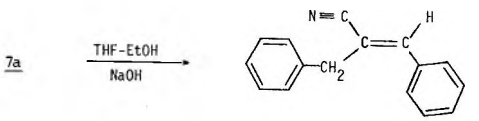
14. Although several mechanisms can be evoked whereby **17** is formed from **4** in the presence of water, no direct experimental evidence has been obtained so far for its formation. Attempts to generate **17** by treating the sulfone (**14**) with alcoholic KOH or dimethylamine in chloroform were unsuccessful. Chalcone forms immediately under these conditions as expected.[18] Perhaps the sulfinic acid if formed also readily decomposes to chalcone.

Addition Reactions. The addition of HCN to thiete (**4**) gave *cis*-2,4-diphenyl-3-cyanothietane 1,1-dioxide (**7a**). The reaction proceeds best using a solution of HCN in ethanol, catalyzed by a small amount of KCN. An excess of KCN or other base can lead to intractable black tars. The cis configuration of the phenyl rings was apparent from the equivalence of the benzylic protons and the magnitude of the vicinal coupling constant (10.5 Hz) in the NMR spectrum. The absence of trans isomer was not unexpected considering the instability of *trans*-2,4-diphenyl-3-dimethylaminothietane 1,1-dioxide (**1b**) relative to the cis isomer **1a**.[1b] The course of the addition may be rationalized in terms of approach of cyanide ion from the least hindered side of the thiete (**4**), i.e., side opposite the phenyl group at C-4, to generate an intermediate carbanion. Protonation of the carbanion then occurs to give the more stable cis isomer. Even if some trans isomer were

initially formed, epimerization to **7a** could occur under the basic conditions (KCN) of the reaction.

By analogy, the hydrogen cyanide adduct **7b** from a mixture of **5a** and **5b** was assigned a cis configuration as was the adduct **7c** obtained from **6.** The sensitivity of these cyano compounds to basic conditions was readily apparent in the case of **7c.** Column chromatographic work-up of the reaction residue after isolation of **7c** gave two additional compounds which from the IR appeared to be conjugated nitriles. Sulfone bands were absent. Elemental analyses were in agreement with the geometric isomers **18** and **19.**





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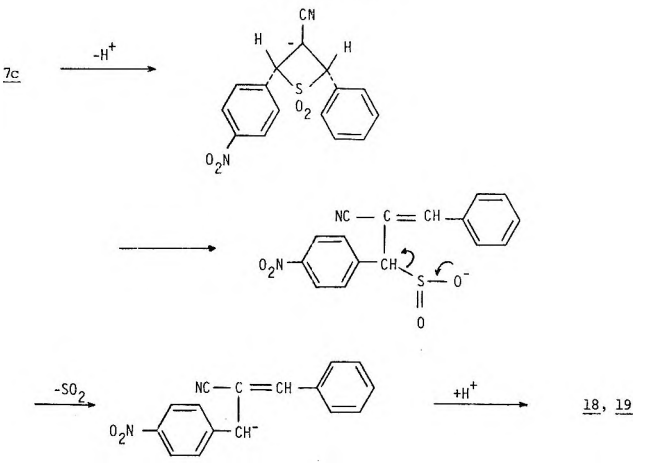
To confirm that the conjugated nitriles isolated from the HCN addition reaction were derived from cyclic product, **7c** was treated with base and gave a 2.5:1 mixture of **18** and **19** as estimated by NMR and GC. Similar treatment of **7a** gave a small quantity of conjugated nitrile, **20,** and considerable polymerized solids.

Irradiation of a methanol solution of the isomers (2.5:1/18:19) reversed the ratio to give a mixture of 1:2.5 of **18** and **19** at equilibrium. The possibility that **18** and **19** were positional rather than geometric isomers is thus ruled unlikely. Isomer **18,** λ_{max} 278 nm (ϵ 26 700), was assigned the (*Z*) configuration and **19,** λ_{max} 270 nm (ϵ 39 000), assigned (*E*). These values are comparable to the reported values of (*Z*) and (*E*) isomers of cinnamic acid nitrile, 273 (16 596) and 272 (39 500), respectively.[13c] In the NMR spectrum of **19** the benzylic and vinylic protons are shifted downfield compared to **18** and may be the result of a greater degree of deshielding of these protons by the cyano group and aromatic ring, respectively, in isomer **19.** The conjugated nitrile, **20,** was assigned the (*E*) configuration based on the UV spectral data, λ_{max} 278 nm (ϵ 42 000). The λ_{max} observed for **20** also supports the assigned structures of **18** and **19.** Had the *p*-nitrophenyl group been conjugated with the nitrile a bathochromic shift of λ_{max} for **18** and **19** would have been expected (consider the trans isomers of cinnamic and 4-nitrocinnamic acid (λ_{max} 273 nm and 300 nm, respectively).[13c]

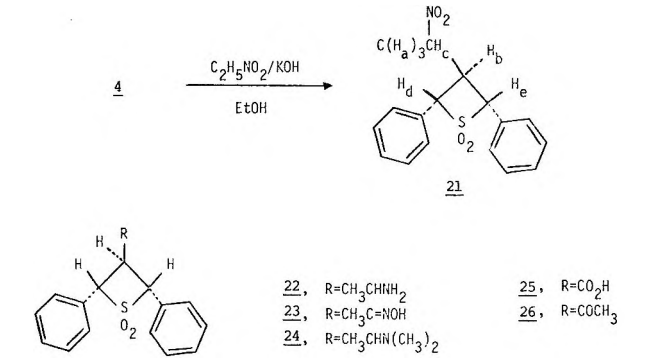
A possible mechanism for a base catalyzed elimination to form conjugated nitriles is outlined in Scheme III. Ring opening to give the allylic carbanion shown is perhaps preferred because of the inductive nature of the *p*-nitro substituent.

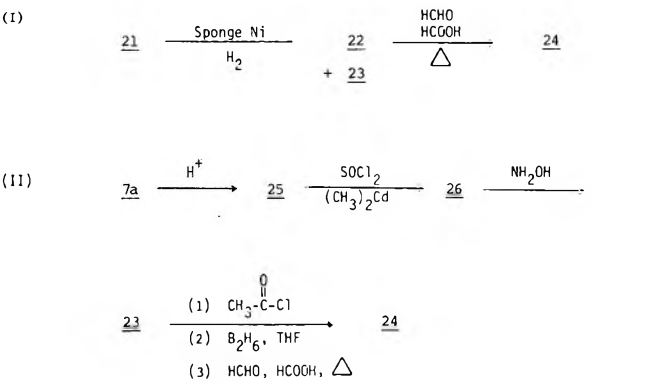
Reduction of the 3-cyano compounds with diborane followed by dimethylation of the resulting primary amines **8a, b,** and **c** afforded the final compounds **9a, b** and **c.** Although a derivative of **9c** suitable for elemental analysis could not be prepared, its IR and NMR spectra were in agreement with the assigned structure.

Scheme III



Scheme IV





cis-2,4-Diphenyl-3-(1-dimethylaminomethyl)thietane 1,1-dioxide (**24**) was prepared by two routes (Scheme IV). The more efficient method involved Michael addition of nitroethane to **4** to give **21.** Crystals of this adduct obtained from hexane–benzene contained one molecule of benzene for every two molecules of **21** (NMR and GC). In the NMR spectrum H_d and H_e were nonequivalent and appeared as overlapping doublets. It was reasonable to assume that nitroethane, in the same manner as HCN, added to **4** to give a thietane 1,1-dioxide derivative with the phenyl rings cis. Therefore, the nonequivalence of the benzylic protons was attributable to the asymmetry of the 1-nitroethyl substituent at C-3. Catalytic reduction of **21** gave a mixture of the primary amine **22** and the oxime **23.** Elemental analyses were not obtained for **22** and **23** but spectroscopic data and two different reaction schemes involving these compounds were considered sufficient criteria for identification. The equivalence of the benzylic protons and the magnitude of the vicinal coupling constant (10 Hz) in the NMR spectrum of **23** indicated that this compound possessed

a cis configuration. Assuming that no epimerization occurred during the hydrogenation procedure, this observation supported the assignment of a cis configuration to **21**. Dimethylation of **22** gave the desired product **24**. Compounds **22** and **24** were considered to possess the same configuration as **21**.

A second approach to **24** utilized the 3-cyano compound **7a**. Acid hydrolysis of the nitrile gave *cis*-2,4-diphenyl-3-carboxythietane 1,1-dioxide (**25**) in 89% yield. Treatment of the acid chloride of **25** with dimethylcadmium afforded the ketone **26**. No product could be isolated when attempts were made to prepare **26** directly by reacting **7a** with methyllithium or methylmagnesium bromide. Attempts to synthesize **22** or **24** from **26** by application of the Leuckart reaction[19] were unsuccessful. The ketone decomposed under the reaction conditions of prolonged heating. It has been reported that oxime acetates are reduced to primary amines by diborane.[20] Preparation of **24** via this procedure was investigated in a preliminary fashion. Ketone **26** was converted to the oxime **23** which was acetylated and then treated with diborane. Dimethylation of the crude product gave **24** in low yield.

The analgetic activities of the thietane 1,1-dioxide derivatives described in this paper will be reported elsewhere.

Experimental Section

The instrumentation was as previously described.[1b] Columns used for gas–liquid chromatography (GC) were 6 ft × 5/32 in. (i.d.) silanized glass. Packings were 5% SE-30 on Chromport (70–80 mesh), 3% QF-1 on Gas-Chrom Q (100–120 mesh), and 3% OV-225 on Gas Chrom Q (100/120). GC/MS data of the unsaturated nitrile isomers were obtained using a Varian Mat 111 spectrometer at 70 eV. An AEI MS9 with computer interface (courtesy of UBC Chemistry) was used for accurate mass determinations.

The GC calibration curves referred to below were prepared using authentic samples of chalcones which were synthesized according to literature procedures and crystallized from hexane–ethanol: *trans*-benzylideneacetophenone (**11a**),[22] mp 55–56 °C (lit.[22] 55–57 °C); *trans*-benzylidene-*p*-chloroacetophenone (**11b**),[23b] mp 96.5–98 °C (lit.[24] 94–96 °C); and *trans*-*p*-chlorobenzylideneacetophenone (**11c**),[23a] mp 112–113.5 °C (lit.[23a] 114.5 °C). The hydrogen cyanide solution used in the synthesis of the 3-cyano adducts **7a, b** and **c** was prepared by mixing 80 mL of liquefied HCN[25a] with 2 L of ice-cold 100% ethanol.

2,4-Diphenylthiete 1,1-Dioxide (4). To a slurry of 14.5 g (0.048 mol) of **1a** in 14.5 mL of glacial acetic acid cooled in an ice–water bath was added 43.5 mL of 40% peracetic acid dropwise over a period of 45 min. After stirring for 17 h the reaction mixture was neutralized with a saturated solution of Na_2CO_3 and then extracted with 300 mL of $CHCl_3$. The $CHCl_3$ layer was washed with 10% HCl and then dried over $MgSO_4$. Evaporation under reduced pressure with the aid of a lukewarm water bath gave 10.5 g (85%) of beige solid. Crystallization from hexane–benzene afforded 9.3 g (76%) of **4** as white, fluffy needles, mp 137–138 °C dec (lit.[3] 133–134 °C); IR 1303, 1150 cm^{-1} (sulfone); NMR δ 7.77–7.27 (m, 10, phenyls), 7.03 (d, 1, J = 2 Hz, H-3), and 5.92 (d, 1, J = 2 Hz, H-4); UV_{max} 255 (CH_3CN) nm (ϵ 19 600) (lit.[3] (EtOH) 257 nm (ϵ 17 400)). Essentially the same yield of product was obtained when the starting material was a mixture of **1a** and **b**.

Anal. Calcd for $C_{15}H_{12}O_2S$ (256.32): C, 70.29; H, 4.72. Found: C, 69.93; H, 4.92.

2-(4-Chlorophenyl)-4-phenylthiete 1,1-Dioxide (5a). In the same manner as described above, 27.0 g (0.080 mol) of **2b** in 27 mL of glacial acetic acid was reacted with 80 mL of 40% peracetic acid. Work-up afforded a yellow solid which upon crystallization from EtOH gave 13.7 g (59%) of **5a** as white needles, mp 128–129 °C dec; IR 1302, 1160 cm^{-1} (sulfone); NMR δ 7.67–7.25 (m, 9, aromatics), 7.02 (d, 1, J = 2 Hz, H-3), and 5.91 (d, 1, J = 2 Hz, H-4); UV_{max} 262 (ϵ 26 300) and 294 nm (shoulder) (ϵ 1400).

Anal. Calcd for $C_{15}H_{11}ClO_2S$ (290.77): C, 61.96; H, 3.81; Cl, 12.19. Found: C, 61.93; H, 4.25; Cl, 12.31.

2-Phenyl-4-(4-chlorophenyl)thiete 1,1-Dioxide (5b). In the same manner as described above, 35.4 g (0.0105 mol) of **2a** in 35 mL of glacial acetic acid was reacted with 106 mL of peracetic acid. Crystallization of the product from EtOH gave 13.2 g (43.2%) of white solid which was found to be a mixture of **5a** and **b** by IR analysis. Evaporation of the mother liquor and crystallization of the residue from EtOH gave a further 4.1 g (13.4%) of isomer mixture enriched in **5b**. Repeated recrystallization of the latter solid from EtOH gave pure **5b** as white, shiny leaflets, mp 130–131 °C dec; IR 1310, 1160 cm^{-1} (sulfone); NMR δ 7.70–7.08 (m, 9, aromatics), 6.98 (d, 1, J = 2 Hz, H-3); and 5.85 (d, 1, J = 2 Hz, H-4); UV_{max} 230 (shoulder) (ϵ 20 300), 256 (ϵ 22 600), and 290 nm (shoulder) (ϵ 800).

Anal. Calcd for $C_{15}H_{11}ClO_2S$ (290.77): C, 61.96; H, 3.81; Cl, 12.19. Found: C, 61.72; H, 4.12: Cl, 12.10.

Effect of Starting Material Configuration on the 5a:5b Product Ratio. To a stirred solution of 0.50 g (1.5 mmol) of **2a** in 45 mL of THF was added 3.0 mL of 40% peracetic acid dropwise over a period of 2 min. The reaction temperature was maintained at 27 ± 1 °C by cooling the reaction flask in an ice–water bath when necessary. After stirring for 5 h, the solution was evaporated under reduced pressure to a volume of about 10 mL. Upon adding 40 mL of distilled water a white solid precipitated. The mixture was carefully neutralized with a saturated Na_2CO_3 solution and the solid was collected and dried, yield 0.40 g (92%). The IR spectrum indicated a mixture of **5a** and **b** free of starting material. In the 100 MHz spectrum H-3 and H-4 of **5a** appeared as doublets at δ 7.017 and 5.904 and the corresponding protons of **5b** appeared as doublets at δ 6.980 and 5.858. From the doublet integrals the product compostion was determined to be 65% **5a** and 35% **5b**.

When an identical reaction in THF was run using 0.5 g of **2b**, the product (0.37 g, 85%) was found by 100 MHz NMR to consist of 18% **5a** and 82% **5b**.

In the same manner as described for the preparation of **4**, 1.90 g (5.7 mmol) of **2b** in 2.0 mL of glacial acetic acid was reacted with 6.0 mL of 40% peracetic acid for 20 h. The reaction mixture was then diluted with water until precipitation of solid was no longer evident. After collecting and drying, the solid weighed 1.46 g (89%). NMR analysis gave the composition as 95% **5a** and 5% **5b**.

2-(4-Nitrophenyl)-4-phenylthiete 1,1-Dioxide (6). Because of the instability of **3** to crystallization, crude material containing approximately 12% acyclic isomer[1b] as impurity was used. In the same manner as described for the preparation of **4**, 20.3 g of starting material in 20 mL of glacial acetic acid was reacted with 61 mL of 40% peracetic acid. After stirring for 2 h, the reaction was worked up to give 15.0 g (96%) of crude product, mp 139–142 °C. Crystallization from EtOH gave **6** as pale yellow leaflets, mp 147–148 °C dec; IR 1520, 1320 (nitro group), 1300, 1155 cm^{-1} (sulfone); NMR (Me_2SO-d_6) δ 8.57–8.30, 8.07–7.83 (m, 4, AA'BB' pattern due to *p*-nitrophenyl), 8.18 (d, 1, J = 2 Hz, H-3), 7.50 (s, 5, phenyl), and 6.49 (d, 1, J = 2 Hz, H-4); UV_{max} 288 nm (ϵ 19 000).

Anal. Calcd for $C_{15}H_{11}NO_4S$ (301.32): C, 59.79; H, 3.68; N, 4.65. Found: C, 59.83; H, 3.75; N, 4.79.

Thermolysis of 4. A stoppered 8 × 70 mm test tube containing 30.0 mg (0.117 mmol) of **4** was placed in a 166 °C oil bath for 3.0 min. During the first minute the solid melted and a gas was rapidly evolved from the melt. Upon cooling, the brownish-yellow residue was dissolved in sufficient $CHCl_3$ to give 10 mL of solution which was immediately analyzed for *trans*-benzylideneacetophenone (**11a**) by GC using the 3% QF-1 column with the injection port, oven and detector at 240, 170, and 270 °C, respectively, and the nitrogen flow at 67 mL/min. By reference to a straight-line calibration curve (peak area vs. concentration) the total amount of **11a** (retention time 6.3 min) in the solution was determined to be 22 mg (92%). A second minor peak in the chromatogram possessed the same retention time (3.2 min) as *cis*-benzylideneacetophenone.[21] The IR spectrum (neat) of another thermolysate obtained in the same manner was essentially identical with that of an authentic sample of **11a**.

Thermolysis of 5a. In the same manner as described for the thermolysis of **4**, 30.0 mg (0.103 mmol) of **5a** was heated in a 164 °C bath for 3 min. Upon cooling, the orange solid was dissolved in $CHCl_3$ with 0.1% benzil as internal standard and immediately analyzed for *trans*-benzylidine-*p*-chloroacetophenone (**11b**) using the 3% QF-1 column with the injection port, oven and detector at 240, 200, and 270 °C, respectively, and the nitrogen flow at 67 mL/min. By reference to a straight-line calibration curve (peak height **11b**/peak height internal standard vs. conc. **11b**) the total amount of **11b** (retention time 3.6 min) was determined to be 20 mg (80%). A minor peak at 1.9 min was attributed to *cis*-benzylidene-*p*-chloroacetophenone.[21] The IR spectrum of a second thermolysate showed only slight discrepancies from that of an authentic sample of **11b**.

Thermolysis of 5b. In a manner identical with that described for the thermolysis of **5a, 5b** was thermolyzed to give 21 mg (85%) of *trans*-*p*-chlorobenzylideneacetophenone (**11c**) (retention time 3.9 min). A minor peak at 2.2 min in the chromatogram was attributed to *cis*-*p*-chlorobenzylideneacetophenone.[21] The IR spectrum of the solid product obtained in a second thermolysis was almost identical with that of authentic **11c**.

Decomposition of 4 in Aqueous Tetrahydrofuran. *trans*-

1,3-Diphenylpropene-3-sulfonic Acid (13). A solution of 2.56 g (0.01 mol) of **4** in a mixture of 40 mL of THF and 10 mL of water was refluxed for 41 h. Evaporation in vacuo gave a viscous, yellow oil which was dissolved in 20 mL of $CHCl_3$ and extracted with 40 mL of water. The aqueous layer (acidic to indicator paper) was evaporated under vacuum to give a pale yellow, crystalline solid (1.95 g, 71%). Crystallization from hexane–$CHCl_3$ afforded **13** as fine, off-white needles, mp 97–102 °C dec; IR 3700–2400, 1225, 1050 cm^{-1} (sulfonic acid); UV_{max} (H_2O) 253 (ε 21 600), 282.5 (shoulder) (ε 2740) and 292 (ε 1450). The free acid was unstable and slowly decomposed during a period of a week. Evaporation of a $CHCl_3$ solution of **13** which had been treated with excess dimethylamine afforded the salt as a white solid. Crystallization from hexane–benzene gave white needles, mp 169–170 °C; IR 3040–2480 (ammonium band), 1250, 1225, 1160, 1027 cm^{-1} (sulfonic acid salt); NMR δ 7.91–7.10 (m, 12, phenyls and NH_2), 7.01–6.30 (m, AB portion of ABX, 2, vinylic protons), 4.72–4.85 (m, X portion of ABX, 1, benzylic). Compound **13** was submitted for analysis as its dimethylamine salt.

Anal. Calcd for $C_{17}H_{21}NO_3S$ (319.42): C, 63.92; H, 6.63. Found: C, 63.93; H, 6.53.

Evaporation of the dried (Na_2SO_4) $CHCl_3$ layer from the extraction of **13** gave a brown oil, the IR spectrum (neat) of which indicated the presence of **11a.** The chalcone was extracted with two 20-mL portions of hot hexane and then quantitated by GC (3% QF-1 column), yield 0.15 g (7%).

Decomposition of 4 in Ethanol. Bis(1,3-diphenyl-3-oxopropyl) Sulfone (14). A solution of 2.56 g (0.010 mol) of **4** in 250 mL of 95% ethanol was heated at reflux for 2 h and then evaporated under reduced pressure to give a yellow oil. When a solution of the oil in 20 mL of hot ethanol was allowed to cool a white solid precipitated. The solid was collected and the filtrate was evaporated and treated again with ethanol to give additional solid. Repeating the process twice gave a total of 0.41 g (17%) of **14.** The product was fractionated by heating it in ethanol or hexane–methyl ethyl ketone and then filtering to remove material that was reluctant to dissolve. Upon cooling, the filtrate gave white needles, mp 184–185 °C dec; IR 1683, 1241 (benzoyl group), 1307, 1138 cm^{-1} (sulfone); UV_{max} (CH_3OH) 244 nm (ε 25 000); NMR δ 7.93–7.67 (m, 4, ortho protons of benzoyl groups), 7.53–7.23 (m, 16, phenyls and remaining protons of benzoyl groups), 4.70 (m, X portion of ABX pattern, 2, benzylic H) and 4.20–3.39 (m, AB portion of ABX pattern, 4, methylenes).

Anal. Calcd for $C_{30}H_{26}O_4S$ (482.60): C, 74.66; H, 5.43; O, 13.26; S, 6.64. Found: C, 74.21; H, 5.66; O, 13.62; S, 7.00.

Crystallization of the less soluble portions of the product from ethanol or hexane–methyl ethyl ketone gave transparent plates, mp 196–197 °C dec; IR 1683, 1241 (benzoyl group), 1310, 1292, 1138 cm^{-1} (sulfone).

Evaporation of the final filtrate from the isolation of the ketonic sulfone gave a brownish-yellow oil. The IR spectrum (neat) of this material showed strong bands at 1665 and 1600 cm^{-1} attributable to **11a.** Vacuum distillation afforded 0.2 g (10%) of crude **11a** as a yellow, viscous liquid which solidified upon collection, bp 120–130 °C (0.1 mm) [lit.[26] 208 °C (25 mm)]. Crystallization from petroleum ether (bp 60–80 °C) gave *trans*-**11a** as pale yellow prisms, mp 54–55 °C (lit.[26] 57–58 °C). The infrared spectrum was superimposable with that of an authentic sample. Coinjection with authentic *trans*-**11a** on a 5% SE-30 column with the injection port, oven and detector at 282, 193, and 253 °C, respectively, and the nitrogen flow at 80 mL/min gave one peak, retention time 5.1 min.

Synthesis of Bis(1,3-diphenyl-3-oxopropyl) Sulfone (14). A mixture of 2.08 g (0.010 mol) of *trans*-**11a**,[27] 2.42 g (0.010 mol) of **15**[28] and 20 mg of benzoyl peroxide was heated on a steam bath for 6 h. Mixing the product with Et_2O caused a white solid (1.86 g) to separate which was collected and tentatively identified as an α-hydroxy sulfide.[16] Evaporation of the supernatant gave 2.64 g of yellow oil (**16**). In the IR spectrum (neat) S–H stretching absorption was absent and a strong aromatic ketone band appeared at 1680 cm^{-1}. To a cooled solution of the oil in 10 mL of $CHCl_3$ and 10 mL of glacial acetic acid was added 4.6 mL of 40% peracetic acid dropwise over a period of 5 min. After 20 h, evaporation of the $CHCl_3$ under reduced pressure caused a white solid (**14**) to precipitate. Dilution of the supernatant with water and extraction with $CHCl_3$ followed by evaporation of the dried (Na_2SO_4) organic layer gave a yellow oil from which additional solid product was isolated by warming with ethanol. The total yield of **14** was 1.70 g (60%, based on weight of **16**). Fractional crystallization from hexane–methyl ethyl ketone gave white needles and transparent plates which were identical with the low and high melting isomers of **14,** respectively.

Thermolysis of 14. A sample of **14** (low melting diastereoisomer) in a stoppered 8 × 70 mm test tube was placed in a 160 ° C oil bath which was then rapidly heated to 200 °C. When the evolution of gas from the melt had subsided (2 min), the tube was removed. The IR spectrum (neat) of the resulting yellow syrup was very similar to that of *trans*-**11a.** Analysis by GC using a 3% QF-1 column with the injection port, oven and detector at 240, 170, and 270 °C, respectively, and the nitrogen flow at 67 mL/min gave two peaks which corresponded to *cis*-**11a** (3.2 min) and *trans*-**11a** (6.3 min). The ratio of cis to trans based on peak area was 1:4.

***cis*-2,4-Diphenyl-3-cyanothietane 1,1-Dioxide (7a).** A solution of 10.00 g (0.039 mol) of **4** in 250 mL of $CHCl_3$ was diluted with 500 mL of EtOH (100%) and 250 mL of HCN solution. Addition of 575 mg of powdered KCN caused the reaction to turn bright yellow. After stirring for 18 h a precipitate was present which was collected and washed with 400 mL of water. Air drying gave 8.57 g (77.6%) of pale yellow powder, mp 235–237 °C. Crystallization from *n*-butyl alcohol afforded **7a** as white, feather-shaped crystals, mp 236–237 °C; IR 2245 (nitrile), 1338, 1178, 1138 cm^{-1} (sulfone); NMR (Me_2SO-d_6) δ 7.81–7.33 (m, 10, phenyls), 6.34 (d, 2, J = 10.5 Hz, H-2 and H-4), and 4.77 (t, 1, J = 10.5 Hz, H-3).

Anal. Calcd for $C_{16}H_{13}NO_2S$ (283.35): C, 67.82; H, 4.63; N, 4.94. Found: C, 67.80; H, 4.73; N, 4.84.

***cis*-2-(4-Chlorophenyl)-3-cyano-4-phenylthietane 1,1-Dioxide (7b).** In a manner identical with that described for the preparation of **7a,** 15.00 g (0.0516 mol) of a mixture of **5a** and **b** was reacted to give 6.80 g (42.0%) of **7b** as a white crystalline solid, mp 198–199 °C. Evaporation of the filtrate and fractional crystallization of the resulting yellow solid from EtOH afforded 2.26 g (14.0%) of additional product and 2.07 g (13.8%) of starting material. Crystallization from EtOH gave **7b** as fine, white needles, mp 199–200 °C; IR 2280 (nitrile), 1333, 1180, 1148 cm^{-1} (sulfone); NMR (Me_2SO-d_6) δ 7.89–7.43 (m, 9, aromatics), 6.39 (d, 2, J = 11 Hz, H-2 and H-4), and 4.76 (t, J = 11 Hz, H-3).

Anal. Calcd for $C_{16}H_{12}ClNO_2S$ (317.79): C, 60.47; H, 3.81; Cl, 11.16. Found: C, 60.26; H, 3.82; Cl, 11.18.

***cis*-2-(4-Nitrophenyl)-3-cyano-4-phenylthietane 1,1-Dioxide (7c).** The procedure was similar to that described for the preparation of **7a.** A solution of 10.26 g (0.0341 mol) of **6** in 308 mL of THF was diluted with 256 mL of HCN solution and 590 mg of powdered KCN was added. After stirring for 5 h, the reaction solution was evaporated under reduced pressure to give an orange-brown oil. Washing the oil with EtOH caused a solid to separate. The supernatant was evaporated and the resulting oil was again treated with EtOH. Repeating the process several times gave a total of 7.52 g (67%) of pale yellow solid. Crystallization from hexane–$CHCl_3$ afforded **7c** in two polymorphic forms: white needles, mp 164–165 °C, and pale yellow rosettes, mp 152–153 °C; IR 2275 (nitrile), 1530, 1353 (nitro group), 1334, 1177, 1145 cm^{-1} (sulfone); NMR (Me_2SO-d_6) δ 8.57–8.28, 8.15–7.91 (m, 4, AA′BB′ pattern due to *p*-nitrophenyl), 7.88–7.40 (m, 5, phenyl), 6.56 (d, 1, J = 10.5 Hz, H-2), 6.48 (d, 1, J = 10.5 Hz, H-4), and 4.92 (t, 1, J = 10.5 Hz, H-3). Compound **7c** was submitted for analysis as the low melting polymorph.

Anal. Calcd for $C_{16}H_{12}N_2O_4S$ (328.34): C, 58.53; H, 3.68, N, 8.53. Found: C, 58.65; H, 3.75; N, 8.58.

Isolation of Unsaturated Nitriles (18, 19, 20). The final filtrate from the work-up of **7** (4.5 g of orange-brown oil) was heated in 20 mL of benzene and filtered. The filtrate was applied to a 2.5 × 60 cm column of 95 g of silica gel and developed with benzene. Fractions 1 and 2 were a mixture of **18** and **19** and **7c,** respectively. Two other fractions contained small amounts of unidentified substances. Fraction 1 was recrystallized with hexane–benzene and the resulting needles and plates separated by hand. Further recrystalllization of the plates gave **18,** mp 100–101 °C; IR (KBr) 2220 (α,β-unsaturated nitrile), 1626 (conjugated double bond), 1520, 1348 cm^{-1} (nitro); NMR ($CDCl_3$) δ 8.37–8.07 (m, 2, H ortho to nitro), 7.97–7.27 (m, 7, H meta to nitro and remaining phenyl), 7.08 (s, 1, vinylic), and 3.83 (s, 2, benzylic); UV_{max} (CH_3CN), 278 nm (ε 26 700); GC/MS *m/e* 264 (M^+, 71) 247 (42), 218 (29), 217 (100), 140 (34), 109 (41), 106 (30), 91 (39).

Further recrystallization of the needles gave **19,** mp 132–133 °C; IR (KBr) 2225, 1625, 1516 and 1348 cm^{-1}; NMR ($CDCl_3$) δ 8.36–8.09 (m, 2, H ortho to nitro), 7.61–7.28 (m, 8, remaining phenyl plus vinylic), and 3.93 (s, 2, benzylic); UV_{max} (CH_3CN) 270 nm (ε 39 000); GC/MS, *m/e* 264 (M^+, 70), 247 (41), 218 (29), 217 (100), 140 (34), 109 (42), 106 (26), 91 (35).

Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.28): C, 72.72; H, 4.58. Found **18:** C, 72.58; H, 4.66. Found **19:** C, 72.53; H, 4.48.

Treatment of 0.33 g of **7c** in 10 mL of THF and 50 mL of EtOH with dropwise addition of 2 mL of 1 N NaOH caused a deep magenta color to form which gradually disappeared. After 30 min 2 mL of glacial acetic was added and the solution evaporated to an orange solid. The

solid was dissolved in $CHCl_3$ and extracted several times with H_2O. The $CHCl_3$ layer dried (Na_2SO_4) and the $CHCl_3$ removed gave 0.26 g of orange solid. The NMR indicated a mixture of **18** and **19** which approximately accounts for 90% of the crude solid. Impurities were also present; δ 4.31, 2.4, and 1.25. GC analysis (3% QF-1, oven 210 °C, N_2 65 mL/min) gave peaks with identical retention times to **18** and **19** previously isolated (R_t = 14.3 and 13.1 min, respectively). Irradiation of a 1% solution of the isomers in methanol (450-W Hanovia arc lamp at room temperature through Pyrex) for 2 h gave an equilibrium mixture of 1:2.5 of **18** and **19**, respectively. Further irradiation or prolonged refluxing in benzene did not change this equilibrium.

Treatment of 2.0 g of **7a** dissolved in 160 mL of THF–EtOH (50:50) with 18 mL of 1 N NaOH while heating at 60–70 °C resulted in the precipitation of a white solid (polymer). Glacial acetic acid (20 mL) was added and the solution evaporated to dryness. The residue was extracted with benzene and chromatographed on a column as described for the isolation of **18** and **19**. A white solid (0.6 g) **20** was isolated which after recrystallization from EtOH gave fine colorless needles, mp 212–213 °C, IR (KBr) 2225, 1395, 695 cm^{-1}; NMR ($CDCl_3$) δ 7.18–7.48 (m, 11, aromatic plus vinylic proton), 4.53 (s, 2, benzylic); UV_{max} (CH_3CN) 278 nm (ϵ 42 000); GC/MS m/e 219 (M^+, 12), 218 (50), 140 (100); accurate mass measurement, calculated/observed, 219.1047/219.1022 ($C_{16}H_{13}N$), 218.0969/218.0968 ($C_{16}H_{12}N$).

***cis*-2,4-Diphenyl-3-aminomethylthietane 1,1-Dioxide (8a).** To a slurry of 14.15 g (0.050 mol) of finely powdered **7a** in 125 mL of dry THF was added 250 mL of a 0.3 M solution of diborane[29] in THF dropwise over a period of 1.5 h. The system was protected from moisture. After stirring for 13 h, the excess diborane was decomposed by the dropwise addition of EtOH followed by refluxing for 1 h. Upon cooling, the solution was treated with HCl gas until it turned a slight yellow. Evaporation in vacuo gave a pale yellow syrup which was dissolved in 100 mL of water and suction filtered. The filtrate was basified with 18 N NaOH and extracted with 250 mL of $CHCl_3$. The $CHCl_3$ layer was washed with 10% NaCl and dried over Na_2SO_4. Evaporation under reduced pressure gave 7.20 g (50%) of pale yellow solid. Crystallization from water–EtOH afforded **8a** as large transparent prisms, mp 110–113 °C; IR 3425, 3365 (NH_2 group), 1310, 1165, 1150 cm^{-1} (sulfone); NMR δ 7.61–7.23 (m, 10, phenyls), 5.21 (d, 2, J = 10 Hz, H-2 and H-4), 3.38–2.80)m, 3, H-3 and CH_2), and 1.60–1.15 (band, 2, NH_2).

Anal. Calcd for $C_{16}H_{17}NO_2S$ (287.38): C, 66.87; H, 5.96; S, 11.16. Found: C, 67.03; H, 6.32; S, 11.33.

***cis*-2-(4-Chlorophenyl)-3-aminomethyl-4-phenylthietane 1,1-Dioxide (8b).** In a manner identical with that described for the preparation of **8a**, 12.9 g (9.041 mol) of **7b** in 101 mL of dry THF was reacted with 203 mL of 0.3 M diborane in THF to give 9.8 g (75%) of **8b** as a white solid, mp 39–45 °C; IR 3500–3300 (NH_2 group), 1320, 1150 cm^{-1} (sulfone); NMR δ 7.60–7.30 (m, 9, aromatics), 5.23 (d, 1, J = 10 Hz, H-4), 5.20 (d, 1, J = 10 Hz, H-2), 3.33–2.80 (m 3, H-3 and CH_2), and 1.18 (s, 2, NH_2). Compound **8b** was analyzed as the picric acid salt, mp 249–250 °C dec (from 10% acetic acid).

Anal. Calcd for $C_{22}H_{19}ClN_4O_9S$ (550.93): C, 47.96; H, 3.48; N, 10.17. Found: C, 48.31; H, 3.36; N, 10.03.

***cis*-2-(4-Nitrophenyl)-3-aminomethyl-4-phenylthietane 1,1-Dioxide (8c).** In the same manner as described for the preparation of **8a**, 9.0 g (0.027 mol) of **7c** dissolved in 73 mL of dry THF was reacted with 146 mL of 0.3 M diborane in THF. Work-up gave a yellow syrup which was dissolved in 20 mL of $CHCl_3$–EtOH (9:1) and chromatographed in two equal portions on 60 × 2.5 cm silica gel columns (60–200 mesh, 94 g per column), using $CHCl_3$–EtOH (9:1) as the developing solvent. Two main fractions were obtained from each column. The second fractions were pooled and evaporated under vacuum to give 5.9 g (66%) of pale yellow, viscous oil which did not solidify when triturated with various solvents. The oil appeared to be the desired product **8c** according to its spectroscopic properties: IR (neat) 3400, 3340 (NH_2 group), 1515, 1350 (nitro group), 1310, 1150 cm^{-1} (sulfone); NMR δ 8.41–8.13, 7.85–7.55 (m, 4, AA'BB' pattern due to *p*-nitrophenyl), 7.55–7.32 (m, 5, phenyl), 5.37 (d, 1, J = 10 Hz, H-2), 5.31 (d, 1, J = 10 Hz, H-4), 3.41–2.88 (m, 3, H-3 and CH_2), and 1.20 (s, 2, NH_2). Minor impurity signals in the NMR spectrum occurred at δ 1.07 and 0.98. The intention was to submit **8c** for elemental analysis as its dimethylated derivative **9c**.

***cis*-2,4-Diphenyl-3-dimethylaminomethylthietane 1,1-Dioxide (9a).** The procedure was adopted from the literature.[30] A mixture of 1.77 g (6.2 mmol) of **8a**, 3.2 g of 90.7% formic acid and 2.9 mL of 37% formaldehyde solution was heated at 93± 1 °C in an oil bath for 18 h. A pale yellow solution was rapidly obtained and during the first 0.5 h a vigorous evolution of gas occurred. The solution was mixed with 6.5 mL of 4 N HCl and evaporated under vacuum to give a viscous oil. A solution of the oil in 60 mL of water was basified with 10 N NaOH and extracted with 60 mL of $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and dried over Na_2SO_4. Evaporation under reduced pressure gave 1.67 g (86%) of pale yellow solid. Crystallization from hexane–ethanol with charcoal treatment afforded **9a** as fine, white needles, mp 123–124 °C; IR 1315, 1154 cm^{-1} (sulfone); NMR δ 7.63–7.27 (m, 10, phenyls), 5.13 (d, 2, J = 10 Hz, H-2 and H-4), 3.45–2.83 (m, 1, H-3), 2.62 (d, 2, J = 6 Hz, CH_2), and 2.06 (s, 6, *N*-methyls).

Anal. Calcd for $C_{18}H_{21}NO_2S$ (315.44): C, 68.54; H, 6.71; N, 4.44. Found: C, 68.74; H, 6.65; N, 4.58.

***cis*-2-(4-Chlorophenyl)-3-dimethylaminomethyl-4-phenylthietane 1,1-Dioxide (9b).** In a manner similar to that described for the preparation of **9a**, 9.0 g (0.028 mol) of **8b** was reacted with 40 mL of 90.7% formic acid and 37 mL of 37% formaldehyde solution for 19 h. Work-up gave 9.6 (98%) of pale yellow solid. Crystallization from hexane–ethanol with charcoal treatment afforded **9b** as short, white needles, mp 124–125 °C; IR 1325, 1155 cm^{-1} (sulfone); NMR δ 7.48 (s, 9, aromatics), 5.13 (d, 1, J = 10 Hz, H-4), 5.09 (d, 1, J = 10 Hz, H-2), 3.39–2.75 (m, 1, H-3), 2.60 (d, 2, J = 6 Hz, CH_2), and 2.06 (s, 6, N-methyl).

Anal. Calcd for $C_{18}H_{20}ClNO_2S$ (349.88): C, 61.79; H, 5.76; N, 4.00. Found: C, 61.64; H, 5.81; N, 3.91.

***cis*-2-(4-Nitrophenyl)-3-dimethylaminomethyl)-4-phenylthietane 1,1-Dioxide (9c).** In a similar manner as described for the preparation of **9a**, 4.8 g (0.015 mol) of **8c** was reacted with 23 mL of 90.7% formic acid and 20 mL of 37% formaldehyde solution for 11 h. Work-up gave 3.5 g of straw-colored syrup. The syrup was dissolved in 150 mL of anhydrous Et_2O and treated with anhydrous HCl gas. The resulting white precipitate was collected and dissolved in 50 mL of water. Neutralization with a saturated solution of Na_2CO_3 gave a copious white precipitate which upon collection reverted to a straw-colored oil. While sitting for 2 weeks the oil changed to a glass, mp 39–43 °C; IR 1520, 1350 (nitro group), 1320, 1155 cm^{-1} (sulfone); NMR δ 8.44–8.19, 7.87–7.58 (m, 4, AA'BB' pattern due to *p*-nitrophenyl), 7.50 (s, 5, phenyl), 5.23 (d, 1, J = 10 Hz, H-2), 5.17 (d, 1, J = 10 Hz, H-4), 3.35–2.83 (m, 1, H-3), 2.64 (d, 2, J = 6 Hz, CH_2), and 2.10 (s, 6, *N*-methyls). Attempts to crystallize the HCl and picric acid derivatives of **9c** were unsuccessful.

***cis*-2,4-Diphenyl-3-carboxythietane 1,1-Dioxide (25).** A mixture of 10.00 g (0.0353 mol) of **7a** and 70 mL of Me_2SO was heated to give a solution to which was added 50 mL of 50% H_2SO_4. The resulting mixture was heated at reflux for 3 h. Upon cooling, the solution was poured onto 200 g of crushed ice with stirring and the mixture was diluted with 500 mL of water. An off-white precipitate was collected and dried. Crystallization from 1,2-dichloroethane gave 9.45 g (89%) of **25** as white, fluffy needles, mp 223–224 °C; IR 3270, 1730 (carboxylic acid), 1305, 1172, 1130 cm^{-1} (sulfone); NMR (Me_2SO-d_6) δ 7.83–7.33 (m, 10, phenyl), 5.90 (d, 2, J = 10 Hz, H-2 and H-4), and 4.15 (t, 1, J = 10 Hz, H-3).

Anal. Calcd for $C_{16}H_{14}SO_4$ (302.35): C, 63.56; H, 4.67; S, 10.60. Found: C, 63.40; H, 4.79; S, 10.54.

***cis*-2,4-Diphenyl-3-acetylthietane 1,1-Dioxide (26).** A mixture of 40.00 g (0.132 mol) of **25** and 400 mL of freshly distilled thionyl chloride was heated at reflux for 5 h. The system was protected from moisture. Evaporation of the excess thionyl chloride under reduced pressure gave the acid chloride as a cream-colored solid, mp 140–141 °C; IR 1780 (acid chloride), 1333, 1180, 1137 cm^{-1} (sulfone); carboxylic acid bands at 3270 and 1730 cm^{-1} were absent. A solution of the unpurified acid chloride in 140 mL of dry THF was drained into a vigorously stirred organocadium reagent which was cooled in an ice–water bath. The reagent was prepared just prior to the reaction by reacting 4.01 g (0.165 mol) of Mg turnings in 40 mL of dry THF and then adding 15.13 g (0.0825 mol) of anhydrous $CdCl_2$ according to a method adopted from the literature.[25] When the addition of the acid chloride was complete, the ice–water bath was removed and the reaction was stirred at room temperature for 8 h. Approximately 180 mL of THF was evaporated under reduced pressure. The gray suspension was poured onto a mixture of 200 g of crushed ice and 100 mL of dilute H_2SO_4. The mixture was then extracted with a total of 350 mL of $CHCl_3$. The combined $CHCl_3$ extracts were evaporated under reduced pressure to a volume of approximately 150 mL and extracted with 200 mL of 10% NaOH. Acidification of the basic extracts gave a 22.5% recovery of **25**. The $CHCl_3$ layer was washed with water, dried over $MgSO_4$ and evaporated in vacuo to give 27.03 g (68.4%) of white solid. Crystallization from hexane–EtOH with charcoal treatment afforded **26** as white, shiny leaflets, mp 125–126 °C; IR 1715 (ketone), 1330, 1172, 1140 cm^{-1} (sulfone); NMR δ 7.64–7.32 (m, 10, phenyls), 5.50 (d, 2, J = 10 Hz, H-2 and H-4), 3.90 (t, 1, J = 10 Hz, H-3), and 2.03 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{16}O_3S$ (300.37): C, 67.98; H, 5.37; S, 10.67.

Found: C, 68.15; H, 5.33; S, 10.64.

The oxime derivative **23** of **26** was prepared using a method from the literature.[31] Crystallization from water–EtOH gave **23** as small, white needles, mp 181–186 °C dec; IR 3440 (hydroxyl), 1315, 1170, 1135 cm^{-1} (sulfone); NMR (Me_2SO-d_6) δ 7.80–7.36 (m, 10, phenyl), 5.81 (d, 2, J = 10 Hz, H-2 and H-4), 4.08 (t, 1, J = 10 Hz, H-3), and 1.68 (s, 3, CH_3).

2,4-Diphenyl-3-(1-nitroethyl)thietane 1,1-Dioxide (21). A solution of 4.50 g (0.0176 mol) of **4** in 90 mL of nitroethane was diluted with 90 mL of ethanol and then 9.0 mL of a solution prepared by dissolving 1.0 g of KOH in a mixture of 10 mL of ethanol and 5 mL of nitroethane was added. The bright yellow solution was stirred for 7 h and acidified with 9.0 mL of glacial acetic acid. Evaporation in vacuo gave a white solid which was triturated with water, collected, and dried. Crystallization from hexane–benzene afforded 4.79 g (73.5%) of **21** as fine, white needles, mp 181–182 °C; IR 1554 (nitro group), 1324 (nitro group and sulfone), 1147 cm^{-1} (sulfone). The NMR spectrum showed a doublet at δ 7.48 (10, phenyl), two overlapping doublets, one at δ 5.33 (1, H_e, J_{eb} = 10 Hz) and the other at δ 5.14 (1, H_d, J_{db} = 11 Hz), a multiplet centered at δ 4.83 (1, H_c, J_{cb} = 8 Hz, J_{ca} = 7 Hz), a multiplet centered at δ 3.50 (1, H_b, J_{be} = 10 Hz, J_{bd} = 11 Hz, J_{bc} = 8 Hz), and a doublet at δ 1.33 (3, $C(H_a)_3$, J_{ac} = 7 Hz). The high-field signal of the doublet at δ 5.14 overlapped the low-field signal of the multiplet at δ 4.83. A singlet at δ 7.38 (3 H) was assigned to benzene. A solution prepared by dissolving 20.0 mg of crystalline **21** in 1.20 mL of anhydrous DMSO was calculated to contain 1.76 mg/mL of benzene. The solution was analyzed for benzene by GC using the 3% OV-225 column with the injection port, oven and detector at 250, 35, and 272 °C, respectively, and the nitrogen flow at 32 mL/min. One peak was observed which possessed a retention time and area identical with that recorded by injecting an equal volume of a reference solution containing 1.75 mg/mL of benzene in anhydrous DMSO. As insufficient **21** was on hand to crystallize from a solvent other than benzene, it was submitted for analysis as the benzene-containing crystals.

Anal. Calcd for $(C_{17}H_{17}NO_4S)_2$-C_6H_6 (740.89): C, 64.85; H, 5.44; N, 3.78; O, 17.28; S, 8.65. Found: C, 65.04; H, 5.31; N, 3.96; O, 17.33; S, 8.62.

2,4-Diphenyl-3-(1-dimethylaminoethyl)thietane 1,1-Dioxide (24). A solution of 4.00 g (0.0121 mol) of **21** in 30 mL of THF was diluted with 50 mL of EtOH and hydrogenated over 8 g of sponge nickel catalyst (W. R. Grace & Co., No. 986) at an initial hydrogen pressure of 52 psi using a Parr hydrogenator. After 7 h the catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give a viscous, pale yellow syrup. The syrup was dissolved in 20 mL of $CHCl_3$ and extracted with 40 mL of 4 N HCl followed by 20 mL of water. The pooled aqueous extracts were basified with 18 N NaOH and extracted with 50 mL of $CHCl_3$. The $CHCl_3$ extract was washed with 10% NaCl, dried over Na_2SO_4 and evaporated in vacuo to give 2.19 g (60%) of **22** as a pale yellow solid, mp 145–147 °C; IR 3440–3360 (NH_2), 1310, 1145 cm^{-1} (sulfone); NMR δ 7.67–7.30 (m, 10, phenyls), 5.26 (d, 1, J = 10 Hz, benzylic), 5.16 (d, 1, J = 10 Hz, remaining benzylic), 3.50–2.65 (m, 2, H-3 and CH_3CHNH_2), 1.22 (s, 2, NH_2), and 0.87 (d, 3, J = 6.5 Hz, CH_3). The $CHCl_3$ layer from the acid extraction was washed with water, dried over Na_2SO_4, and then evaporated under reduced pressure to give 1.36 g (36%) of beige solid. The IR and NMR spectra of the crystallized material (water–ethanol) was superimposable with those of *cis*-2,4-diphenyl-3-acetylthietane 1,1-dioxide oxime (**23**).

The amine **22** was dimethylated without further purification using a procedure similar to that described for the preparation of **9a**. After heating 2.2 g (0.007 mole) of **22** in 6.6 mL of 90.7% formic acid and 6.0 mL of 37% formaldehyde solution for 3 h, the reaction was worked up to give 1.9 g (79%) of pale beige solid. Crystallization from hexane–EtOH with charcoal treatment gave **24** as white needles, mp 145–146 °C; IR 1310, 1150 cm^{-1} (sulfone); NMR δ 7.60–7.31 (m, 10, phenyls), 5.26 (d, 1, J = 9 Hz, benzylic), 5.07 (d, 1, J = 9 Hz, remaining benzylic) 3.25–2.67 (m, 2, H-3 and $CH_3CHN(CH_3)_2$), 1.97 (s, 6, *N*-methyls), and 0.75 (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{19}H_{23}NO_2S$ (329.46): C, 69.27; H, 7.04; N, 4.25. Found: C, 69.17; H, 7.03; N, 4.43.

Preparation of 24 Using 23. The procedure was investigated in a preliminary fashion. A stirred solution of 2.24 g (0.0071 mol) of **23** in 25 mL of dry THF was cooled in an ice–water bath and reacted with 2.0 mL of acetyl chloride[32] for 1.5 h. Evaporation of the solvent under reduced pressure gave an oil which was dissolved in 100 mL of Et_2O, washed with 200 mL of 3% $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent gave an oil, the IR spectrum (neat) of which showed the absence of the oxime hydroxyl band and the presence of an ester functionality. A solution of 1.2 g (0.003 mol) of the crude ester in 20 mL of dry THF was reacted with 25 mL of 0.3 M diborane in THF for 16 h.[20] A dry nitrogen atmosphere was provided throughout the reaction period and the system was protected from moisture. The excess diborane was decomposed by drop-wise addition of water and then the colorless solution was gently refluxed for 1 h. Removal of the solvent in vacuo gave a white solid which was treated directly with 5 mL of 90.7% formic acid and 4.5 mL of 37% formaldehyde solution in a manner similar to that described for the preparation of **9a**. Work-up gave 0.16 g (14%) of pale yellow solid. Crystallization from hexane–EtOH afforded white needles, mp 144–145 °C. The IR spectrum of this material was superimposable with that of **24**.

Acknowledgments. The authors wish to thank the Medical Research Council (Grant MA-3044) for financial support.

Registry No.—**1a,** 63268-45-1; **1b,** 63268-46-2; **2a,** 63231-37-8; **2b,** 63268-47-3; **3,** 63231-38-9; **4,** 18744-26-8; **5a,** 63250-64-6; **5b,** 63250-65-7; **6,** 63250-66-8; **7a,** 63284-66-2; **7b,** 63250-67-9; **7c,** 63250-68-0; **8a,** 63250-69-1; **8b,** 63250-62-4; **8b,** picrate, 63250-63-5; **8c,** 63284-69-5; **9a,** 63250-70-4; **9b,** 63250-71-5; **9c,** 63250-72-6; *cis*-**11a,** 614-46-0; *trans*-**11a,** 614-47-1; **13,** 63284-67-3; **13** dimethylamine salt, 63284-68-4; **14** isomer 1, 63250-73-7; **14** isomer 2, 63250-74-8; **15,** 5076-35-7; **16,** 63250-75-9; **18,** 63284-70-8; **19,** 63250-76-0; **20,** 52958-88-0; **21,** 63250-77-1; **22,** 63250-78-2; **23,** 63250-79-3; **24,** 63250-80-6; **25,** 63250-81-7; **25** acid chloride, 63250-82-8; **26,** 63250-83-9.

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(1) (a) Taken in part from the Ph.D. thesis of J. E. Coates, University of British Columbia, 1972; (b) For previous paper, see: F. S. Abbott, J. E. Coates, and K. Haya, *J. Org. Chem.*, **42,** 3502 (1977); (c) L. Paquette and M. Rosen, *J. Org. Chem.*, **33,** 3027 (1968); (d) D. Dittmer and M. Christy, *J. Am. Chem. Soc.*, **84,** 399 (1962).

(2) When used in this paper with respect to thietane 1,1-dioxide derivatives, the terms cis and trans refer to the relationship of the aryl groups on the heterocyclic ring.

(3) Compound **4** has previously been prepared from 2,4-diphenyl-3-diethylaminothietane 1,1-dioxide: D. R. Eckroth and G. M. Love, *J. Org. Chem.*, **34,** 1136 (1969). Using 2-phenylthiete 1,1-dioxide[4] as a reference compound, it is apparent that their assignment of the heterocyclic protons in the NMR spectrum of **4** is reversed.

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(8) The mechanistic significance of the presence of some *cis*-chalcone in the thermolysates of **4, 5a,** and **5b** is not clear at the present time because of the ease with which calcones undergo thermal and photochemical isomerization.[21]

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Photochemical Synthesis of Benzo[*f*]quinolines[1]

Nicholas R. Beller,[2] Douglas C. Neckers,*[3] and Eleftherios P. Papadopoulos[4]

Departments of Chemistry, The University of New Mexico, Albuquerque, New Mexico 87131, and Bowling Green State University, Bowling Green, Ohio 43403

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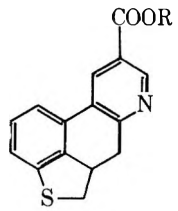
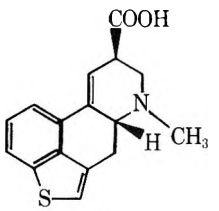
Benzo[*f*]quinolines with a sulfur-containing substituent at position 7 have been synthesized photochemically from the corresponding 2-stilbazoles. An improved synthesis of *o*-(methylthio)benzaldehyde is described.

In the course of a general study of the photochemistry of benzo[*b*]thiophene,[5] we became interested in the possibility of photochemical synthesis of a heterocyclic ring system, **1**, capable of subsequent elaboration to 1-deaza-1-thialysergic acid (**2**).



1



2

Since benzo[*b*]thiophene is an isostere of indole, sulfur analogs of biologically active indole derivatives are obvious targets of research and their synthesis as well as pharmacology have been investigated extensively.[6] Among other derivatives, sulfur isosteres of various tryptamines, including serotonin, have been synthesized and found to have pharmacological properties similar to those of the nitrogen compounds.[7] In view of the extraordinary pharmacological activity of lysergic acid and many of its derivatives, it is not surprising that an attempt has been made to synthesize its sulfur isostere, 1-deaza-1-thialysergic acid (**2**). Campaigne and Knapp modeled their approach to **2**[8] after Kornfeld and Woodward's synthesis of lysergic acid,[9] but their effort could not be carried through to the desired compound.

In attacking the problem of the synthesis of a ring skeleton of **2**, we chose to construct first the benzo[*f*]quinoline system **8**, functionalized appropriately with a sulfur containing group at position 7, intending to close the sulfur ring after the simpler heterocycle was intact.

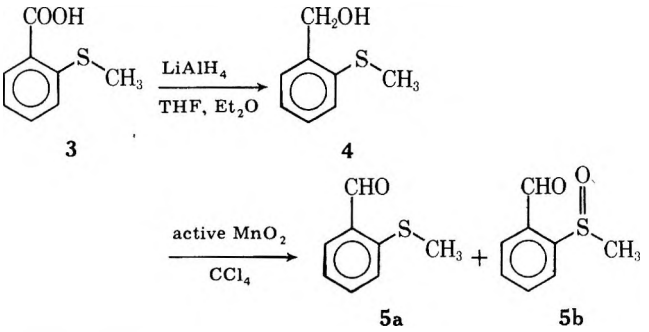
We present herein photochemical preparations of some benzo[*f*]quinolines as possible intermediates in the synthesis of a parent ring system of thiolysergic acid.

Results and Discussion

Our choice as a method of preparation of the three-ring system of **8** was the photocyclization of appropriate 2-stilbazoles. Because of its simplicity, this oxidative ring closure has been used on numerous occasions as a direct route to azaphenanthrenes,[10] in spite of generally modest yields. Thus, Kumler and Dybas prepared a variety of benzo[*f*]quinolines by photochemical ring closure of corresponding 2-stilbazoles.[11]

A suitable synthesis had to be developed for *o*-(methylthio)benzaldehyde (**5a**), the starting material for most of the stilbazoles we needed. The reported synthesis of **5a** by $LiAlH_4$ reduction of *N*-methyl-*o*-(methylthio)benzanilide in THF[12] failed in our hands, giving only trace quantities of the desired product. Lithium tri-*tert*-butoxyaluminohydride reduction of o-(methylthio)benzoyl chloride using Brown and Subba Rao's procedure[13] gave aldehyde **5a** in 37% yield, still not a particularly satisfactory yield for further synthetic use. An attempt to carry out a Reimer–Tiemann formylation of thiophenol combined with methylation of the mercapto group also was unsuccessful.

Good yields of the desired aldehyde were obtained, however, from a 2-step synthesis in which *o*-(methylthio)benzoic acid (**3**) was reduced to o-(methylthio)benzyl alcohol (**4**) which was



then oxidized to aldehyde **5a** using active manganese dioxide. The oxidation procedure[14] was adapted from Papadopoulos, Jarrar, and Issidorides[15] using the Morton[16] method to prepare active manganese dioxide.

Although certain sulfides are oxidized with active manganese dioxide,[17] we were able to arrive at conditions of solvent and temperature (Table I) in which very little oxidation to the corresponding sulfoxide **5b** occurred. Thus, treatment of 0.1 mol of **4** with a 5-fold (w/w) amount of active MnO_2 in CCl_4, at room temperature, led to reproducible, excellent yields of **5a** containing virtually no alcohol **4** and only traces of sulfoxide **5b**.

Because use of this procedure routinely resulted in overall conversion of about 80% starting from o-(methylthio)benzoic acid, we feel that it deserves consideration as a method of preparation of *o*-(methylthio)benzaldehyde. For purposes of identification, but also for use as starting material for the synthesis of appropriate benzo[*f*]quinolines, o-(methylsulfinyl)benzaldehyde (**5b**) was prepared in essentially quantitative yield by sodium metaperiodate oxidation of **5a**.[18]

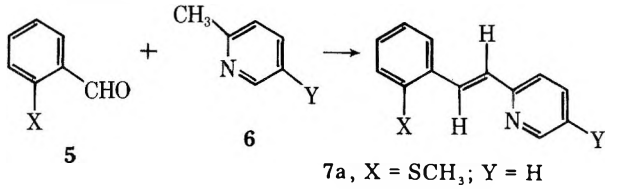
The precursor 2-stilbazoles needed in our work were pre-

Table I. Product Distribution for the Active Manganese Dioxide Oxidation of *o*-(Methylthio)benzyl Alcohol in Various Solvents[a]

Solvent	Mol %[b] Unreacted 4	5a	5b
Benzene	22	64	14
Cyclohexane	8	89	3
Anhydrous ether	12	70	18
Carbon tetrachloride	5	91	4
Chloroform	15	73	12
Methylene chloride	27	64	9
Ethyl acetate	30	65	5
Acetone	34	59	7
Water	46	45	9

[a] A mixture of 0.5 g of **4** in 25 ml of solvent and 2.5 g of active manganese dioxide was magnetically stirred at room temperature for 8 h. [b] Determined from the peak areas of the benzylic protons of **4** (δ 4.57), methylthio protons of **5a** (δ 2.39) and methylsulfinyl protons of **5b** (δ 2.70) in the NMR spectra of the crude products.

pared mostly by aldol-type condensations of suitably substituted benzaldehydes **5** with 2-picolines **6**.[11,19] Thus, refluxing of benzaldehyde or o-(methylthio)benzaldehyde and ethyl 6-methylnicotinate in acetic anhydride yielded stilbazoles **7d** and **7e**, respectively.



5 **6**

7a, X = SCH_3; Y = H
b, X = $SOCH_3$; Y = H
c, X = SO_2CH_3; Y = H
d, X = H; Y = COOEt
e, X = SCH_3; Y = COOEt
f, X = $SOCH_3$; Y = COOEt
g, X = SO_2CH_3; Y = COOEt

Stilbazole **7a** was obtained by heating o-(methylthio)-benzaldehyde and 2-picoline with a catalytic amount of zinc chloride in a sealed tube. The sulfur in the side chain of **7a** and **7e** was readily oxidized using the elegant Leonard–Johnson procedure[18] and, in this manner, methylsulfinylstilbazoles **7b**, **7f** and methylsulfonylstilbazoles **7c**, **7g** were prepared.

Stilbazoles **7a–g** were assigned the trans configuration about the double bond on the basis of spectral data. Thus, in their NMR spectra, the vinyl proton peaks (readily identifiable even though overlapping to a varying extent with other signals) exhibited a coupling constant of 16 Hz. Further, the infrared spectra contained absorption bands at 990–965 cm^{-1} typical of trans olefinic C–H bonds (out-of-plane bending). Finally, the ultraviolet spectra showed two absorption bonds beyond 250 nm, of which the one at longer wavelength was more intense, again indicating trans configuration about the double bond.[11,20]

The photocyclization of *trans*-2-stilbazoles is believed to occur stepwise, through the *cis*-2-stilbazoles and the dihydrobenzo[*f*]quinolines.[11] From the work of Kumler and Dybas it was known that *tert*-butyl alcohol or nonpolar solvents and irradiation through Corex filters gave the best yields of benzo[*f*]quinolines. Filter selection is critical in order that light absorption by the product be prevented and light absorption by the stilbazole be maximized. The ultraviolet spectra of stilbazoles **7a–g** are similar to that of unsubstituted 2-stilbazole, having *K* bands in the 310–330-nm region and aromatic absorption bands at shorter wavelengths. As shown in Figure 1, use of a Corex 9700 filter appears to allow excitation

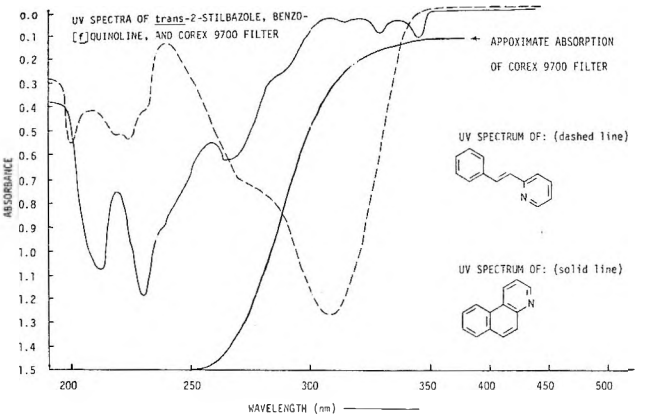
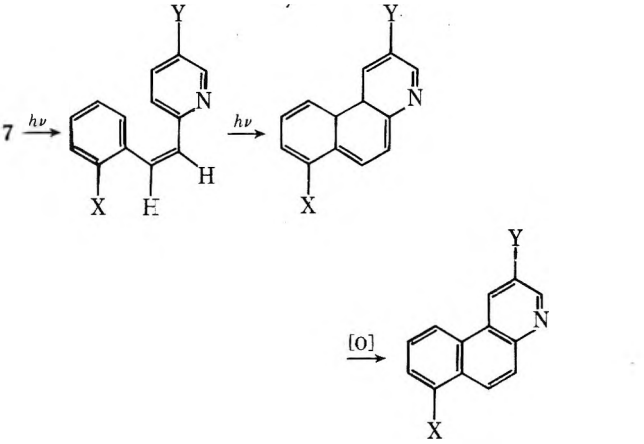


Figure 1.

of the stilbazoles at their wavelength of maximum absorption and at the same time protect the photoproducts from wavelengths of light that could cause further reaction.

Photolyses of stilbazoles **7a–g** were carried out in *tert*-butyl alcohol–benzene mixtures, in the presence of oxygen, using a Corex 9700 filter and were monitored by thin-layer chromatography. Any material which did not correspond to the precursor stilbazole was removed from the TLC plate and had its ultraviolet spectrum compared with that of unsubstituted benzo[*f*]quinoline.[21] Photolysates which gave UV spectra similar to that of the parent benzo[*f*]quinoline were then subjected to isolation procedures.

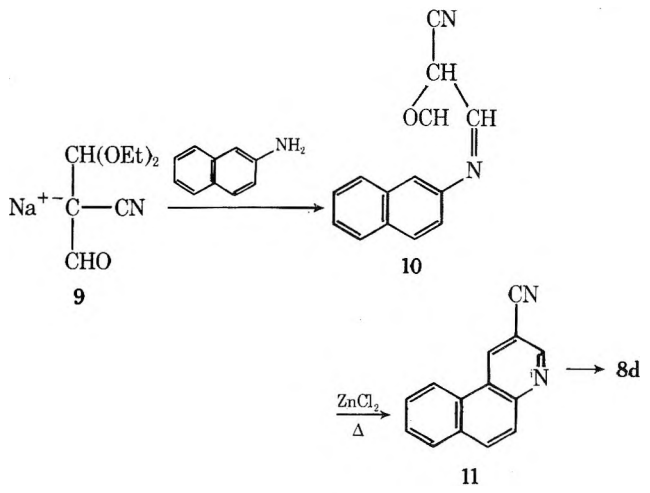
Photolysis of stilbazoles **7c**, **d**, and **g** yielded the corresponding benzo[*f*]quinolines **8c**, **d**, and **g**, in 21, 19, and 26%



8c, X = SO_2CH_3; Y = H
d, X = H; Y = COOEt
g, X = SO_2CH_3; Y = COOEt

yield, respectively. No useful product could be isolated from the photolysates of stilbazoles **7a**, **b**, **e**, and **f**. There was extensive decomposition (perhaps not unexpectedly, in view of the known lability of the carbon–sulfur bond under photolytic conditions[22]) and no evidence could be found for the presence of a cyclized product in any fraction of the photolysates, except in the case of stilbazole **7f**. Repeated column and thin-layer chromatographic treatments of that photolysate yielded traces of a colorless solid, which had a UV spectrum consistent with a cyclized product, but which could not be fully characterized because of insufficient available material.

The structure of photoproduct **8d** was confirmed by an independent, nonphotochemical preparation based on a series of reactions used by Uhle and Jacobs[23] for the synthesis of dihydrolysergic acid. Thus, the sodium salt of the diethyl acetal of cyanomalondialdehyde (**9**) was condensed with 2-naththylamine to imine **10**, which was cyclized by heating with



zinc chloride to 2-cyanobenzo[*f*]quinoline (**11**). Hydrolysis of **11** followed by esterification yielded **8d**, identical in all respects with the photochemically obtained material.

Work will be continued at a later date on the subsequent step of the synthetic sequence, base catalyzed ring closure involving the 7-methylsulfonyl group and position 6 of benzo[*f*]quinolines **8c** and **8g**, to complete construction of the benzo[*b*]thiophene portion of the thioergoline ring system **1**.

Experimental Section[24]

***o*-(Methylthio)benzoic acid** was prepared from o-mercaptobenzoic acid (Aldrich) by the method of Arndt.[25]

***o*-(Methylthio)benzyl alcohol (4).** Into a three-neck, 1-L round-bottom flask equipped with a reflux condenser, calcium chloride drying tube, and mechanical stirrer was placed 25.0 g (149 mmol) of *o*-(methylthio)benzoic acid (**3**). After the addition of 200 mL of anhydrous THF, the acid was made to dissolve by stirring and heating the contents of the flask. The resulting solution was cooled to room temperature, diluted with 400 mL of anhydrous ether, and further cooled in an ice bath for 15 min. Then 5.08 g (134 mmol) of lithium aluminum hydride was added, in small portions with stirring and cooling, during 10 min, and the reaction mixture was allowed to stir at room temperature for an additional 2.5 h. Excess lithium aluminum hydride was then decomposed, first by cautious addition of wet ether and then addition of 500 mL of 10% hydrochloric acid. Following separation of the ether layer, the aqueous layer was extracted with three 250-mL portions of ether and the combined ether solutions were washed with two 250-mL portions of 10% aqueous sodium hydroxide and finally with water. After drying over anhydrous sodium sulfate, the solvent was removed on a rotary evaporator and the residual oil distilled under reduced pressure to yield 18.6 (81%) of **4** as a clear liquid: bp 115–118 °C (1.1 Torr); lit.[26] bp 88 °C (10^{-3} Torr); IR (neat) 3650–3100 cm^{-1} (OH); ^1H NMR δ 2.28 (s, 3 H, CH_3–), 3.43 (s broad, 1 H, –OH), 4.52 (s, 2H, benzyl H's), 6.96 (s, 4H, Ar H's).

***o*-(Methylthio)benzaldehyde (5a).** Into a 2-L, three-neck flask equipped with a mechanical stirrer and calcium chloride drying tube were placed 100 g of freshly powdered active manganese dioxide, 1 L of carbon tetrachloride, and 20.0 g (130 mmol) of *o*-(methylthio)benzyl alcohol. The reaction mixture was allowed to stir for 24 h at room temperature and filtered, and the filter cake of manganese dioxide was washed with three 250-mL portions of acetone. The combined carbon tetrachloride and acetone filtrates were filtered again through a pad of Celite and the clear, light-yellow solution distilled of solvent on a rotary evaporator to give a residual oil. Distillation of this oil under reduced pressure yielded 19.0 g (96%) of **5a** as a light-yellow liquid: bp 96–101 °C (1.4 Torr); lit.[12] bp 149 °C (19 Torr); IR (neat) 1700–1675 cm^{-1} (C=O); ^1H NMR δ 2.35 (s, 3 H, CH_3–), 6.8–7.7 (m, 4 H, Ar H's), 9.97 (s, 1 H, CHO).

***o*-Methylsulfinylbenzaldehyde (5b).** To 138 mL of 0.5 M aqueous sodium metaperiodate (69 mmol of $NaIO_4$), stirred magnetically and maintained at 3 °C, was added 10.0 g (66 mmol) of *o*-(methylthio)benzaldehyde (**5a**) and the resulting mixture was stirred at 3 °C for 15 h. After filtration, the filter cake of sodium iodate was washed with two 50-mL portions of chloroform and the two-phase filtrate shaken in a separatory funnel. The chloroform layer was separated and the aqueous layer extracted with two 50-mL portions of chloroform. The combined chloroform solutions were dried over anhydrous sodium sulfate and the solvent was distilled under reduced pressure to yield a yellow oil which solidified when triturated with cold ether. The resulting crystalline material was collected, washed with a small amount of cold ether, and air dried to yield 10.7 g (96%) of an off-white crystalline product: mp 73–74 °C, lit.[12] mp 73–75 °C; IR (KBr) 1695–1670 cm^{-1} (C=O), 1025(S–O); ^1H NMR δ 2.73 (s, 3 H, CH_3–), 7.4–8.3 (m, 4 H, Ar H's), 9.85 (s, 1 H, CHO).

***trans*-2'-Methylthio-2-stilbazole (7a).** A mixture of 15.2 g (0.100 mol) of *o*-(methylthio)benzaldehyde, 9.31 g (0.100 mol) of 2-picoline and 0.200 g of zinc chloride was heated in a sealed tube, at 200 °C, for 16 h. The product was distilled under reduced pressure to yield 13.1 g (58%) of **7a** as a yellow, viscous oil: bp 158–164 °C (0.25 Torr); IR 970 cm^{-1} (*trans*-CH=CH); NMR δ 2.34 (s, 3, CH_3S–), 6.7–8.1 (m, 9, Ar H and =CH), 8.31 (d, 1, J = 4 Hz, 6-H); UV λ_{max} ($\epsilon \times 10^{-3}$) sh 352 nm (6.8), 310 (18.2), 266 (17.2), 208 (14.2).

Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16. Found: C, 73.89; H, 5.61; N, 6.04.

***trans*-2'-Methylsulfinyl-2-stilbazole (7b).** The mixture of a solution of 1.14 g (5 mmol) of **7a** in 80 mL of MeOH and 11.0 mL of 0.500 M aqueous sodium metaperiodate (5.5 mmol of $NaIO_4$) was stirred at room temperature for 24 h. After filtration, the filter cake of sodium iodate was washed with 40 mL of MeOH and the combined filtrate and washings evaporated to about 20 mL. This concentrate was diluted with 250 mL of water and the resulting solution extracted with three 75-mL portions of $CHCl_3$. The extract was dried (Na_2SO_4) and distilled to a viscous, oily residue. This material could not be induced to crystallize, nor could it be distilled under reduced pressure without decomposition. Partial purification by chromatography on an alumina column yielded 0.79 g (65%) of **7b** in the form of a viscous, yellow oil, the NMR spectrum of which showed that it was uncontaminated by the corresponding sulfide or sulfone: IR 1070, 1035 (S–O), 970 cm^{-1} (*trans*-CH=CH); NMR δ 2.61 (s, 3, CH_3SO–), 6.7–8.0 (m, 9, Ar H and =CH), 8.35 (d, 1, J = 4 Hz, 6-H); UV λ_{max} ($\epsilon \times 10^{-3}$) 314 nm (21.0), 226 (11.6), 233 (11.2), 207 (13.8).

Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76. Found: C, 67.32; H, 5.14; N, 5.51.

***trans*-2'-Methylsulfonyl-2-stilbazole (7c).** The mixture of a solution of 4.55 g (17.5 mmol) of **7a** in 400 mL of MeOH and 100 mL of 0.5 M aqueous sodium metaperiodate (50 mmol of $NaIO_4$) was refluxed for 18 h. A second 100 mL of 0.5 M aqueous sodium metaperiodate was then added and followed by a further 18 h of reflux. The reaction mixture was cooled and filtered, and the filter cake washed with 40 mL of MeOH. The combined filtrate and washings were diluted with water to three times its original volume to yield 3.09 g (60%) of **7c** as a colorless solid: mp 100–102 °C; IR 1295, 1150, 1123 (SO_2), 980 cm^{-1} (*trans*-CH=CH); NMR δ 3.03 (s, 3, CH_3SO_2–), 6.8–8.5 (m, 10, Ar H and =CH); UV λ_{max} ($\epsilon \times 10^{-3}$) 312 nm (22.2), 271 (13.0), 231 (12.0), 208 (15.8).

Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.99; H, 5.15; N, 5.37.

***trans*-5-Ethoxycarbonyl-2-stilbazole (7d).** A mixture of 10.6 g (0.100 mol) of benzaldehyde, 16.5 g (0.100 mol) of ethyl 6-methylnicotinate[27] and 20.4 g (0.200 mol) of acetic anhydride was refluxed for 12 h, then cooled and poured into ice. The resulting mixture was made basic to litmus with 10% aqueous NaOH and stirred until the organic material solidified. The solid was collected by filtration and recrystallized from EtOH–H_2O to yield 10.9 g (45%) of **7d** as tan crystals: mp 97–99 °C; IR 985 (*trans*-CH=CH), 1710 cm^{-1} (C=O); NMR δ 1.32 (t, 3 H, J = 7 Hz, CH_3CH_2–), 4.23 (q, 2 H, J = 7 Hz, CH_3CH_2–), 6.7–8.1 (m, 9 H, Ar H and vinylic H's), 8.90 (d, 1 H, J = 2 Hz, 6-H); UV λ_{max} ($\epsilon \times 10^{-3}$) 333 nm (33.0), 232 (10.2), 207 (15.0).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.74; H, 5.92; N, 5.58.

***trans*-5-Ethoxycarbonyl-2'-methylthio-2-stilbazole (7e).** From 15.2 g (0.100 mol) of *o*-(methylthio)benzaldehyde, 16.5 g (0.100 mol) of ethyl 6-methylnicotinate and 15.3 g (0.150 mol) of acetic anhydride, as described for **7d**, there was obtained (after recrystallization from MeOH) 18.8 g (63%) of **7e** in the form of a yellow solid: mp 89.5–91 °C; IR 1720 (C=O), 960 cm^{-1} (*trans*-CH=CH); NMR δ 1.37 (t, 3, J = 7 Hz, CH_3CH_2–), 2.42 (s, 3, CH_3S–), 4.29 (9, 2, J = 7 Hz, CH_3CH_2–), 6.7–8.2 (m, 8, Ar H and =CH), 8.97 (d, 1, J = 2 Hz, 6-H); UV λ_{max} ($\epsilon \times 10^{-3}$) sh 352 nm (12.6), 324 (19.5), 272 (13.2), 226 (16.2), 209 (15.9).

Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.18; H, 5.83; N, 4.62.

***trans*-5-Ethoxycarbonyl-2'-methylsulfinyl-2-stilbazole (7f).** The mixture of a solution of 1.50 g (5 mmol) of **7e** in 125 mL of MeOH and 11.0 mL of 0.5 M aqueous sodium metaperiodate (5.5 mmol of $NaIO_4$) was stirred at room temperature for 24 h. Following filtration,

the filter cake of sodium iodate was washed with 40 mL of MeOH and the combined filtrate and washings diluted with 600 mL of ice-cold water to yield 1.21 g (77%) of **7f** as a cream-colored solid: mp 128–130 °C; IR 1710 (C=O), 1075, 1035 (S–O), 970 cm^{-1} (*trans*-CH=CH); NMR δ 1.38 (t, 3, J = 7 Hz, CH_3CH_2–), 2.65 (s, 3, CH_3SO–), 4.30 (q, 2, J = 7 Hz, CH_3CH_2–), 6.8–8.2 (m, 8, Ar H and =CH), 8.97 (d, 1, J = 2 Hz, 6-H; UV λ_{max} ($\epsilon \times 10^{-3}$) sh 351 nm (16.5), 330 (28.8), 273 (10.5), 230 (12.9), 208 (16.2).

Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.54; H, 5.51; N, 4.44.

***trans*-5-Ethoxycarbonyl-2′-methylsulfonyl-2-stilbazole (7g).** The mixture of a solution of 1.50 g (5 mmol) of **7e** in 200 mL of MeOH and 30 mL of 0.5 M aqueous sodium metaperiodate (15 mmol of $NaIO_4$) was refluxed for 24 h. After addition of a second 30 mL of 0.5 M aqueous sodium metaperiodate and refluxing for a further 24 h, the reaction mixture was cooled and filtered. The filter cake was washed with 40 mL of MeOH and the combined filtrate and washings diluted with 500 mL of ice-cold water to yield 1.54 g (93%) of **7g** as a cream-colored solid: mp 157–159 °C; IR 1720 (C=O), 1315, 1155, 1120 (SO_2), 960 cm^{-1} (*trans*-CH=CH); NMR δ 1.38 (t, 3, J = 7 Hz, CH_3CH_2–), 3.04 (s, 3, CH_3SO_2–), 4.32 (q, 2, J = 7 Hz, CH_3CH_2–), 6.8–8.6 (m, 8, Ar H and =CH), 8.97 (d, 1, J = 2 Hz, 6-H); UV λ_{max} ($\epsilon \times 10^{-3}$) sh 351 nm (12.6), 325 (29.4), 280 (11.1), 236 (11.1), 209 (16.2).

Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.55; H, 5.25; N, 4.01.

7-Methylsulfonylbenzo[*f*]quinoline (8c). A solution of 1.30 g (5 mmol) of **7c** in 1 L of *tert*-butyl alcohol–benzene (1:1) was placed in a 1-L photochemical reaction vessel and irradiated with a 450-W Hanovia, medium-pressure, mercury-arc (type 679 A36) lamp contained in a quartz, water-cooled jacket and surrounded by a tubular Corex 9700 filter. Oxygen was bubbled through the solution for 0.5 h prior to and during the 8-h photolysis period, at the end of which the reaction mixture was distilled of solvent to give 3.36 g of a gummy residue. This was dissolved in 50 mL of $CHCl_3$ and the resulting solution mixed with 7.0 g of neutral alumina (Baker No. 0540) to a slurry which was evaporated to dryness under reduced pressure. The solid material was then ground to a powder and placed at the top of a chromatography column[28] of 25.0 g of neutral alumina in a 1 in. glass tube. Elution with benzene–chloroform (1:1) allowed isolation of 0.47 g of a viscous, yellow oil corresponding to a yellow band on the column. This was made to crystallize by trituration with anhydrous ether and yielded 0.27 g (21%) of **8c** as a light-yellow solid: mp 153–156 °C; IR 1307, 1148 cm^{-1} (SO_2); NMR δ 3.17 (s, 3, CH_3SO–), 7.1–8.4 (m, 4, Ar H), 8.64 (d, 4, J = 9 Hz, Ar H); UV λ_{max} ($\epsilon \times 10^{-3}$) 343 nm (0.09), 327 (0.09), 300 (12.0), sh 286 (14.4), 275 (22.2), 242 (34.2), 211 (20.1).

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.17; H, 4.43; N, 5.43.

2-Ethoxycarbonylbenzo[*f*]quinoline (8d). A. Photochemical Synthesis. A solution of 1.27 g (5 mmol) of **7d** in 1 L of *tert*-butyl alcohol–benzene (9:1) was photolyzed as described for **8c**, for 8 h. The resulting solution was evaporated under reduced pressure to 1.55 g of a viscous, brown residue which was dissolved in the minimum amount of chloroform and chromatographed on a column of 40.0 g of neutral alumina in a 1 in. glass tube. The column was eluted with chloroform and the progress of the band corresponding to the photoproduct was monitored by its fluorescence under UV light. The eluate containing the fluorescent band was evaporated to 1.03 g of a viscous, tan residue which was dissolved in the minimum amount of acetone. A portion of this solution, containing 275 mg of the residue, was applied on an 8 × 8 in., 2 mm silica gel preparative thin layer chromatographic plate. Development of the plate with chloroform yielded a fluorescent band near the origin. The absorbent material containing this band was scraped off the plate and extracted with acetone to yield, after removal of the solvent, 70 mg of a viscous oil which was made to crystallize by trituration with cyclohexane. There was obtained 64 mg (19%) of **8d** as a tan solid, mp 103–105 °C (a 1:1 mixture of this material with that obtained by the following nonphotochemical synthesis (mp 101–104 °C) had a melting point range of 102.5–104 °C); IR 1725 cm^{-1} (C=O); NMR δ 1.45 (t, 3, J = 7 Hz, CH_3CH_2–), 4.42 (q, 2, J = 7 Hz, CH_3CH_2–), 7.3–7.75 (m, 3, 7-H, 8-H, and 9-H), 7.81 (s, 2, 5-H and 6-H), 8.37–8.50 (m, 1, 10-H), 9.26 (s, 2, 1-H and 3-H); UV λ_{max} ($\epsilon \times 10^{-3}$) 350 nm (3.6), 337 (4.8), 318 (8.4), 271 (16.4), 263 (16.8), 237 (35.2), sh 220 (24.8).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.54; H, 5.27; N, 5.60.

B. Nonphotochemical Synthesis. A 125-mL Erlenmeyer flask containing 10.0 g of zinc chloride was immersed in an oil bath the temperature of which was being raised at a rate of about 5 °C/min. When the bath temperature reached 180 °C, 10.0 g (45 mmol) of **10** was added into the flask over a period of 2 min with continual stirring of the solid mixture. At a bath temperature of 210 °C the mixture melted and shortly thereafter the flask was removed from the heating bath and allowed to cool. The solidified product was mixed with water, broken into pieces, collected by filtration, and ground into a powder. After it had been washed repeatedly with water, the powdered material was refluxed overnight with 250 mL of 18% hydrochloric acid. The resulting solution was evaporated under reduced pressure to a solid residue which was then refluxed overnight with 1 L of absolute ethanol containing 20 mL of concentrated sulfuric acid. Following distillation of most of the ethanol, the concentrate was mixed with a solution of 100 g of K_2CO_3 in 400 mL of H_2O and the resulting mixture was extracted with several portions of chloroform. After the combined extracts had been dried (Na_2SO_4), the chloroform solution was evaporated to a solid residue, which was mixed with a small amount of anhydrous ether and filtered to yield 2.24 g (20%) of **8d** as a light tan solid: mp 101–104 °C. The IR and NMR spectra of this product were identical with those of the product of the immediately preceding photochemical synthesis.

***N*-(2-Cyano-2-formylethylidene)-2-naphthylamine (10).** Sodium (2.30 g, 0.100 mol) was added to a solution of 14.3 g (0.100 mol) of 1-cyano-2,2-diethoxyethane[23] and 8.00 g (0.108 mol) of ethyl formate in 250 mL of anhydrous ether and the resulting mixture was stirred until all of the sodium had reacted. Following addition of 100 mL of water and separation of the layers, the aqueous solution was run into a warm solution of 14.3 g (0.100 mol) of 2-naphthylamine in a mixture of 100 mL of ethanol and 360 mL of 3% hydrochloric acid. The precipitated yellow solid was collected by filtration and recrystallized from ethanol to yield 10.6 g (48%) of **10** as a salmon-colored solid: mp 214–216 °C; IR 2225 (C≡N), 1645 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 7.0–8.0 (m, 7, Ar H's), 8.60 (d, 1, J = 15 Hz, –N=CH–), 9.16 (s, 1, –CHO), 11.06 (d, 1, J = 15 Hz, >CH–CN).[29]

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.52; H, 4.67; N, 12.60.

2-Ethoxycarbonyl-7-methylsulfonylbenzo[*f*]quinoline (8g). A solution of 1.66 g (5 mmol) of **7g** in 1 L of *tert*-butyl alcohol–benzene (1:1) was photolyzed, as before, for 7 h. The resulting solution was evaporated under reduced pressure to 3.28 g of a gummy residue which was chromatographed, as described for **8c**, on a column of 25.0 g of neutral alumina in a 1-in. glass tube. Elution with benzene–chloroform (1:1) yielded 0.87 g of a light yellow solid corresponding to a yellow band in the column. This crude product, triturated and washed with anhydrous ether, gave 0.53 g of an off-white solid, mp 219–222 °C. NMR analysis of this material indicated that, in addition to **8g**, it contained 18% of the starting stilbazole **7g**. Attempts to purify the photoproduct by recrystallization resulted in an increase of the stilbazole starting material, as evidenced by NMR analysis. A somewhat purer sample was obtained by purification of the photoproduct using preparative TLC on silica gel: IR 1720 cm^{-1} (C=O); NMR δ 1.47 (t, 3, J = 7 Hz, CH_3CH_2–), 3.22 (s, 3, $-SO_2CH_3$), 4.47 (q, 2, J = 7 Hz, CH_3CH_2–), 7.5–8.5 (m, 3, 5-H, 6-H, and 9-H), 8.82 (s, 1, 8-H or 10-H), 8.95 (d, 1, J = 3 Hz, 8-H or 10-H), 9.40 (s, 2, 1-H and 3-H); UV λ_{max} ($\epsilon \times 10^{-3}$) 347 nm (1.2), 333 (2.1), 310 (12.3), 300 (12.3), 281 (15.3), 243 (32.4), 216 (21.0).

Anal. Calcd For $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59; N, 4.25. Found: C, 60.71; H, 4.74; N, 4.07.

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Registry No.—**3**, 3724-10-5; **4**, 33384-77-9; **5a**, 7022-45-9; **5b**, 62351-49-9; **5** (X = H), 100-52-7; **6** (Y = H), 109-06-8; **6** (Y = COOEt), 21684-59-3; **7a**, 63133-63-1; **7b**, 63104-22-3; **7c**, 63104-23-4; **7d**, 63104-24-5; **7e**, 63104-25-6; **7f**, 63104-26-7; **7g**, 63104-27-8; **7** (X = Y = H), 538-49-8; **8c**, 63104-28-9; **8d**, 63104-29-0; **8g**, 63104-30-3; **8** (X = Y = H), 85-02-9; **10**, 63104-31-4; 1-cyano-2,2-diethoxyethane, 2032-34-0; 2-naphthylamine, 91-59-8; ethyl formate, 109-940-4.

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(2) Department of Chemistry, Oklahoma State University, Stillwater, Okla., 74074.
(3) Fellow of the Alfred P. Sloan Foundation, 1971–1976; Department of Chemistry, Bowling Green State University.
(4) Department of Chemistry, The University of New Mexico.
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Carbon-13 Nuclear Magnetic Resonance Studies of Sulfur Heterocycles. Evidence for Intramolecular 1,3 Electronic Interaction in 3,3-Disubstituted 2*H*-Tetrahydrothiapyran-1-*N*-*p*-tosylsulfimides[1]

John R. DeMember,* Richard B. Greenwald, and David H. Evans

Research Laboratories, Polaroid Corporation, Cambridge, Massachusetts 02139

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Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra of several mono- and disubstituted 2*H*-tetrahydrothiapyrans and dithianes have been recorded and assigned. The compounds studied provide a series which is amenable to correlation by the additivity of substituent effects in ^{13}C NMR spectroscopy. The $\Delta\delta$'s between calculated and observed ^{13}C NMR shifts provided a sensitive probe for substituent–substituent interactions in compounds **6–8**, **13**, and **14**. The ^{13}C NMR data obtained suggest an intramolecular 1,3 electronic interaction in 3,3-dimethyl- and 3,3-dialkoxy-1-*N*-*p*-tosylthianes and dithianes (**6–8**) and **13** and **14**. Specifically, the data suggest a weak coulombic attractive interaction between the molecular orbitals of the sulfur with the formal positive charge S^1 and the electrons of the C^2–C^3 bond.

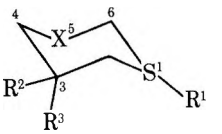
Proton nuclear magnetic resonance (^1H NMR) studies of 2*H*-tetrahydrothiapyran (thiane) and dithiane derivatives have centered primarily on conformational analyses.[2] Recent reports of ^{13}C NMR studies of substituted six-membered-ring hydrocarbons and heterocycles have shown the power of ^{13}C NMR in conformational analysis.[2i,j,3] In many cases, ^{13}C NMR data related to intramolecular 1,3 steric and/or electronic interactions which lead to conformational preferences for six-membered rings have been obtained.[2m] However, definitive elucidation and differentiation of steric and/or electronic interactions based on ^{13}C NMR data have not been possible generally.[4]

Since the chemistry of sulfur compounds is important in many biological and photographic processes, the elucidation of intramolecular interactions and their relation to the physical and chemical properties of thiane derivatives are of interest. Presently, we report a ^{13}C NMR study which provides *direct* ^{13}C NMR spectroscopic evidence for a transannular 1,3 *electronic* interaction in 3,3-disubstituted thiane derivatives.

Results and Discussion

The compounds studied are thiane (**X** = CH_2) derivatives **1–8** and dithiane derivatives (**X** = S) **9–14**.[2,13]

Data for the thiane ring carbon atoms of compounds **1–14** are shown in Table I. Assignments for **1–14** are based on line



X = CH_2		X = S
1	R^1 = electron pair; R^2, R^3 = H	**9**
2	R^1 = *N*-*p*-tosyl; R^2, R^3 = H	**10**
3	R^1 = electron pair; R^2, R^3 = C^7H_3, C^8H_3	**11**
4	R^1 = electron pair; R^2, R^3 = OC^7H_3, OC^8H_3	
5	R^1 = electron pair; R^2, R^3 = $-O-C^7H_2C^8H_2-O-$ (cyclic ketal)	**12**
6	R^1 = *N*-*p*-tosyl; R^2, R^3 = C^7H_3, C^8H_3	**13**
7	R^1 = *N*-*p*-tosyl; R^2, R^3 = OC^7H_3, OC^8H_3	
8	R^1 = *N*-*p*-tosyl; R^2, R^3 = $-O-C^7H_2C^8H_2-O-$ (cyclic ketal)	**14**

intensity, ^{13}C–H coupling constants and the chemical shifts of model compounds. The ^{13}C NMR spectrum of **2** was recorded at −90 °C in CH_2Cl_2.[2c] The high-field signals in the spectrum (−90 °C) of compound **2** have been assigned to those of the axial 1-*N*-*p*-tosyl isomer.[2c] From the relative area of the ^{13}C NMR signals of C^2 in **2** at 41.7 ppm (axial) and 47.9 (equatorial), the axial/equatorial isomer ratio has been determined to be 1.44. This correlates well with the ratio of 1.50 determined from ^1H NMR by Lambert et al.[2c]

Calculated shifts for the ring carbon atoms of compounds

Table I. ^{13}C NMR Chemical Shifts for the Ring Carbon Atoms of Thiane and Dithiane Derivatives[a]

Registry no.	Compd	Chemical shifts[b] C^2	C^3	C^4	C^5	C^6	C^7(a)	C^8(e)
16131-51-0	**1**[h]	29.1	27.8	26.5	27.8	29.1		
13553-73-6	**2** (a)[c]	41.7	16.2	23.2	16.2	41.7		
	2 (e)[c]	47.9	23.7	23.5	23.7	47.9		
57259-83-3	**3**[h]	41.1	29.7	39.3	23.8	28.7	28.3[e]	28.3[e]
63449-32-1	**4**	33.2	96.7	32.6	25.6	28.0	47.5[e]	47.5[e]
177-13-9	**5**	35.5	105.3	35.1	27.1	27.5	64.6[e]	64.6[e]
31815-14-2	**6**[d]	58.2	33.5	36.4	19.3	47.1	25.1[f]	31.4[g]
63449-33-2	**7**[d]	52.2	98.4	30.4	18.5	46.8	47.9[f]	48.2[g]
63449-34-3	**8**[d]	53.7	105.6	33.4	21.4	46.2	65.1[f]	65.2[g]
505-23-7	**9**[h]	28.9	26.3	28.9		30.9		
58484-97-2	**10**	46.4	26.2	26.5		46.5		
60311-39-9	**11**[h]	41.9	26.8	41.9		31.5	27.5[e]	27.5[e]
177-14-0	**12**	36.4	100.4	36.3		30.4	65.1[e]	65.1[e]
63449-35-4	**13**[d]	60.0	37.7	40.1		48.6	24.7[f]	30.8[g]
63449-36-5	**14**[d]	53.2	105.5	33.6		45.1	65.1[e]	65.1[e]

[a] ^{13}C NMR data were recorded at 35 ± 0.1 °C in a 10-mm tube with a Varian CFT-20 spectrometer at 15% (w/v) in Me_2SO-d_6. [b] Chemical shifts are reported as δ in parts per million downfield (+) of tetramethylsilane. [c] These isomers were frozen out in CH_2Cl_2 solution 5% (w/v) at −90 °C in an 8-mm tube (see ref 2c). [d] These compounds have the 1-*N*-*p*-tosyl group in the equatorial position. [e] Averaged signal at 28 °C in $CDCl_3$. [f] Axial group based on shielding effect. [g] This δ is assigned to the equatorial group based on deshielding effect. [h] These data have been reported previously by various authors (see ref 2).

6–8, 13, and **14** were obtained by the additivity of substituents as shown in eq 1–3,[3] where δ is the chemical shift in parts per million (Table I) of the C^n carbon atom of the numbered compound (**1–14**) and a = axial; e = equatorial. This method has been shown to have general success in predicting the ^{13}C NMR shifts of unknown compounds.[5] The Δδ values obtained from these calculated and observed shifts are shown in Table II. The additivity of substituent effects has been used in several instances to predict effectively the chemical shifts of saturated heterocycles.[3] Even with appropriate models, as the number of polar substituents in a molecule is increased, the accuracy of additivity relationships can drop dramatically depending upon substituent–substituent interactions in the unknown compound studied. With appropriate structural models, therefore, large Δδ values between predicted and observed shifts can be interpreted in terms of structural changes which originate directly from substitutent interactions that cannot occur in the models.

Thiane axial:

$$\delta^{C^n}\mathbf{6}(a)(\mathbf{7}(a) \text{ or } \mathbf{8}(a)) = \delta^{C^n}\mathbf{2}(a) - \delta^{C^n}\mathbf{1} + \delta^{C^n}\mathbf{3}(\mathbf{4} \text{ or } \mathbf{5}) \quad (1)$$

Thiane equatorial:

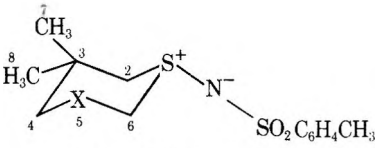
$$\delta^{C^n}\mathbf{6}(e)(\mathbf{7}(e) \text{ or } \mathbf{8}(e)) = \delta^{C^n}\mathbf{2}(e) - \delta^{C^n}\mathbf{1} + \delta^{C^n}\mathbf{3}(\mathbf{4} \text{ or } \mathbf{5}) \quad (2)$$

Dithiane equatorial:

$$\delta^{C^n}\mathbf{13} \text{ (or } \mathbf{14}) = \delta^{C^n}\mathbf{10} - \delta^{C^n}\mathbf{9} + \delta^{C^n}\mathbf{11} \text{ (or } \mathbf{12}) \quad (3)$$

The small average deviations between the predicted and observed ^{13}C NMR shifts for *equatorial* and the large positive average deviations for the *axial* 1-*N*-*p*-tosyl conformation clearly show that this substituent is *equatorial* in thiane compounds **6–8**.[2] The 1-*N*-*p*-tosyl group is known to prefer the *equatorial* conformation in thiane derivatives **3** and **6** and dithiane derivatives **10, 13,** and **14**.[2b,21,3d]

The ^{13}C and ^1H NMR signals of the methyl carbons C^7 and C^8 and of the methyl protons in compounds **3** and **11**, respectively, occur as averaged signals at 28 °C in $CDCl_3$ (see Table I and Experimental Section). Under identical conditions, these methyl carbons and protons in 3,3-dimethyl compounds **6** and **13** are observed as two separate signals. The numerical averages of these two signals for 1-*N*-*p*-tosyl derivatives **6** and **13** are identical to the averaged NMR signals of the methyl groups observed for **3** and **11**, respectively. This

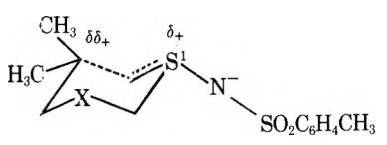


6, X = CH_2; **13**, X = S

shows that there is no observable steric or electronic perturbation of the methyl groups in **6** and **13** resulting from the presence of the 1-*N*-*p*-tosyl moiety. The resolution of separate signals for the two methyl groups in compounds **6** and **13** is related only, therefore, to the predominance of one conformer. Furthermore, that the NMR spectra of compounds **7–8, 13** and **14** are temperature independent is evidence for the exclusive existence of compounds **6** and **13** as the equatorial 1-*N*-*p*-tosyl conformers.

The ^{13}C NMR signals of the exocyclic C^7 and C^8 methoxy and methylene carbons in the thiane compounds **4** and **5** are very weakly shielded ($\Delta\delta^{max}$ <1.0 ppm) relative to those same carbons in 1-*N*-*p*-tosyl derivatives **7** and **8** (Table I). For dithiane **12** the ^{13}C NMR signals of the exocyclic methylene groups are identical to those observed for 1-*N*-*p*-tosyl compound **14** (Table I). The ^1H NMR signals for the pendant groups of dithiane compounds **11–14** are also insensitive to any 1,3 interactions in these compounds.

With the knowledge that the conformation of the 1-*N*-*p*-tosyl group in **6**[21], **7, 8, 13**,[21] and **14** is equatorial, further information related to intramolecular interactions in these molecules can be gleaned from the relative magnitudes of the deviations shown in the *equatorial* columns of Table II. It is evident that large Δδ values are observed for the C^3 and C^5 carbon atoms of **7**, and for the C^3 carbon atoms of **13, 14, 8,** and **6**.



6, X = CH_2; **13**, X = S

Considerable evidence has been reported previously indicating that dithiane compounds analogous to **9–14** exist predominately in the chair conformation.[2b] Δδ values could possibly reflect a difference in conformation of the compounds **6–8, 13,** and **14** from some or all of their model compounds.

Table II. Deviations ($\Delta\delta$ and $\Delta(\Delta\delta)$ values) between Predicted and Observed C^{13} NMR Shifts for Thiane and Dithiane Derivatives[a]

Carbon atom	Compound 6		13		7		14		8	
	$\Delta\delta a^b$	$\Delta\delta e^c$	$\Delta\delta e$	$\Delta(\Delta\delta)e^d$	$\Delta\delta a^b$	$\Delta\delta e^c$	$\Delta\delta e$	$\Delta(\Delta\delta)e$	$\Delta\delta a^b$	$\Delta\delta e$
C^2	*+4.6*	**−1.7**[e]	**+0.6**	**−2.3**	*+6.4*	**+0.2**	**−0.7**	**−0.9**	*+5.6*	**−0.6**
C^3	*+14.8*	**+7.9**	**+12.0**	**+4.1**	*+13.3*	**+5.8**	**+5.2**	**−0.6**	*+11.9*	**+4.4**
C^4	*+0.4*	**+0.1**	**+0.6**	**+0.5**	*+0.9*	**+0.8**	**−0.3**	**−1.1**	*+1.6*	**+1.2**
C^5	*+7.1*	**+0.6**			*+4.5*	**−3.0**			*+5.7*	**−1.6**
C^6	*+5.8*	**−0.4**	**+1.5**	**+1.9**	*+5.9*	**0.0**	**−0.9**	**−0.9**	*+6.5*	**+0.7**

[a] $\Delta\delta = \delta c^n$ observed $- \delta c^n$ calculated; δc^n values calculated were determined from eq 1, 2, or 3. $\Delta\delta$ = ppm and positive (+) number indicates that the observed shift is to lower field of that calculated. For the numbers shown in this table, only those larger than ±2.0 ppm are considered significant. Although no actual estimate of the error for these numbers is available, it is evident that any attempt to interpret $\Delta\delta$ values < ±2.0 in terms of molecular structure would be tenuous and could lead to specious conclusions. [b] See eq 1. [c] See eq 2. [d] $\Delta(\Delta\delta) = \Delta\delta e^n$ dithiane $- \Delta\delta e^n$ thiane. [e] Numbers shown in boldface type are those assigned to the compound. Those in italics are based on the hypothetical axial 1-*N*-*p*-tosyl isomer and are not real (see text).

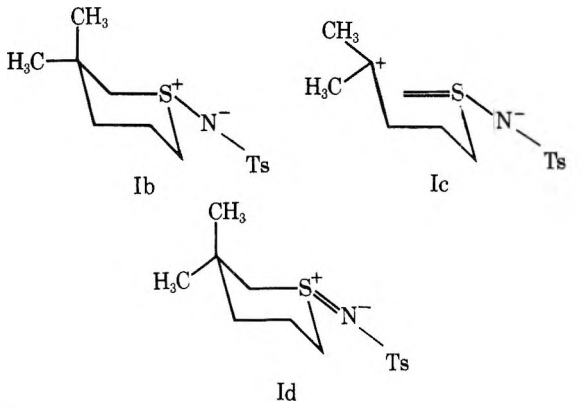
However, the substantial $\Delta\delta$ values for compounds **6, 8, 13,** and **14** are localized at C^3, and those for compound **7** at C^3 and C^5. This indicates that the $\Delta\delta$ values in Table II are very probably related to a specific interaction of the substituents in the chair conformation and not to a change in overall conformation (i.e., chair → boat). The lack of any substantial differences in the ^1H and ^{13}C NMR shifts of the substituent carbons C^7 and C^8 (see Table I) of compounds **6–8, 13,** and **14** relative to the models is a further indication of a localized interaction, since any overall conformational changes would be expected to result in changes in the NMR shifts of these atoms.

Since the 1-*N*-*p*-tosyl group is equatorial in compounds **6** and **13,** any interactions leading to large $\Delta\delta$ values for these compounds would be expected to be predominately electronic and not steric. A steric effect at C^3 would be expected to affect the ^{13}C and ^1H NMR shifts of thianes **6** and **13** to give more shielded signals and hence larger negative $\Delta\delta$ values (in the order $\Delta\delta^{C^7} > \Delta\delta^{C^3} > \Delta\delta^{C^5} > \Delta\delta^{C^2}$) than those found in Table II for the C^7, C^5, and C^2 carbon atoms. Alternatively, the severe 1,3 steric repulsion of the substituents in all of the compounds **6–8, 13,** and **14** with the axial 1-*N*-*p*-tosyl group is implied by the exclusive predominance of the equatorial 1-*N*-*p*-tosyl isomer.

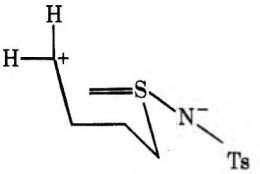
It is evident that the quaternary nature of C^3 in **6** and **13** is important to the interpretation of the substantially deshielded $\Delta\delta$ values of C^3, since the ^{13}C NMR shifts of C^3 and C^5 in the model thiane derivative **2** *equatorial* are shielded by the introduction of the equatorial 1-*N*-*p*-tosyl group. This shielding effect produced by the introduction of the 1-*N*-*p*-tosyl group occurs also in compound **6** at C^5. This is shown by the δ calculated for C^5 using **2** *equatorial* as a model. *The absence of any $\Delta\delta$ for C^5 demonstrates that no interaction or absence of interaction originates at C^5 in* **6** *that does or does not occur in the models.*

It is known that tertiary carbenium ions are thermodynamically much more stable than primary ions.[6] The positively charged carbon in tertiary carbenium ions is deshielded by about 180 ppm relative to the corresponding neutral species, while the α-carbons are deshielded by 20–30 ppm.[6] The enhanced deshielding of C^3 in compounds **6** and **13** of +7.9 and +12.0 ppm, respectively, therefore suggests a weak coulombic attractive interaction between the molecular orbitals of the formal positively charged sulfur S^1 and the electrons of the C^2–C^3 bond. Based on analogy with the chemical-shift data for carbon atoms α to a carbenium carbon,[5] if such an interaction gives rise to a deshielding effect at C^3 of 8–12 ppm the deshielding effect on C^2, C^4, C^7, and C^8 should be negligible. This is in accordance with our findings.

If we consider the three structures of **6** and **13,** *viz.*, Ib–d, we can predict the relative weight that each has in the molecular orbitals of I in light of the NMR data. The magnitude



of the deshielding effect at C^3 is consistent with only a small but measurable contribution from structure Ic. As the weight of the uncharged sulfimide canonical form Id in the molecular orbitals of **6** and **13** increases, the potential for the proposed interaction of S^1 and the C^2–C^3 bond decreases. Alternatively, when the much lower energy of Ic as compared to 2b is considered, weak hyperconjugative interaction of the C^2–C^3 bond appears to be a plausible explanation for the measurable large positive $\Delta\delta$ values of C^3 in compounds **6** and **13.**



2b

In compounds **7, 8,** and **14,** an additional heteroatom, oxygen, is attached to the C^3 carbon atom. It is evident from Table II that in addition to the deshielding ($\Delta\delta^{C^3}$ = +5.8 ppm) of C^3 in **7** there is a smaller shielding ($\Delta\delta^{C^5}$ = −3.0 ppm) of C^5. The shielding ($\Delta\delta^{C^5}$ = −1.6 ppm) of C^5 in **8,** where the oxygen atoms are held rigidly away from the thiane ring, is substantially diminished.

Based on similar arguments to those presented above for the 3,3-dimethyl compounds **6** and **13,** significant deshielding of C^3 in compounds **7, 8,** and **14** therefore suggests very weak hyperconjugation of the C^2–C^3 bond. That this overall deshielding of C^3 is smaller for compounds **7, 8,** and **14** than that observed for **6** or **13** is consistent with the much lower deshielding of alkoxycarbenium ion carbons relative to their alkyl carbenium ion analogues.

The $\Delta(\Delta\delta)$ values reported in Table II are the $\Delta\delta$ values between the thiane and dithiane derivatives. They reflect the effect of sulfur S^5 upon the chemical shifts of the carbon atoms of the corresponding dithiane.

Table II shows a substantial $\Delta(\Delta\delta)$ of +4.1 ppm for C^3 in thiane **6** relative to dithiane **13**. No significant $\Delta(\Delta\delta)$ values are observed for compounds **8** and **14**. Thus, a significant localized perturbation is produced at C^3 in compound **13** by the sulfur in the 5 position (S^5). This additional deshielding of C^3 in **13** relative to **6** may indicate that S^5 enhances the small changes in bonding at C^3 as discussed above. For compounds **8** and **13**, where oxygen is directly bonded to C^3 and can directly participate in the interactions of C^2–C^3 with S^1, the introduction of S^5 has no marked effect, as would be expected.

Experimental Section

Samples of thiane (**1**) and 1,3-dithiane (**9**) were obtained from Aldrich Chemical Co.; the corresponding *N*-*p*-tosyl sulfimide derivatives **2** and **10** were prepared by published procedures.[2c,3c] Carbon-13 magnetic resonance spectra were obtained on a Varian Associates CFT-20 spectrometer; proton NMR spectra were obtained on a Varian T-60. Reported melting and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3,3-Dimethylthiapyran-*N*-*p*-tosylsulfimide[8] (6). (A) 2,2-Dimethylpentane-1,5-diol.[9a,b] To a solution (70% in benzene) of Vitride (260 mL, 935 mmol) in 150 mL of sieve-dried tetrahydrofuran (THF) contained in a dried 3-L three-necked, round-bottomed flask equipped with an air-driven stirrer, reflux condenser, nitrogen inlet, and dropping funnel, a solution of 2,2-dimethylglutaric acid[11] (25 g, 156 mmol) in 120 mL of THF was added dropwise over 0.5 h. An exothermic reaction commenced immediately, and a thick precipitate began to separate which then dissolved as the reaction mixture spontaneously attained a slow reflux. Following completion of addition, the reaction mixture was heated for 2 h at reflux and then allowed to cool and to stand at room temperature overnight. The nearly colorless solution was chilled to 0 °C in an ice–salt water bath, and a chilled (5 °C) solution of 125 mL of concentrated sulfuric acid in 400 mL of water was added *very* slowly to control the strongly exothermic reaction. When the addition was complete, 500 mL of ether was added and vigorous stirring was maintained for 2 h. The organic phase was separated and dried over magnesium sulfate, and the solvents were removed in vacuo to give a pale amber syrup (33 g) which was distilled under reduced pressure to give the title compound (13.3 g, 65%), bp (~16 mm) 144–145 °C [lit.[10] bp (~16 mm) 140–142 °C].

(B) **2,2-Dimethyl-1,5-pentyl di-*p*-toluenesulfonate.** A stirred solution of 2,2-dimethylpentane-1,5-diol (3.6 g, 27.2 mmol) in 35 mL of dry pyridine was chilled to 0 °C in an ice–salt water bath, and *p*-toluenesulfonyl chloride (11.4 g, 60 mmol) was added in portions over 20 min so that the internal temperature did not exceed 5 °C. The reaction mixture was stirred at 0–5 °C for 4 h and then stored in a refrigerator overnight. The white crystalline mass was poured onto excess ice, collected, washed thoroughly with cold 5% hydrochloric acid, and air-dried to give a homogeneous creamy white solid, mp 71–73 °C (10.8 g, 90%), which on crystallization from ethanol-2B (1 g/30 mL) afforded white needles, mp 78–79 °C. Anal. Calcd for $C_{21}H_{28}O_6S_2$: C, 57.30; H, 6.37. Found: C, 57.63; H, 6.52.

(C) A mixture of 2,2-dimethyl-1,5-pentyl di-*p*-toluenesulfonate (16.8 g, 38.2 mmol) and freshly ground sodium sulfide nonahydrate (9.2 g, 38.2 mmol) was taken up in 80 mL of *N,N*-dimethylformamide at room temperature. A transiently green-beige suspension resulted, and the temperature rose spontaneously ~6 °C. The reaction mixture was heated slowly to reflux. A rich emerald-green solution was attained at 85 °C which slowly changed to amber as reflux was approached. After an additional 4.5 h at reflux, the reaction mixture was cooled and poured into 500 mL of cold water to give a milky suspension from which some amorphorous solid separated on standing overnight. The mixture was filtered by suction, and the filtrate was extracted with 3 × 150 mL of ether. The combined organic extracts were washed with 3 × 100 mL of water, dried over magnesium sulfate, and evaporated in vacuo to give a pale yellow syrup (3.6 g, 72%).[12] the crude 3,3-dimethylthiapyran (**3**) (ca. 25 mmol) was taken up in 100 mL of methanol and filtered to remove a small amount of insoluble material. The methanol solution was treated with Chloramine T trihydrate (8.45, 30 mmol) in small portions over 0.5 h. The reaction mixture was allowed to stir for 1 h; the solvent was removed in vacuo, and the residue was taken up in chloroform. Insoluble material was removed by filtration; the filtrate was dried over magnesium sulfate and evaporated to give an amber syrup. Clusters of white needles formed on standing overnight which were triturated with acetone and collected to give the title compound **6** (3.3 g, ca. 44%), mp 175–177 °C (lit.[8] 173–174 °C).

5,5-Dimethyl-1,3-dithiane-1-*N*-*p*-tosylsulfimide (13). (A) 5,5-Dimethyl-1,3-dithiane (11). To a solution of boron trifluoride etherate (5 mL), acetic acid (10 mL), and chloroform (150 mL) in a dry 500-mL three-necked, round-bottomed flask fitted with mechanical stirrer, coil condenser, and nonpressure equalizing dropping funnel, 2,2-dimethyl-1,3-propanedithiol[13] (5.7 g, 42 mmol) and dimethoxymethane (3.5 g, 46 mmol) were added according to the method of Corey and Seebach.[14] Workup following the described procedure afforded crude 5,5-dimethyl-1,3-dithiane as a pale yellow liquid (6.1 g, 98%) which was homogeneous by TLC (silica gel/benzene): NMR ($CDCl_3$) δ 1.15 (s, 6 H), 2.86 (s, 4 H), 3.58 (s, 2 H).

(B) To a stirred methanolic solution (25 mL) of 5,5-dimethyl-1,3-dithiane (1 g, 6.75 mmol), Chloramine T trihydrate (2.3 g, 8.1 mmol) was added in portions over 5 min. A white solid began to separate after 5 min. The reaction mixture was stirred for 1.5 h at ambient temperatures and then poured into 75 mL of water and stirred for 5 min. The homogeneous solid sulfimide **13** was collected and dried (1.9 g, 89%), mp 187–190 °C. An analytical sample was obtained by crystallization from ethanol-2B (1 g/15 mL), mp 188–190 °C. Anal. Calcd for $C_{13}H_{19}NO_2S_3$: C, 49.16; H, 5.99; N, 4.42. Found: C, 49.24; H, 5.94; N, 4.38.

1,4-Dioxaspiro[4.5]-7-thiadecane-7-*N*-*p*-tosylsulfimide (8). A suspension of sodium hydride (57% in mineral oil, 14.5 g, 346 mmol) in 200 mL of dry THF was heated to 65 °C, and 3-thiaheptanedioic acid diethyl ester[15] was added dropwise over 1 h according to the method of Lüttringhaus and Prinzbach.[16] Workup following the described procedure afforded a mixture of the crude thiapyran keto esters (22.3 g, 72%) which on treatment with 10% sulfuric acid for 6 h at reflux, extraction with ether, washing with 5% sodium bicarbonate solution, and drying over magnesium sulfate gave an orange oil (9.8 g, 71%). Purified 3-oxothiapyran (5.2 g, 38%) was obtained by distillation under reduced pressure, bp (~25 mm) 113–115 °C [lit.[17] bp (~18 mm) 101–102 °C]. Ketalization was effected by heating 3-oxothiapyran (5.2 g, 44.7 mmol) in 10 mL of ethylene glycol saturated with hydrogen chloride on the steam bath for 1 h. The cooled reaction mixture was poured into cold 5% sodium hydroxide and extracted with ether. Following removal of solvent in vacuo, the residual amber syrup was heated for 1 h with 30% sodium bisulfite solution. Upon extraction with ether, washing with water, drying over magnesium sulfate, and evaporation of solvent, an amber syrup (5.4 g, 75%) remained which showed no carbonyl absorption in the IR. Distillation under reduced pressure gave 1,4-dioxaspiro[4.5]-7-thiadecane (**5**) (4.5 g, 63%), bp (~17 mm) 126–128 °C, shown to be homogeneous by GLC. A solution of the ketal **5** (2 g, 12.5 mmol) in 30 mL of methanol was treated with Chloramine T trihydrate (3.9 g, 13.8 mmol) in portions over 10 min. The reaction mixture was allowed to stir for 2 h at ambient temperatures and then poured into 150 mL of cold water. The precipitated white solid was collected, washed, and dried to give the title compound **8** (3.4 g, 83%, mp 168–169 °C). Crystallization from ethanol-2B (1 g/25 mL) left the melting point unchanged. Anal. Calcd for $C_{14}H_{19}NO_4S_2$: C, 51.12; H, 5.77; N, 4.26. Found: C, 51.21; H, 5.79; N, 4.20. NMR (Me_2SO-d_6) δ 1.6 (m, 4 H), 2.3 (s, 3 H), 3.1 (m, 4 H), 4.0 (s, 4 H), 7.4 (AB m, 4 H)

1,4-Dioxaspiro[4.5]-7,9-dithiadecane-7-*N*-*p*-tosylsulfimide (14). A solution of 5-oxo-1,3-dithiane dimethylene ketal **12** (1 g, 6.2 mmol) prepared according to the method of Howard and Lindsey[18] was treated with Chloramine T trihydrate (2.1 g, 7.4 mmol) in the manner described for **8** to give the title sulfimide **14** (1.3 g, 62%). Crystallization from ethanol-2B (1 g/40 mL) afforded an analytical sample, mp 185–187 °C. Anal. Calcd for $C_{13}H_{17}NO_4S_3$: C, 45.00; H, 4.89; N, 4.04. Found: C, 45.06; H, 4.99; N, 4.07. NMR (Me_2SO-d_6) δ 2.3 (s, 3 H), 2.9 (m, 2 H). 3.35 (s, 2 H), 4.0 (s, 4 H), 4.3 (s, 2 H), 7.45 (AB m, 4 H)

3,3-Dimethoxythiapyran-1-*N*-*p*-tosylsulfimide (7). A solution of 3-oxothiapyran (3.2 g, 27.5 mmol) in 20 mL of methanol was chilled and saturated with hydrogen chloride over 15 min. After standing at room temperature for 1.5 days, workup as described for **5** gave a brown liquid (2.8 g, 63%) which was distilled under reduced pressure to give 3,3-dimethoxythiapyran **4** (0.95 g, 22%) as a colorless liquid, bp (~8 mm) 93–95 °C. Treatment of the purified sample (0.95 g, 6.5 mmol) in 15 mL of methanol with Chloramine T trihydrate (2.8 g, 10 mmol) gave the title compound **7** (1.5 g, 60%), white solid, mp 126–128 °C. Crystallization from benzene (1 g/20 mL) gave an analytical sample, mp 130–132 °C. Anal. Calcd for $C_{14}H_{21}NO_4S_2$: C, 50.70; H, 6.34; N, 4.23. Found: C, 50.39; H, 6.09; N, 4.62.

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the authors thank Drs. J. R. Bartels-Keith, J. W. Foley, and A. L. Borror for helpful discussions.

Registry No.—2,2-Dimethylglutaric acid, 681-57-2; 2,2-dimethyl-1,5-pentyl di-*p*-toluenesulfonate, 62718-14-3; 2,2-dimethylpentane-1,5-diol, 3121-82-2; 3-thiaheptanedioic acid diethyl ester, 63449-37-6; 3-oxothiapyran, 19090-03-0.

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New Effective Desulfurization Reagents

Howard Alper* and Hang-Nam Paik

Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 6N5

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Hydrocarbons and amines are formed in good yields by treatment of thioketones and thioamides, respectively, with iron pentacarbonyl and potassium hydroxide [i.e., $HFe(CO)_4^-$]. A different, and useful, desulfurization reaction occurred by the use of dicobalt octacarbonyl, the cobalt tetracarbonyl anion, or cyclopentadienyliron dicarbonyl dimer as reagents. Mechanisms are proposed for several of these reactions.

There is considerable current interest in the desulfurization of fuel oil and flue gases. A variety of materials (e.g., butagas)[1] have been employed, with mixed success, as desulfurization reagents. We have initiated a study directed toward the development of new desulfurization reagents, the results of such an investigation being potentially applicable to the fuel oil desulfurization problem. This paper describes the use of several iron and cobalt carbonyls in the desulfurization of thiocarbonyl compounds.[2]

Iron pentacarbonyl reacts with 3 equiv of hydroxide ion to generate the hydridotetracarbonylferrate anion [$HFe(CO)_4^-$]. The latter can effect a variety of interesting transformations including the room temperature reduction of nitroarenes to anilines in high yields.[3] We have now found the hydride to be a convenient desulfurization reagent.

Aliphatic and aromatic thioketones (**1**) react with 4 equiv

$$\underset{\mathbf{1}}{R_2CS} + Fe(CO)_5 + KOH \xrightarrow[\text{or } [C_5H_5Fe(CO)_2]_2]{C_6H_6,\ Co_2(CO)_8 \text{ or } (Ph_3P)_2N^+Co(CO)_4^-} \underset{\mathbf{2}}{R_2CH_2}$$

$$R_2C{=}CR_2$$

of $HFe(CO)_4^-$ in hot 1,2-dimethoxyethane (8–12 h) to give the corresponding hydrocarbon, **2**, in 60–81% yield. Thioamides also react with $HFe(CO)_4^-$ affording amines in lower, but reasonable, yields as compared to thioketones. Product yields and melting points or boiling points are listed in Table I.

Treatment of 4,4′-dimethoxythiobenzophenone (**1**, R = *p*-$CH_3OC_6H_4$) with $DFe(CO)_4^-$ [from KOD and $Fe(CO)_5$] affords the dideuterio compound, $(p\text{-}CH_3OC_6H_4)_2CD_2$, in 74% yield. Similarly 2,2′-dideuterioadamantane was obtained in 78% yield from adamantanethione.

A different desulfurization reaction takes place when the cobalt tetracarbonyl anion is employed as the reagent. Reaction of bis(triphenylphosphine)iminium tetracarbonylcobaltate [$(Ph_3P)_2N^+Co(CO)_4^-$][4] with thiobenzophenones in benzene at 90–100 °C (Carius tube) affords tetraarylethylenes (**3**) in 45–70% yields (Table II). Significantly higher yields of **3** (71–83%) could be realized by simply refluxing a mixture of the thione and dicobalt octacarbonyl [$Co_2(CO)_8$)] in benzene for 5 h. Desulfurization was also observed using the cyclopentadienyliron dicarbonyl dimer $[C_5H_5Fe(CO)_2]_2$, but this reagent is less effective than dicobalt octacarbonyl.

Possible pathways for the $HFe(CO)_4^-$ ion reaction are illustrated in Scheme I. Thiophilic addition of the iron hydride to the thione would give **4** which can then undergo a hydride shift to form **5**. The latter is convertible to the hydrocarbon **2**, either by attack of another molecule of $HFe(CO)_4^-$ or by

Table I. Products Obtained from Reactions of Organosulfur Compounds with $Fe(CO)_5$ and KOH

Registry no.	Reactant	Product[a]	Yield, %	Mp or bp, °C	Lit. mp or bp, °C
1450-31-3	Ph_2CS	Ph_2CH_2	60	265–267	264.3[b]
1141-08-8	$(p\text{-}CH_3C_6H_4)_2CS$	$(p\text{-}CH_3C_6H_4)_2CH_2$	61	138–140 (4 mm)	150 (10 mm)[c]
958-80-5	$(p\text{-}CH_3OC_6H_4)_2CS$	$(p\text{-}CH_3OC_6H_4)_2CH_2$	77	52–53	52–53[d]
1226-46-6	$(p\text{-}(CH_3)_2NC_6H_4)_2CS$	$(p\text{-}(CH_3)_2NC_6H_4)_2CH_2$	81	90–91	91–92[b]
23695-65-0	Adamantanethione	Adamantane	74	266–268	268[b]
636-04-4	PhCSNHPh	$PhCH_2NHPh$	38	36–38	37–38[b]
637-53-6	$CH_3CSNHPh$	CH_3CH_2NHPh	51	100–103 (20 mm)	97.5–98 (18 mm)[b]

[a] Infrared, nuclear magnetic resonance, and mass spectral data were in excellent accord with those for authentic samples. [b] "Handbook of Chemistry and Physics", 50th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1969. [c] A. B. Galun, A. Kaluszyner, and E. D. Bergmann, *J. Org. Chem.*, **27**, 1426 (1962). [d] L. H. Conover and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3586 (1950).

Table II. Yields of Olefins (3) Formed By Reaction of $[(Ph_3P)_2N^+Co(CO)_4^-]$ (A), $Co_2(CO)_8$ (B), or $[C_5H_5Fe(CO)_2]_2$ (C) with Thiones (1)

1, R =	Metal carbonyl	Yield of 3,[a] %	Mp, °C	Lit.[b] mp, °C
Ph	A	45	222–224	224–226
	B	71		
	C	55		
p-$CH_3OC_6H_4$	A	70	184–185	184.5–186
	B	75		
	C	68		
p-$CH_3C_6H_4$	A	58	149–150	150.0–150.5
	B	83		
	C	68		

[a] Spectral properties [IR, NMR (^1H, ^{13}C), MS] were in excellent accord with that for authentic samples. Yields are based on **1**. [b] C. E. Coffey, *J. Am. Chem. Soc.*, **83**, 1623 (1961).

decomplexation to the carbanion **6**, followed by protonation.

Thiophilic addition (to give **7**) is also the probable initial step in the reaction of **1** with $(Ph_3P)_2N^+$ $Co(CO)_4^-$ (Scheme II). Since no hydride is present in **7**, a second thiophilic addition can take place to give **8**. Intramolecular displacement of $^-SCo(CO)_4$ from **8** would generate the thiirane (episulfide), **9**. Desulfurization of the latter by $Co(CO)_4^-$ [or perhaps by the generated $^-SCo(CO)_4$] results in olefin formation. Some support for the conversion of **9** to **3** comes from the observed desulfurization of *trans*-2,3-diphenylthiirane to *trans*-stilbene in 71% yield by the cobalt tetracarbonyl anion. A similar mechanism has been suggested by Beak and Worley[5] for the reaction of thiobenzophenones with Grignard and organolithium reagents.

For the neutral metal carbonyl, $Co_2(CO)_8$, the initial step may involve formation of the sulfur–donor ligand complex **10** (Scheme III). The transformation of **10** to the alkene **3** may occur via the sulfur bridging zwitterionic complex **11**, or via reaction with additional thione to give **12**.

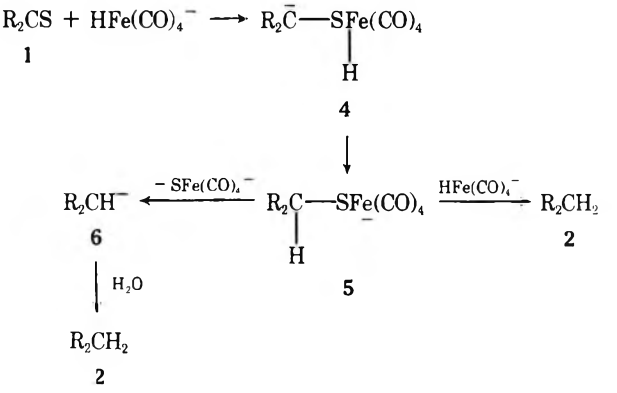
Experimental Section

General. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 1R20A spectrometer. Nuclear magnetic resonance spectra were determined using a Varian T60 spectrometer, and a Varian MS902 spectrometer was employed for recording mass spectra.

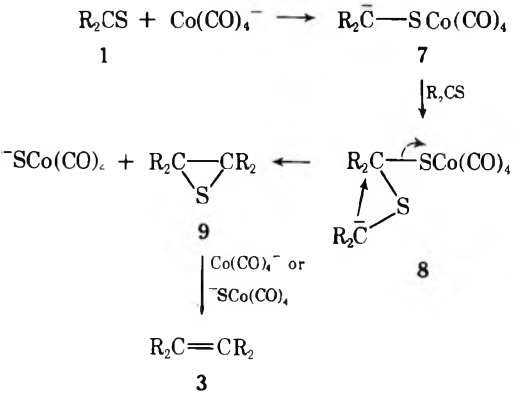
The thioketones were prepared by reaction of the corresponding ketones with phosphorus pentasulfide.[6,7] Cyclopentadienyliron dicarbonyl dimer was purchased from Pressure Chemical Co., and was used as received. Bis(triphenylphosphine)iminium tetracarbonylcobaltate was synthesized from dicobalt octacarbonyl according to the procedure of Ruff and Schlientz.[4]

Solvents were dried by standard techniques. All reactions were run under a dry nitrogen atmosphere.

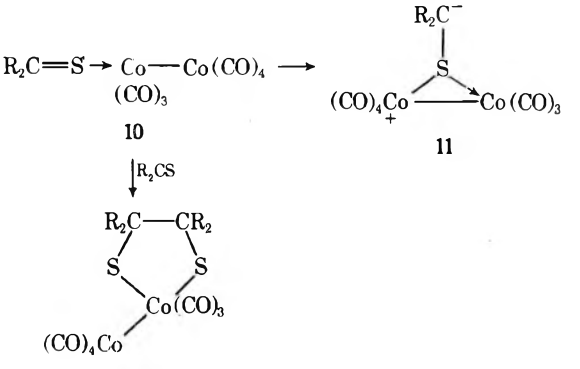
Scheme I



Scheme II



Scheme III



General Procedure for Reaction of Organosulfur Compounds with the Hydridotetracarbonylferrate Anion. A mixture of iron pentacarbonyl (3.0 mL, 22.1 mmol), KOH (3.69 g, 66 mmol), and water (6.0 mL) was refluxed in 1,2-dimethoxyethane (90 mL) for 1.5 h to generate $HFe(CO)_4^-$. The organosulfur compound (5.0–5.6 mmol)

in 1,2-dimethoxyethane (15–35 mL) was added to this solution and the mixture was refluxed for 8–12 h. The solution was cooled and filtered, and the filtrate was concentrated in vacuo. The crude product was treated with ether (150–200 mL) and filtered, and the filtrate was washed with equal volumes of water until the aqueous layer was colorless (three or four washings). The ether extract was dried ($MgSO_4$), percolated through a short column of Florisil (if necessary), and concentrated to give the pure desulfurized product.

General Procedure for Reaction of Thiones with Bis(triphenylphosphine)iminium Tetracarbonylcobaltate and Cyclopentadienyliron Dicarbonyl Dimer. The thioketone (2.5 mmol) and $(Ph_3P)_2N^+Co(CO)_4^-$ or $[C_5H_5Fe(CO)_2]_2$ (1.4 mmol) in benzene (5–7 mL) was heated in a Carius tube at 90–100 °C for 4 days. During this period, a large amount of black precipitate was formed. The tube was opened, the black material was filtered, and the filtrate was concentrated to 2–3 mL. The latter was chromatographed on silica gel using petroleum ether (bp 80–100 °C). Elution with benzene–petroleum ether (1:5 to 1:1) gave the olefin **3**.

General Procedure for the Reaction of Thiones with Dicobalt Octacarbonyl. A mixture of the thione (2.7 mmol) and dicobalt octacarbonyl (0.51 g, 1.5 mmol) in benzene (50 mL) was refluxed for 5 h. The solution was cooled and filtered, and evaporation of the filtrate gave **3**. Crystallization of the latter from benzene–petroleum ether gave the pure crystalline olefin **3**.

Acknowledgment. We are grateful to Imperial Oil Ltd. for support of this research.

Registry No.—$Fe(CO)_5$, 13463-40-6; $[(Ph_3P)_2N^+Co(CO)_4^-]$, 53433-12-8; $Co_2(CO)_8$, 10210-68-1; $[C_5H_5Fe(CO)_2]_2$, 12154-95-9; $HFe(CO)_4^-$, 18716-80-8.

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Chemistry of Heterocyclic Compounds. 25. Selective Metalation of the Pyridine Nucleus at the 3-Position[1]

George R. Newkome,* Joe D. Sauer,[2a] and S. K. Staires[2b]

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

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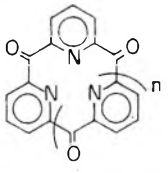
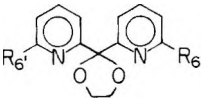
Treatment of bis(6-bromo-2-pyridyl) ketone ketal (**3**) with *n*-butyllithium in diethyl ether at −40 °C resulted in the isolation of pyridone **6** after normal hydrolytic workup. Selective metalation of the 3 position of **3** has been demonstrated by labeling studies. The formation of pyridone **6** is proposed to occur by first 1,4-elimination–fragmentation of one pyridine nucleus, followed by cyclization upon workup.

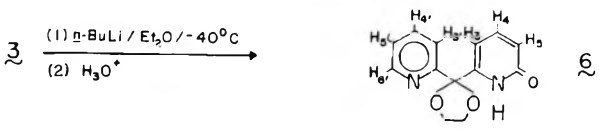
In one of our synthetic routes to trione **1a**,[3] as well as the related pyridine-based xanthoporphinogen model compounds (**1b**), the intermediary bis(6-lithio-2-pyridyl) ketone ketal (**2**) was of pivotal importance. Attempted conversion of **3**[4] to either diacid **4**, according to the standard metalation–carboxylation procedure of Gilman et al.,[5] or to 2,2-bis(2-pyridyl)-1,3-dioxolane (**5**) via metalation–hydrolysis, gave in both cases the undesired pyridone **6** as a major side product. We herein describe the directive metalation of the 3-position of the pyridine nucleus under normal metalation conditions[5] and propose procedures to circumvent, as well as a rationale for, pyridone formation.



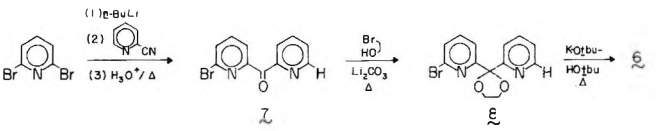
1 a(n=1) b(n=2)



2 (R=Li) **4** (R=$-CO_2H$)
3 (R=Br) **5** (R=H)



Treatment of bis(6-bromo-2-pyridyl) ketone ketal (**3**) with *n*-butyllithium (10% mol excess) in diethyl ether at −20 °C for 1 h, followed by carboxylation and mild hydrolysis, gave (30%) pyridone **6** along with the starting ketal as the major nonacidic components. Structure proof of **6** was achieved by reaction of methyl 2-pyridinecarboxylate and 2-bromo-6-lithiopyridine,[5,6] affording (70%) 2-pyridyl 6-bromo-2-pyridyl ketone (**7**), which upon base-catalyzed ketalization[4] gave (75%) ketal **8**. Treatment of **8** with potassium *tert*-butoxide

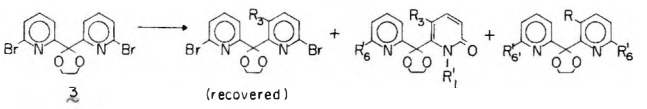


in anhydrous *tert*-butyl alcohol[7] afforded a 39% overall yield of pyridone **6**. In general, hydrolyses of these pyridyl ketals occur only under rigorous conditions (6 h in refluxing concentrated hydrochloric acid or 12–18 h in warm 80% acetic acid); thus, the ketals herein described would be unaffected by the hydrolytic workup procedure.

Pyridone **6** was isolated from **3** in comparable yield when the carboxylation step was eliminated. In order to assure the complete exclusion of oxygen, rigorous degassing procedures[8] were conducted and the reaction was conducted under an argon atmosphere; the yield of **6** remained virtually constant. However, either utilization of better anion stabilizing solvents, such as dimethoxyethane or tetrahydrofuran, or reduced reaction temperatures (−60 to −90 °C) suppressed pyridone formation, in favor of products arising from lithiated ketal. Table I summarizes the diversified reaction conditions vs. the product distribution.

In order to ascertain the position(s) of lithiation, ketal **3** was

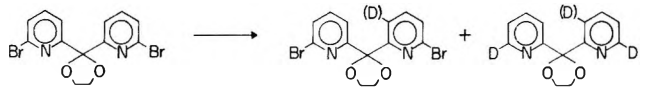
Table I



Reaction temp, °C	Solvent	Trapping agent	Isolated yields, %[a]		
−40 to −20	Et_2O	CO_2/H_3O^+	34 (R = H)	32 (R = R′ = H)	*b*
	THF	H_3O^+	51 (R = H)	<1 (R = R′ = H)	42 (R = R′ = H)
	DME	H_3O^+	50 (R = H)	<2 (R = R′ = H)	43 (R = R′ = H)
	Et_2O	D_3O^+	35 (R = H, D)	21 (R = R′ = >90% D)	Traces
−55 to −40	Et_2O	D_3O^+	30 (R = 26% D)	<2 (R′ = >90% D; R = H, D)[c]	52 (R′ = >95% D; R = 25% D)
−78 to −60	Et_2O	D_3O^+	48 (R = 23% D)	≪1[d]	47 (R′ = >95% D; R = 19% D)

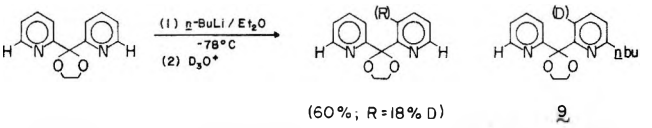
[a] Isolated, recrystallized product yields. [b] Traces of 5 were found; the diacid 4, from the carboxylation step, was not isolated. [c] Isotopic distribution was not determined. [d] Insufficient sample to determine isotopic distribution.

subjected to a 10% mol excess of *n*-butyllithium in diethyl ether at −78 °C, then quenched with 10% D_2SO_4. Two partially deuterated ketals were isolated and characterized by NMR and confirmed with mass spectral data: the recovered starting material (**3**) had incorporated (23%) a deuterium atom at position 3 of one pyridine ring as determined by the decreased integration of the doublet of doublets at δ 7.82. The second major product, deuterated **5**, showed nearly complete absence of the characteristic broad doublet at δ 8.65 for the 6-pyridyl hydrogen and a 19% decrease in the aromatic region as compared to the ketal singlet. Under these conditions pyridone **6** was not detected. Isolation of partially deuterated starting ketal **3** from the reaction suggests directive lithiation at the 3 position being a result of the proximity of the ketal or



pyridyl moiety. There are numerous examples of ethereal directivity in metalation in aromatic nuclei;[9a] however, this is the first example of selective metalation of the normally unreactive (toward metalation) 3 position of a pyridine ring. Reaction temperatures above −55 °C resulted in marginal increases in both label incorporation as well as isolable pyridone. At −40 °C, pyridone **6** has deuterons incorporated in positions 1, 3, and 6′ to the extent of >90% based upon its NMR spectral data, which show complete absence of both the broad, 6-pyridyl doublet (δ 8.65) and doublet of doublet at δ 6.51. The pyridone nucleus shows only two doublets at δ 7.35 (H_4) and 6.42 (H_5); this pattern does not change upon hydrolysis; however, a new broad peak at δ 10.45 appears for the NH group. To confirm the exchangeability of the 3 position, pyridone **6** was dissolved in 10% deuteriosulfuric acid and the exchange rate monitored via NMR. After 40 h at 38 °C, negligible, if any, deuterium incorporation was observed; at increased temperatures, hydrolysis of the ketal moiety resulted.

Further confirmation of this selective metalation was demonstrated by treatment of **5** with *n*-butyllithium (10% mol excess) in diethyl ether at −78 °C, followed by quenching with 10% D_2SO_4. The recovered "starting" ketal has deuterium incorporation (ca. 18%) predominantly at the 3 position as determined by NMR spectral integration and mass spectral data [*m/e* 228–229 (18%); $M^+ - C_5H_4N \rightarrow C_8H_8NO_2$ (*m/e* 150) *m/e* 150 → 151 (~10%)]; as expected upon more rigorous conditions, alkylation at the 6 and/or 6′ position(s) afforded the *n*-butyl incorporation products (e.g. **9**). Giam et al. have adequately demonstrated the enamine character of the 1,2-dihydro intermediates, which afford these 2-alkylpyridines;[10]



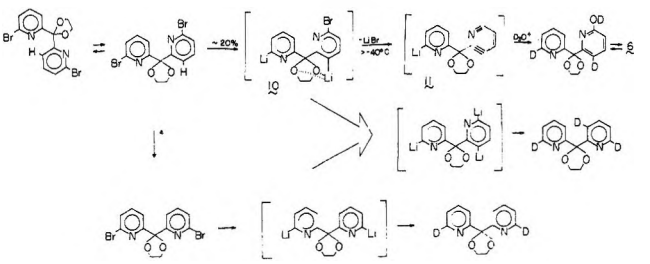
(60%; R = 18% D) **9**

thus, deuterium incorporation in the 3 and/or 5 positions would be expected in any alkylated products. Longer reaction times, different temperatures, and numerous other factors will alter the percentage of label incorporation; these variables were not investigated.

The proposed explanation of the formation of pyridone **6** from ketal **3** is shown in Scheme I. Ketal **3** undergoes (ca. 20–30%) selective metalation at the 3 position of a single pyridine ring under these reaction conditions. This directivity of metalation results from both initial complexation of the organolithium reagent with either the 1,3-dioxolane group[9a,b] or other nitrogen atom[9c] as well as a conformational preference about the sp^3–sp^2 bond.[11] This is further substantiated by the above labeling studies and the observation that good complexing solvents retard the directive metalation, since the intramolecular solvation cannot compete with the solvent–metal interactions.

At reduced temperatures (<−60 °C), the dilithiated ketal **5**-d_2 can be generated by normal metal–halogen exchange along with approximately 20% of the trilithiated ketal **5**-d_3, which arose by both metal–halogen exchange and directive metalation. At −40 to −20 °C, the partially metalated intermediate **10** can fragment at the elevated temperatures via 1,4-elimination of lithium bromide to generate ynenenitrile **11**. Similar fragmentations of the pyrimidine nucleus have been reported[12] and recently Utimoto et al.[13] have described a related cleavage of the pyridine ring to give dienenitriles. No attempts have been made to isolate the ynenenitrile intermediate.[14] Cyclization of **11** under the workup conditions affords pyridone **6** in approximately the same isolated percentages as that of the selective deuterium incorporation studies. Although there is no exact precedence for the cyclization step, Perveev and co-workers[15] have demonstrated the facile cyclization of alkyl-substituted ynenenitriles in the

Scheme I



presence of alkyl- and dialkylamines at room temperature to generate (70–80%) the pyridine nucleus. Related dienenitriles have been shown[16] to give dihydropyridines when subjected to mild acidic conditions, such as the typical workup (dilute mineral acid at room temperature for several minutes). Directive protonation may also facilitate this cyclization.

In order to dispel the obvious reactions which could conceivably convert **3** into **6**, ketal **3** was subjected to conditions in excess of normal workup procedures: (a) refluxed **3** in 5% HCl for 12 h; (b) refluxed **3** in 12 N HCl in methanol for 24 h; or (c) heated **3** in alcoholic potassium hydroxide at 60 °C for 4 h resulting in isolation of either recovered starting ketal **3** (100%), bis(6-bromo-2-pyridyl) ketone (>90%), or **3** (100%), respectively.

This directive metalation and novel fragmentation of the pyridine nucleus are currently being evaluated as a convenient synthon for polyfunctional C_5 and C_6 units.

Experimental Section

All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared and ultraviolet spectra were recorded on a Beckmann IR-7 and Cary 14 spectrophotometers, respectively. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian HA-100 spectrometer and are recorded in parts per million downfield of the internal standard of tetramethylsilane. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMS-4 spectrometer by Ms. Paula Moses. Elemental analyses were performed by Mr. R. Seab in these laboratories.

The recorded R_f values were determined by a standardized thin-layer chromatograph (TLC) procedure: 0.025-mm Brinkmann silica gel HF eluting with the stipulated solvent system. For preparative thick-layer chromatography (ThLC), 2-mm silica gel (Brinkmann PF-254-366) plates were used, eluting with the stated solvents.

Bis(6-bromo-2-pyridyl) ketone was prepared, according to the procedure of Holm et al.,[6] from 2,6-dibromopyridine and ethyl chloroformate: mp 155–156 °C (lit.[6] mp 155–156.5 °C).

2-Pyridyl 6-bromo-2-pyridyl ketone (7) was synthesized from 2-bromo-6-lithiopyridine and methyl 2-pyridinecarboxylate by standard procedures: mp 85–86 °C (lit.[6] mp 84.5–86.5 °C).

2,2-Bis(6′-bromo-2′-pyridyl)-1,3-dioxolane (3) was prepared[4] (75–85%) from the corresponding ketone by treatment with 2-bromoethanol and sodium carbonate: mp 146–148 °C; R_f 0.41 [cyclohexane–ethyl acetate (1:1)]; NMR ($CDCl_3$) δ 4.14 (s, OCH_2CH_2O, 4 H), 7.35 (dd, 5-pyr-H, J = 7, 2 Hz, 2 H), 7.58 (dd, 4-pyr-H, J = 7, 7.7 Hz, 2 H), 7.82 (dd, 3-pyr-H, J = 7.7, 2 Hz, 2 H).

Treatment of 2,2-Bis(6′-bromo-2′-pyridyl)-1,3-dioxolane (3) with *n*-Butyllithium. Method A. Ether Solvent at −40 to −20 °C. A solution of **3** (100 mg, 0.26 mmol) in anhydrous diethyl ether (100 mL; distilled from lithium aluminum hydride under argon) was cooled to −40 °C and *n*-butyllithium (0.3 mL, 2 M in hexane, 0.6 mmol) was added slowly. The reaction was conducted under an argon atmosphere with *complete* exclusion of oxygen. After the addition was complete, the solution was allowed to warm slowly to −20 °C and then maintained at −20 °C for 1 h. Dry ice was added to the solution and the mixture was hydrolyzed by addition of cold 5 N hydrochloric acid (30 mL). The organic solvents were removed at reduced pressure, then the aqueous slurry was extracted with chloroform (10 × 50 mL). The combined extract was washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a beige solid, which was chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (1:1) to give 20 mg (32%) of pyridone **6**: mp 185–187 °C; R_f 0.04 [cyclohexane–ethyl acetate (1:1)]; NMR ($CDCl_3$) δ 4.16 (s, OCH_2CH_2O, 4 H), 6.42 (dd, H_5, J = 7, 1 Hz, 1 H), 6.51 (dd, H_3, J = 9, 1 Hz, 1 H), 7.37 (dd, H_4, J = 9, 7 Hz, 1 H), 7.30 (ddd, $H_{5'}$, J = 6, 5, 2 Hz, 1 H), 7.76 (ddd, $H_{3'}$, J = 5, 2, 0.9 Hz, 1 H), 7.78 (ddd, $H_{4'}$, J = 5, 6, 1.5 Hz, 1 H), 8.63 (ddd, $H_{6'}$, J = 5, 1.5, 0.9 Hz, 1 H), and 10.45 [brs, NH (exchanged with D_2O), 1 H]; IR ($CHCl_3$) 3350 (amide), 3000, 1670 (amide), 1630, 1440, 1200, 1150, 1090, 1040, 950 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.96; N, 11.47. Found: C, 64.11; H, 5.03; N, 11.38.

Unreacted starting material [34 mg (34%)] was also isolated from the ThLC plate, mp 146–148 °C.

Any carboxylated products, specifically **5**, neither moved nor could be easily extracted from the baseline of the chromatography plate.

Method B. Tetrahydrofuran Solvent. Repetition of method A, except for the substitution of tetrahydrofuran as solvent and omission of the carboxylation step, resulted in the isolation of **3** [51 mg (51%)] and **5**: mp 164–165 °C; 24 mg (42%).

Method C. Dimethoxyethane Solvent. Repetition of method A without the carboxylation stage and utilizing dimethoxyethane as solvent afforded 50 mg (50%) of **3** and 25 mg (43%) of **5**.

Method D. Quenching with Deuterated Sulfuric Acid. Method A was repeated without the carboxylation step, and quenched with 10% deuterated sulfuric acid (10 mL, 98% d_2). Purification (ThLC) afforded, along with starting material [35 mg, (35%)], 13.5 mg (21%) of the deuterated pyridone (**6-*1,3,6′-d*$_3$**): mp 185–187 °C; R_f 0.04; NMR ($CDCl_3$) δ 4.16 (s, OCH_2CH_2O, 4 H), 6.42 (d, H_5, J = 8.0 Hz, 1 H), 7.35 (d, H_4, J = 8.0 Hz, 1 H), 7.30 (dd, $H_{5'}$, J = 5, 2 Hz, 1 H), 7.76 (dd, $H_{3'}$, J = 6, 2 Hz, 1 H), 7.78 (dd, $H_{4'}$, J = 6, 5 Hz, 1 H), and 10.65 (brs, NH (exchanged with H_2O), 1 H]; MS (60 eV) m/e 247 (M^+, d_3).

Method E. Temperature Range (−55 to −40 °C). Repetition of method D, except that the initial addition of *n*-butyllithium was at −55 °C and then maintained for 3 h at −40 °C, afforded only a trace (<2%) of pyridone **6**, recovered 3-deuterio ketal **3** [33 mg (33%); mp 145–147 °C; NMR ($CDCl_3$) δ 4.16 (s, OCH_2CH_2O, 4 H), 7.35 (dd, 5-pyr-H, J = 7, 2 Hz, 2 H), 7.58 (brdd, 4-pyr-H, J = 7, ~7 Hz, 2 H), 7.82 (brdd, 3-pyr-H, J = 7.7, 2 Hz; MS (60 eV) m/e 389 (M^+, 36% d_1)], and the "trideuterated" ketal [31 mg (52%); mp 163–165 °C; NMR ($CDCl_3$) δ 4.10 (s, OCH_2CH_2O, 4 H), 7.0–8.0 (m, 3,4,5-pyr-H, 5.8 H), 8.65 (m, 6-pyr-H, 0.05 H); MS m/e 228 (1% d_0), 229 (2% d_1), 230 (72% d_2), 231 (25% d_3)].

Method F. Temperature Range (−78 to −60 °C). Repetition of method D, except that the initial addition of *n*-butyllithium was at −78 °C and the reaction was maintained for 3 h at −60 °C, afforded deuterated starting material **3** [50 mg (50%); mp 146–147 °C; NMR ($CDCl_3$) identical with sample isolated from method E, except for δ 7.81 (3-pyr-H, 1.55 H (77% H))] and the trideuterated ketal [mp 164–166 °C; 30 mg (50%); NMR ($CDCl_3$) identical with sample derived from method E; MS m/e 228 (1% d_0), 229 (1% d_1), 230 (78% d_2), 231 (19% d_3)].

Treatment of 2,2-Bis(2′-pyridyl)-1,3-dioxolane (5) with *n*-Butyllithium. A solution of **5** (180 mg, 0.8 mmol) in diethyl ether (50 mL) was cooled to −78 °C and *n*-butyllithium (1 mL, 2 M in hexane, 2 mmol) was added dropwise. After 3 h at −70 °C, 10% deuterated sulfuric acid (10 mL, 98% d_2) was added. After neutralization with sodium carbonate, the suspension was extracted with chloroform (5 × 50 mL), then the combined extract was dried over anhydrous sodium sulfate and concentrated to afford a gummy residue, which was chromatographed (ThLC), eluting two times with diethyl ether to give starting **5** [110 mg (60%), mp 164–165 °C (needles, petroleum ether); NMR ($CDCl_3$) δ 4.12 (s, OCH_2CH_2O, 4 H), 7.0–8.0 (m, 3,4,5-pyr-H, 5.8 H), 8.66 (ddd, 6-pyr-H, 2 H); MS m/e 228 (81% d_0), 229 (19% d_1)] and 2-(2′-pyridyl)-2-(6′-*n*-butyl-2′-pyridyl)-1,3-dioxolane [20 mg (8%); bp 100 °C (0.1 mm, microdistillation); R_f 0.3; NMR ($CDCl_3$) δ 1.0–1.7 (m, *n*-Pr, 7 H), 2.8 (t, pyr-CH_2, J = 8 Hz, 2 H), 4.18 (s, OCH_2CH_2O, 4 H), 7.0–7.8 (m, pyr-H, 6 H), 8.65 (ddd, 6-pyr-H, J = 4.5, 2, 1 Hz, 1 H).

Attempted Deuterium Exchange of Pyridone 6. A sample of **6** (50 mg, 0.2 mmol) was dissolved in 10% deuteriosulfuric acid (0.3 mL, 98% d_2) and the incorporation was monitored via NMR analysis at 38 °C. After 40 h at 38 °C, negligible, if any, incorporation was observed. The ketal singlet at δ 4.16 was used as the internal standard.

Independent Synthesis of Pyridone 6. A. 2-(2′-Pyridyl)-2-(6′-bromo-2′-pyridyl)-1,3-dioxolane (8). A suspension of **7** (1.03 g, 3.5 mmol), lithium carbonate (15 g, 200 mmol), and 2-bromoethanol (25 mL) was refluxed gently with stirring for 6 h. After cooling, the mixture was poured into 10% aqueous sodium bicarbonate (150 mL). The undissolved solids were filtered and the filtrate was extracted with chloroform (10 × 50 mL). The combined organic extract was dried over anhydrous potassium carbonate and concentrated to afford a pale amber yellow liquid. The attendent 2-bromoethanol was removed via vacuum distillation and the residue was chromatographed (ThLC), eluting with cyclohexane–ethyl acetate (1:1) to afford **8** as colorless rhombohedron crystals: mp 117–117.5 °C (recrystallized from ethyl acetate–cyclohexane); 800 mg (75%); NMR ($CDCl_3$) δ 4.12 (s, OCH_2CH_2O, 4 H), 7.0–7.85 (m, pyr-H, 6 H), 8.47–8.52 (ddd, 6-pyr-H, J = 5, 5, 2, 1 Hz, 1 H); IR ($CHCl_3$) 3000, 1650, 1620, 1575, 1390, 1280, 1160, 995 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}N_2O_2Br$: C, 50.86; H, 3.61; N, 9.13. Found: C, 50.62; H, 3.83; N, 9.23.

B. Pyridone Synthesis. A mixture of **8** (130 mg, 0.425 mmol), anhydrous *tert*-butyl alcohol (8 mL), and potassium *tert*-butoxide (4 g) was refluxed for 12 h. After cooling, the solvent was removed in vacuo, ice water was slowly added, and the solution was extracted with

methylene chloride. The combined extract was dried over anhydrous sodium sulfate, concentrated, and chromatographed (ThLC), eluting three times with cyclohexane–ethyl acetate (3:1) to afford 72.7 mg (75%) of pure pyridone **6**, mp 185–187 °C. This sample was identical in all respects with the sample isolated from method A.

Acknowledgments. The authors gratefully acknowledge partial support of this work by Public Health Service grant from the National Institutes of Health and the Dr. Charles E. Coates Memorial Fund of the L.S.U. Foundation for financial aid (J.D.S.). We also wish to thank Professor Van der Plas for his helpful comments.

Registry No.—**3**, 42772-88-3; **3**-*3*-d_1, 63449-27-4; **3**-*3,6,6'*-d_3, 63449-28-5; **5**, 42772-86-1; **6**, 63449-29-6; **6**-*1,3,6'*-d_3, 63449-30-9; **7**, 49669-19-4; **8**, 63449-31-0; bis(6-bromo-2-pyridyl) ketone, 42772-87-2; 2-bromo-6-lithiopyridine, 37709-60-7; methyl 2-pyridinecarboxylate, 2459-07-6; 2-bromoethanol, 540-41-2.

References and Notes

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(2) (a) Based in part on the Ph.D. dissertation of J.D.S., Louisiana State University (Baton Rouge), 1976. (b) Undergraduate researcher.
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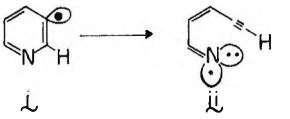

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α-Halogenation of Certain Ketones

Borzoo Modarai* and Ezatollah Khoshdel

Department of Chemistry, Arya Mehr University of Technology, Tehran, Iran

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A variety of α-halo and α-*gem*-dihalo ketones, including the fluoro and iodo compounds, have been prepared. The scope and limitations of their syntheses have been studied. Every attempt at the preparation of 3,3-difluoro-2-butanone gave biacetyl as the only product, although the analogous *gem*-difluoropropiophenone was conveniently obtained. The synthesis of the difluorobutanone could, however, be effected with the introduction of an electronegative atom such as chlorine on the 1 position.

In the course of our stereochemical studies, the need for a number of ketones possessing a halogenated chiral carbon atom led us to investigate the halogenation, in particular fluorination, of one or both methylene hydrogens of 2-butanone, propiophenone, and 1-phenyl-2-propanone. None of the required *gem*-dihalo ketones possessing two different halogens has been previously reported.

α-Chloro or α-fluoro ketones were conveniently converted to their corresponding *gem*-bromohalo analogues by irradiation in the presence of NBS.[1] Table I lists the products with yields. Several alternate reported routes[2,3] were found to be ineffective, leading to bromoform (for methyl ketones) or polybrominated products. Bromination of monofluoroacetone with NBS gave a complex mixture.

Results and Discussion

Preparation of the Fluoro Ketones Although indirect routes have frequently been used for the preparation of fluoro methyl ketones,[4–7] direct exchange of bromine or chlorine for fluorine using metallic fluorides was used in the present work. This method, although preferred, often meets with difficulty due to the marked tendency of bromo and chloro ketones to decompose during the course of fluorination, particularly at high temperatures. The task was in finding a metal fluoride which would exchange its fluorine for halogen at a temperature low enough so as to minimize side reactions and decomposition of both the reactant and product. Mercuric fluoride was found to be a suitable metallic fluoride for the fluorination of most of the bromo ketones. These reactions are presented in Table II.

In the fluorination of **1a** with mercuric fluoride, under absolutely anhydrous conditions, a smooth exchange of bromine took place, leaving the chlorine intact and giving 3-chloro-3-fluoro-2-butanone (**1c**) together with some biacetyl. With antimony trifluoride, thallous fluoride, potassium fluoride, and potassium hydrogen difluoride, either no reaction occurred or extensive polymerization and charring resulted. Efforts to inhibit the formation of biacetyl, in the exchange reaction with mercuric fluoride, met with no success. The fluoro ketone formed an azeotropic mixture with the biacetyl and had to be purified by GLC. Pure **1c** was not hydrolyzed when boiled with water.

1c was also obtained in poor yield by the chlorination of 3-fluoro-2-butanone using *N*-chlorosuccinimide.

2-Bromo-2-chloro-1-phenyl-1-propanone (**3a**) reacted with mercuric fluoride at 85 °C to give, under optimum conditions,

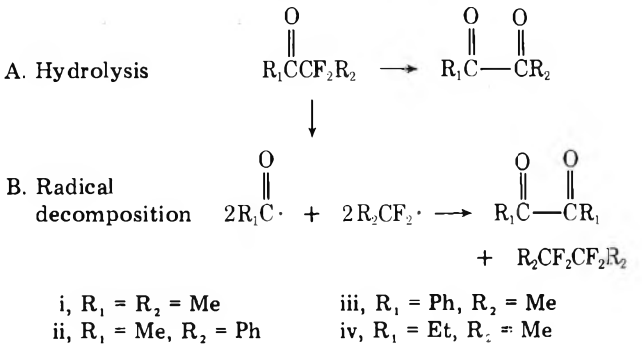
Table I. Reaction of Halo Ketones with NBS

Reactant	Registry no.	Product (yield, %)	Registry no.
1 $CH_3COCHClCH_3$	4091-39-8	1a $CH_3COCBrClCH_3$ (95)	63017-03-8
2 $CH_2ClCOCHFCH_3$	63017-02-7	2a′ $CH_2ClCOCBrFCH_3$ (98)	63017-04-9
3 $C_6H_5COCHClCH_3$	6084-17-9	3a $C_6H_5COCBrClCH_3$ (95)	63017-05-0
4 $C_6H_5COCHFCH_3$	21120-36-5	4a′ $C_6H_5COCBrFCH_3$ (95)	63017-06-1
5 $C_6H_5COCH_2CH_3$	93-55-0	5b $C_6H_5COCBr_2CH_3$ (95)	2114-03-6
6 $CH_3COCHFCH_3$	814-79-9	6a′ $CH_3COCBrFCH_3$ (95)	63017-07-2
7 $CH_3COCH_2CH_3$	78-93-3	7b $CH_3COCBr_2CH_3$ (95)	2648-69-3
8 $CH_3COCHFC_6H_5$	21120-43-4	8a′ $CH_3COCBrFC_6H_5$ (97)	57856-09-4
9 $CH_3COCH_2C_6H_5$	103-79-7	9b $CH_3COCBr_2C_6H_5$ (97)	63017-08-3
10 $CH_3COCHClC_6H_5$	4773-35-7	10a $CH_3COCBrClC_6H_5$ (97)	63017-09-4
11 $CH_3CH_2COCH_2CH_3$	96-22-0	11b $CH_3CH_2COCBr_2CH_3$ (15)	63017-10-7

Table II. Reaction of Bromo Ketones with Mercuric Fluoride

Reactant	Product (yield, %)
1a	1c $CH_3COCFClCH_3$ (32) + $CH_3COCOCH_3$
2a′	2b′ $CH_2ClCOCF_2CH_3$ (75)
3a	3c $C_6H_5COCFClCH_3$ (65) + $C_6H_5COCCl{=}CH_2$ (18)
4a′ or 5b	4b′ $C_6H_5COCF_2CH_3$ (89)
6a′ or 7b	$CH_3COCOCH_3$
11b	$CH_3CH_2COCOCH_2CH_3$

Scheme I



a 65% yield (by NMR) of the fluoro chloro ketone (**3c**) together with ca. 18% of 2-chloro-1-phenyl-2-propen-1-one as a result of dehydrohalogenation. A small quantity of a very volatile fraction, which was presumed to be other elimination products, was also obtained. Contrary to what was expected, no biacetyl resulted from this reaction. Similarly, the bromo fluoro ketone **4a** and the dibromo ketone **5b** gave a good yield of the *gem*-difluoro ketone **4b.** When mercuric fluoride was replaced by a mixture of mercurous fluoride and iodine (often used as a substitute for HgF_2) the reactions failed. The use of other usual metallic fluorides was also unsuccessful, as was the reaction with silver fluoride, even though this compound has been used to exchange fluorine for bromine in 1,1,1-tribromo-3,3,3-trifluoroacetone[8] and in ethyl dibromochloroacetate.[9]

Contrary to **3a,** 1-bromo-1-chloro-1-phenyl-2-propanone (**10a**) resisted all attempts toward fluorination with various metallic fluorides. Although the other ketones reacted smoothly with mercuric fluoride, this was highly reactive such that at room temperature a vigorous exothermic reaction ensued and a dark solid mass resulted. Mercuric fluoride added to **1a** at 0–5 °C appeared to give an exchange reaction, since $HgBr_2$ seemed to be formed. On warming to room temperature, however, the reaction mixture darkened and no identifiable product could be isolated. When carried out at −5 °C and using chloroform or dichloromethane as diluent, the reactions took place in the same manner. **9b** behaved similarly toward fluorination.

Partial formation of biacetyl during the synthesis of **1c** made us curious to investigate the possibility of the preparation of 3,3-difluoro-2-butanone by the same method. Thus fluorination of 3,3-dibromo-2-butanone (**7b**) and also **6a**[1] was attempted with mercuric fluoride under all the feasible conditions, which resulted in their total conversion to biactyl, giving no fluoro ketone. One could suggest that the formation of biacetyl in these reactions may be explained in terms of the immediate hydrolysis[10–11] of the possibly formed *gem*-difluoro ketone, or perhaps a free radical mechanism is taking place as shown in Scheme IB. However, the following experiments rule out the possibility of hydrolysis and suggest that the free radical mechanism is speculative: (a) The same results were obtained when reactions were performed under argon or air-free nitrogen. (b) In reactions ii and iii (Scheme I), 1-phenylpropane-1,2-dione was not obtained (Scheme IA). Neither could any fluorohydrocarbon be trapped (Scheme IB). (c) In reaction IV (Scheme I), 3,4-hexanedione was obtained, and not the hydrolytic product 2,3-pentanedione.

Since the *gem*-difluoropropiophenone could be conveniently prepared while the other two ketones could not, it was inferred that the presence of an electron-withdrawing phenyl group attached to the carbonyl may be a factor in stabilizing the formation of the *gem*-difluoro derivative. This statement is, to some extent, justified, since fluorination of 1-chloro-3-bromo-3-fluoro-2-butanone (**2a′**) with mercuric fluoride under exactly the same conditions as used for **6a′** resulted in a 90% yield (by NMR) of 1-chloro-3,3-difluoro-2-butanone **2b′**. We conclude that, although bromo ketones generally give a smooth reaction with HgF_2 with little or no decomposition, limitations are imposed on its use in some cases, due to the formation of diketones.

Fluorination with KF or KHF_2. 1-Fluoro-1-phenyl-2-propanone (**8**) was synthesized from the chloro ketone by the use of anhydrous acid potassium fluoride (KHF_2) at 230–240 ° C. It could not be prepared by the use of potassium fluoride, although this has been used for the preparation of 3-fluoro-2-butanone.[12]

Because of the difficulties encountered in the preparation of some of the *gem*-difluoro ketones using mercuric fluoride, attempts were made at their synthesis from the *gem*-dichloro precursors using KF or KHF_2. Although the α-monofluoro derivatives of such ketones could be prepared by these metallic fluorides, the dichloro ones resisted fluorination and were recovered unchanged. Similar results were obtained when using KF and crown ether[13] with acetonitrile or diethylene glycol as solvent, even though this method has been used, conveniently, to exchange bromine for fluorine in bromocyclohexanone.[13]

Preparation of the Chloro Ketones. The *gem*-dichloropropiophenone used in this investigation was prepared by the chlorination of propiophenone with sulfuryl chloride, at room temperature. A good yield of the *gem*-dichlorophenylacetone[14] and 3,3-dichlorobutanone was also obtained by a modification of Wyman's method.[15] Chlorination of 2-butanone by sulfuryl

chloride as reported by Wyman and Kaufman[15] yielded mixtures of α-chloro, α,α′-dichloro and α,α-dichloro ketone.

The ketone **2a′** could not in any way be obtained by chlorination of the *gem*-bromofluorobutanone. It was prepared by taking advantage of the unexpected behavior of 3-fluoro-2-butanone towards sulfuryl chloride to give 1-chloro-3-fluoro-2-butanone (**2**) almost quantitatively, leaving the active methylene hydrogen intact, and then brominating **2** with NBS.

Preparation of the Iodo Ketones. The iodo ketones have been studied infrequently due to their relative instability and because only few satisfactory syntheses for them are available.

For the preparation of the iodo ketones the potassium iodide interchange reaction[16] was used. This method, although generally satisfactory, is subject to pronounced steric effects. Alternative iodination with *N*-iodosuccinimide[17] gave unsatisfactory results. Iodination of the bromo ketones were generally carried out with potassium iodide in ethanol or, if hazardous, acetone as solvent. All the *gem*-haloiodo derivatives of the ketones under study were prepared. Most of the iodo ketones obtained were generally quite unstable and become viscous upon evaporation of the solvent or on standing. The order of their stability was observed to be generally iodo > bromoiodo > chloroiodo > fluoroiodo and amongst the three ketones, butanone > propiophenone > phenylacetone. When kept in carbon tetrachloride the iodobutanones were stable.

Experimental Section

NMR Spectra were recorded on a Varian T-60 instrument in CCl_4 solution with $(CH_3)_4Si$ as internal standard. Mass spectra were obtained using a Varian Mat CH5 instrument. Infrared spectra were recorded on a Pye-Unicam SP 1200 spectrometer. A Varian Aerograph gas-liquid chromatograph Model 920 equipped with thermal conductivity detectors was used for the analysis of liquids. An OV-101 on Chromosorb W60/80 mesh column was generally used. All melting and boiling points are uncorrected.

Yields are based on the mercuric fluoride whenever this metallic fluoride is used for fluorination.

Preparation of 3-Bromo-3-chloro-2-butanone (1a). **1** (10.65 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) were refluxed in CCl_4 (150 mL) under illumination from a 300-W tungsten lamp. After 1 h an orange coloration appeared in the mixture and, after an additional 5 h, the color disappeared and the reaction was complete. Filtration followed by evaporation of the solvent yielded **1a** (17.63 g, 0.095 mol, 95%): bp 136 °C (667 mm); n_D^{26} 1.4850; IR 1740 cm^{-1} (C=O); NMR δ 2.20, 2.40. Anal. Calcd for C_4H_6BrClO: C, 25.91; H, 3.23; Br, 43.10. Found: C, 25.82, H, 3.01; Br, 42.93.

The semicarbazone, obtained from an aqueous solution, had mp 292–294 °C. (Anal. Calcd for $C_5H_9BrClN_3O$: C, 26.29; H, 3.94. Found: C, 26.21; H, 3.85.) Mixtures of the diastereoisomeric (−)-menthydrazone derivative was prepared by reaction with (−)-menthyl *N*-aminocarbamate, "(−)-menthydrazide[18]" in dry benzene solution. It crystallized from the same solvent, mp 142.5 °C. (Anal. Calcd for $C_{15}H_{26}BrClN_2O_2$: C, 47.22; H, 6.81. Found: C, 47.20; H, 6.79.)

By the same general method, 2-bromo-2-chloro-1-phenyl-1-propanone (**3a**) was obtained from **3**[19,20] (16.85 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 5 h. Product (23.55 g, 0.095 mol, 95%): n_D^{26} 1.5622; IR 1700 cm^{-1} (C=O); NMR δ 2.25 (s), 7.55 (m). Anal. Calcd for C_9H_8BrClO: C, 43.68; H, 3.23; Br, 32.20. Found: C, 43.50 H, 3.05; Br, 32.11.

The diastereoisomeric (−)-menthydrazone derivative, prepared and crystallized as for **1a**, had mp 121–122 °C. (Anal. Calcd for $C_{20}H_{28}BrClN_2O_2$: C, 54.15; H, 6.31. Found: C, 54.10; H, 6.45.)

1-Bromo-1-chloro-1-phenyl-2-propanone (**10a**) was obtained from **10** (16.85 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 8 h. Product (24.04 g, 0.097 mol, 97%): n_D^{26} 1.5585; IR 1735 cm^{-1} (C=O); NMR δ 2.18 (s), 7.35 (m). Anal. Calcd for C_9H_8BrClO: C, 43.68; H, 3.22; Br, 32.29. Found: C, 43.50; H, 3.39; Br, 32.35. The diastereoisomeric (−)-menthydrazone, prepared and crystallized as in **1a**, had mp 120–122 °C. (Anal. Calcd for $C_{20}H_{28}BrClN_2O_2$: C, 54.15; H, 6.31. Found C, 54.23; H, 6.50.)

3-Bromo-3-fluoro-2-butanone (**6a′**) was obtained from **6** (9.00 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 3–5 h. Product (16.2 g, 0.09 mol, 95%): bp 129–130 °C (667 mm); n_D^{26} 1.4658; IR 1740 cm^{-1} (C=O); NMR δ 2.28 (d, J_{FCH_3} = 4), 2.00 (d, J_{FCH_3} = 20). Anal. Calcd for C_4H_6BrFO; C, 28.43; H, 3.55. Found: C, 28.40; H, 3.60. The semicarbazone, obtained from an aqueous solution and crystallized from water–ethanol, had mp 220–222 °C. Anal. Calcd for $C_5H_9BrFN_3O$: C, 28.33; H, 4.24. Found: C, 28.21; H, 4.00. The diastereoisomeric (−)-menthydrazone derivative, prepared and crystallized in dry benzene, had mp 140–142 °C dec. Anal. Calcd for $C_{15}H_{26}BrFN_2O_2$: C, 49.35; H, 7.12. Found: C, 49.41; H, 7.10.

1-Bromo-1-fluoro-1-phenyl-2-propanone (**8a′**) was obtained from **8** (15.20 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) in 1 h. Product (22.5 g, 0.097 mol, 97%): IR (in CCl_4) 1742 cm^{-1} (C=O); NMR δ 2.44 (d, J_{FCH_3} = 4), 7.48 (m). Analytical sample was prepared by GLC at 85 °C. Anal. Calcd for C_9H_8BrFO: C, 46.79; H, 3.46. Found: C, 46.70, H, 3.21.

2-Bromo-2-fluoro-1-phenyl-1-propanone (**4a′**) was obtained from **4** (15.20 g, 0.1 mol) [prepared as in **8**, bp 35–39 °C (0.5 mm) [lit.[21] 33 °C (0.4 mm)]] and NBS (17.79 g, 0.1 mol) in 4 h. Product (22 g, 0.09 mol, 95%): IR 1698 cm^{-1} (C=O); NMR δ 2.30 (d, J_{FCH_3} = 20), 7.65 (m). Anal. Calcd for C_9H_8BrFO: C, 46.79; H, 3.46. Found: C, 46.69; H, 3.51.

1,1-Dibromo-1-phenyl-2-propanone (**9b**) was obtained from phenylacetone (13.40 g, 0.1 mol) and NBS (35.58 g, 0.2 mol) in 6–10 h. Product (28.52 g, 97%): IR 1730 cm^{-1} (C=O); NMR δ 2.36 (s), 7.46 (m). Anal. Calcd for $C_9H_8Br_2O$: C, 37.03; H, 2.74. Found: C, 37.19; H, 2.70.

2,2-Dibromo-3-pentanone (**11b**) was obtained from **11** (8.60 g, 0.1 mol) and NBS (35.58 g, 0.2 mol) in 3 h. Product (3.65 g, 0.015 mol, 15%): NMR δ 0.95 (t), 1.65 (s), 2.24 (q). Anal. Calcd for $C_5H_8Br_2O$: C, 24.62; H, 3.28; Br, 65.53. Found: C, 24.51; H, 3.02; Br, 65.41. Other products: 2,4-dibromo-3-pentanone (48%) and 2,2,4-tribromo-3-pentanone (20%).

Preparation of 1-Fluoro-1-phenyl-2-propanone (8). **10** (33.70 g, 0.19 mol) was added dropwise to a vigorously stirred mixture of finely ground and thoroughly dried potassium hydrogen fluoride (78.08 g, 1 mol) and diethylene glycol (120 g) at 230–240 °C. The fluorinated material was allowed to distill through a downward condenser by applying a slight vacuum. The temperature at the still head was maintained at 80–110 °C by controlling the rate of addition of the chloro ketone. The contents of the reaction flask were then extracted thoroughly with CCl_4 and the extract was added to the distillate. Fractionation through an efficient column gave **8** (12.50 g, 0.082 mol, 43%): IR 1725 cm^{-1} (C=O); NMR δ 2.18 (d, J_{FCH_3} = 4), 5.55 (d, J_{HF} = 50), 7.25 (m). The spectral data agreed well with those reported by Newman and Angier,[22] who obtained the compound as a side product in the preparation of α-nitro epoxides.

Preparation of 3-Chloro-3-fluoro-2-butanone (1c). **(i)** A carefully dried apparatus initially protected with $CaCl_2$ tube was used. Finely ground mercuric fluoride (15 g, 0.06 mol) was added all at once to carefully purified **1a** (25 g, 0.13 mol) in a 50-mL round-bottom flask equipped with a condenser and receiver immersed in dry ice–methanol. The vigorously stirred mixture was quickly raised to, and maintained at, 140 °C; the visible reaction ensued after a few minutes. The temperature was kept between 140 and 160 °C until the reaction was complete as shown by a color change of mercuric fluoride from red-orange to dark brown. The contents of the flask were then distilled by applying a slight vacuum and the products distilling over between 70 and 100 °C were collected. Fractionation of the liquid so obtained gave 5.55 g of a mixture, bp 92–96 °C, containing **1c** and biacetyl in the ratio of 54:45 (by NMR). Isolation of pure **1c** from this mixture was effected by GLC Autoprep. at 50 °C. It had: bp 102–103 °C; IR 1745 cm^{-1} (C=O); NMR δ 1.62 (d, J_{FCH_3} = 20), 2.02 (d, J_{FCH_3} = 4); mass spectrum *m/e* 126, 124 (M^+). Anal. Calcd for C_6H_6ClFO: C, 38.59; H, 4.82. Found: C, 38.40; H, 4.93. The diasteoisomeric (−)-menthydrazone derivative, prepared and crystallized in CCl_4 solution, had mp 200 °C. (Anal. Calcd for $C_{15}H_{26}ClFN_2O_2$: C, 56.19; H, 8.11. Found: C, 56.18; H, 8.01.)

(ii) **6** (9.00 g, 0.1 mol), NCS (13.35 g, 0.1 mol), and 3 mg of benzoyl peroxide were reacted in benzene (under UV irradiation) and worked up as in the preparation of **1a** to give **1c** (0.32 g, 0.025 mol, 2.5%).

Preparation of 2-Chloro-2-fluoro-1-phenyl-1-propanone (3c). **3a** (24.75 g, 0.1 mol) and HgF_2 (7.5 g, 0.03 mol) were reacted as in the preparation of **1c**. Reaction ensued at 85 °C and was raised up to 125 °C until the reaction was complete. Repeated fractionation of the product gave nearly pure **3c** (3.64 g, 0.019 mol, 65%). Final purification was effected with GLC at 70 °C: IR 1705 (C=O); NMR δ 2.00 (d, J_{FCH_3} = 20), 7.60 (m); mass spectrum *m/e* 188,186 (M^+). Anal. Calcd for C_9H_8ClFO: C, 67.95, H, 4.28. Found: C, 57.79, H, 4.12.

Also obtained was 2-chloro-1-phenyl-2-propen-1-one (0.90 g, 18%): IR 1580 (C=C), 1690 cm^{-1} (C=O); NMR showing the characteristic

AB system with δ 5.98, 5.83 (d, J_{AB} = 2 Hz), 7.60 (m, Ph). Anal. Calcd for C_9H_7ClO: C, 64.90; H, 4.20. Found: C, 65.20, H, 4.38.

A volatile fraction (1 g) boiling at 55–60 °C, which remained unidentified, was also obtained.

Reaction of 1-Bromo-1-chloro-1-phenyl-2-propanone (10a) with Mercuric Fluoride. A. Mercuric fluoride (7.5 g, 0.03 mol) was added all at once at 0–5 °C to **10a** (24.75 g, 0.1 mol). A vigorous reaction started immediately and the contents of the reaction flask became solid. No identifiable product could be isolated; the NMR of the product on warming to room temperature consisted of numerous peaks.

B. Mercuric fluoride was gradually added to **10a** dissolved in pure dry $CHCl_3$ through a section of 1.25-in. rubber tubing which was closed just above the neck by a screw clamp. The contents of the reaction flask were maintained between 5 and 10 °C under vigorous stirring until the addition of HgF_2 was complete. The reaction mixture was then filtered and the residue washed with chloroform, worked up, and dried over calcium chloride. Upon removal of chloroform the residue was found to contain ca. 50% of the unchanged starting material together with other unidentified mixtures. Repetition of this experiment in the presence of dry pyridine in order to prevent possible polymerization and side reactions gave similar results to above.

Reaction of 3,3-Dibromo-2-butanone (7b)[23] with Mercuric Fluoride. Mercuric fluoride (15.00 g, 0.06 mol) was added to **7b** (22.98 g, 0.1 mol) and the temperature was quickly raised to 80 °C where reaction ensued. The temperature was kept at 115–120 °C until the visible reaction subsided. The contents of the flask were allowed to distill over. The first fraction, bp 70–75 °C (4.90 g, 95%), was found to be biacetyl (by NMR, GLC, and preparation of its semicarbazone derivative); the second fraction, bp 90–130 °C, was unchanged **7b** (ca. 2.5 g). Various modifications of this reaction under argon or air-free nitrogen gave only biacetyl. Similarly, the reaction 2,2-dibromo-3-pentanone with HgF_2 gave 3,4-hexanedione as the only product (90%).

Preparation of 2,2-Difluoro-1-phenyl-1-propanone (4b'). A. Mercuric fluoride (30.0 g, 0.12 mol) was added to **5b**[24] (58.37 g, 0.2 mol) at 50 °C. The reaction mixture was then stirred vigorously and the temperature raised to 120–125 °C, where the reaction started. Upon subsidence of the visible reaction (2–3 min), stirring was discontinued and 10 mL of pure CCl_4 was quickly added to the reaction mixture. This mixture was then filtered and the filtrate was fractionated to give **4a** (1.4 g, 5%) and **4b'** (18.4 g. 0.107 mol, 90%): IR 1705 cm^{-1} (C=O) (lit. 5.85[25] prepared from the corresponding alkyne and OF_2); NMR δ 1.76 (t, J_{FCH_3} = 19), 7.68 (m).

B. Mercuric fluoride (15.0 g) and **4a** (23.0 g) reacted and worked up as above gave **4b** (9.5 g, 95%) and unchanged **4a** (5.2 g).

Reaction of 9b with Mercuric Fluoride. 9b (15 g) was dissolved in 20 mL of $CHCl_3$ and mercuric fluoride (6 g) was added to it gradually at 5 °C. The reaction flask, which becomes warm, was kept between 2 and 7 °C until the addition of HgF_2 was complete. Analysis of the reaction mixture by NMR did not show the presence of 1,1-difluoro-1-phenyl-2-propanone,[26] although some characteristic triplet peaks indicative of fluorine coupling were present in the NMR spectrum of the mixture.

Preparation of 1-Chloro-3-fluoro-2-butanone (2). 6 (9.0 g, 0.1 mol) was placed in a 50-mL round-bottom flask and sulfuryl chloride (13.49 g, 0.1 mol) was added to it dropwise at room temperature during 2–3 h while stirring vigorously. The reaction mixture was kept stirring overnight at room temperature. Fractionation of the dark mixture gave unchanged **6** (0.5 g) and almost pure **2** (11.19 g, 90%). Analytical sample was obtained by GLC at 65 °C: n_D^{26} 1.4280; IR 1753 cm^{-1} (C=O); NMR δ 1.52 (dd, J_{FCH_3} = 22, J_{HCH_3} = 6), 5.08 (d, J_{HF} = 50). 4.40 (d, J_{FCH_2} = 4). Anal. Calcd for C_4H_6ClFO: C, 38.59; H, 4.82. Found: C, 38.82; H, 4.91.

Preparation of 3-Chloro-1-fluoro-1-phenyl-2-propanone. 8 (15.20 g, 0.1 mol) reacted with sulfuryl chloride (13.49 g, 0.1 mol) as above at 25 °C during 5 h to give the title compound (15.2 g, 85%) based on NMR. Analytical sample was obtained by GLC at 65 °C: IR 1746 cm^{-1} (C=O); NMR δ 4.10 (d, J_{FCH_2} = 4), 5.60 (d, J_{HF} = 49), 7.10 (m). Anal. Calcd for C_9H_8FClO: C. 57.95; H, 4.28. Found: C, 57.75; H, 4.52.

Preparation of 1-Chloro-3-bromo-3-fluoro-2-butanone (2a'). 2 (12.44 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) were refluxed in CCl_4 (150 mL) as in **1a** for 6 h and worked up to give **2a** (20 g, 98%): IR 1760 cm^{-1} (C=O); NMR δ 2.20 (d, J_{FCH_3} = 22), 7.70 (d, J_{FCH_2} = 3). Anal. Calcd for $C_4H_5BRClFO$: C, 23.62; H, 2.45. Found: C, 23.42; H, 2.51.

3-Chloro-1-bromo-1-fluoro-1-phenyl-2-propanone. 3-Chloro-1-fluoro-1-phenyl-2-propanone (18.65 g) and NBS taken in molar ratios reacted as above for 5–8 h to give the title compound in 96% yield: IR 1755 cm^{-1} (C=O); NMR δ 4.30 (d, J_{FCH_2} = 4), 7.22 (m). Anal. Calcd for $C_9H_7BrClFO$: C, 40.72; H, 2.63. Found: C, 40.41; H, 2.80.

Preparation of 1,3-Difluoro-2-butanone. 2 (12.44 g, 0.1 mol) was reacted with potassium fluoride (8.7 g) in diethylene glycol (10 mL) at 180–200 °C in the usual manner. When product was distilled under reduced pressure while **2** was being added, the liquid mixture so obtained was found to contain ca. 3 g of the title compound by NMR. Analytical sample was obtained by GLC at 45 °C: IR 1755 cm^{-1} (C=O); NMR 1.50 (dd, J_{HCH_3} = 6, J_{FCH_3} = 22), 3.95 (dd, J_{FCH_2} = 4,44), 5.00 (ddq, J_{HF} = 50). Anal. Calcd for $C_4H_6F_2O$: C, 44.47; H, 5.55. Found: C, 44.31; H, 5.20. The major portion of the mixture consisted of a compound which could possibly be an olefin (its NMR having a doublet of doublets at δ 4.6 and 5.4 (J = 46 and 4 Hz). When, however, the product is left in the ethylene glycol/KF mixture and is distilled at the end of the reaction, the sole product is the presumed olefin, as is the case where KHF_2 is used for this fluorination.

Preparation of 1-Chloro-3,3-difluoro-2-butanone (2b'). 2a (18 g, 0.08 mol) and mercuric fluoride (5.7 g, 0.024 mol) were reacted as in **1c**. Threshhold temperature for this fluorination was at 145–150 °C. The product distilling over from the downward condenser was collected in the range 70–80 °C and was subjected to repeated fractionation to give **2b'** (2.68 g, 75%): IR 1765 cm^{-1} (C=O); NMR δ 1.68 (t, J_{FCH_3} = 19), 4.40 (t, J_{FCH_2} = 1). Anal. Calcd for $C_4H_5ClF_2O$: C, 33.72; H, 3.50 Found: C, 33.62; H, 3.71.

Preparation of 2,2-Dichloro-1-phenyl-1-propanone. To propiophenone (13.41 g), sulfuryl chloride (27 g) was added during 20 h at room temperature while stirring vigorously. Analysis of the mixture by NMR indicated the presence of 50% title compound together with ca. 40% of the monochloro ketone. This is a much more convenient method of preparation than that reported in the literature.[27] The *gem*-dichloro analogues of phenylacetone and 2-butanone were prepared similar in 80% yield, respectively (reaction times 25–30 h).

Preparation of 3-Iodo-2-butanone. A mixture of 3-bromo-2-butanone (13.28 g, 0.08 mol) and KI (16.60 g, 0.1 mol) in 20 mL of absolute alcohol was refluxed for 2 h. The reaction mixture was then cooled, dried with magnesium sulfate, and extracted with ether. Fractionation of the evaporated extract gave the title compound (15.12 g, 95%): bp 148–150 °C dec (667 mm); n_D^{26} 1.4288; IR 1730 cm^{-1} (C=O); NMR δ 2.40 (s), 1.80 (d, J_{HCH_3} = 6). 4.80 (q, J_{HCH_3} = 6). Anal. Calcd for C_4H_7IO: C, 24.27; H, 3.52. Found: C, 24.58; H, 3.15. The pure sample should be kept in a dark bottle in vacuo. Under ordinary conditions it partially decomposes within a few hours and a waxy polymeric product results within a week. The diastereoisomeric (−)-menthydrazone derivative was prepared in dry benzene solution, mp 188–190 °C dec. This derivative partially decomposes and turns brown when kept for a few days. The semicarbazone (from an aqueous solution) had mp 212–214 °C dec.

Preparation of 3-Bromo-3-iodo-2-butanone. 3-Iodo-2-butanone (19.79 g, 0.1 mol) and NBS (17.79 g, 0.1 mol) were refluxed in CCl_4 (170 mL) as in **1a**. The reaction was stopped after 5 h to give 10% (by NMR) of the title compound. It is worthy of mention that 3-bromobutanone under the same conditions gave 95% of the dibromobutanone after 5 h. When the reaction was continued for 30–35 h nearly 95% of the title compound was obtained in pure form. This ketone, although more resistant toward decomposition than the chloroiodobutane while evaporating the solvent, could not be isolated from the solvent. It had: IR (CCl_4) 1730 cm^{-1}; NMR δ 2.42 (s), 2.61 (s). Its (−)-menthydrazone prepared in CCl_4 solution had mp 228–230 °C dec. Anal. Calcd for $C_{15}H_{26}BrIN_2O_2$: C, 42.09; H, 6.07. Found: C, 41.63; H, 5.70.

Preparation of 3-Chloro-3-iodo-2-butanone. A mixture of **1a** (13.28 g, 0.08 mol) and KI (16.6 g, 0.1 mol) were refluxed in 20 mL of absolute alcohol for 2 h to give a liquid mixture containing 9.3 g (50%) of the title compound. Separation of the mixture by column chromatography using silica gel and CCl_4 gave the iodo ketone in pure form (fifth fraction): IR 1738 cm^{-1} (C=O); NMR δ 2.32 (s), 2.60 (s). The iodo ketone was pure by NMR, but evaporation of its solvent (CCl_4) even under reduced pressure, in order to obtain an analytical sample, resulted in its partial decomposition. Its menthydrazone derivative prepared in CCl_4 solution had mp 208–210 °C dec. Anal. Calcd for $C_{15}H_{26}ClIN_2O_2$: C, 42.24; H, 6.09. Found: C, 42.41; H, 6.30. The semicarbazone derivative prepared in a split-phase CCl_4–H_2O medium had mp 288 °C dec. Other fractions obtained had only a singlet in their NMR and were not investigated further.

Preparation of 3-Fluoro-3-iodo-2-butanone. A mixture of **6a** (13.52 g, 0.08 mol) and KI (16.6 g, 0.1 mol) in dry acetone (25 mL) was stirred at room temperature for 3 h. Half of the acetone was then evaporated under reduced pressure. The dark red mixture obtained was found to contain the title compound (60% by NMR): IR was obtained by evaporating nearly all the acetone under reduced pressure

and immediately adding CCl_4 to the residue, IR 1735 cm^{-1} (C=O); NMR δ 2.38 (d, J_{FCH_3} = 4), 2.18 (d, J_{FCH_3} = 20). The compound decomposes after 2 days even when kept in CCl_4. The diastereoisomeric (−)-menthydrazone prepared in CCl_4 solution had mp 162–164 °C dec. Anal. Calcd for $C_{15}H_{26}FIN_2O_2$: C, 49.08; H, 7.07. Found: C, 50.69; H, 6.50. Attempted preparation of the title compound in ethanol as solvent gave decomposed mixtures. No reaction occured without the use of any solvent.

Other iodo compounds which were prepared by the same general method but could not be isolated in pure form due to their instability were: 1-Iodo-1-phenyl-2-propanone (98%): IR 1715 cm^{-1} (C=O); NMR δ 2.35 (s), 7.32 (m). 2-Iodo-1-phenyl-1-propanone (26.5%): IR 1693 cm^{-1} (C=O); NMR δ 2.10 (d, J_{HCH_3} = 6), 6.10 (q, J_{HCH_3} = 6), 7.65 (m). 1-Chloro-1-iodo-1-phenyl-2-propanone (96%): IR 1733 cm^{-1} (C=O); NMR δ 2.35 (s), 7.38 (m). 2-Chloro-2-iodo-1-phenyl-1-propanone (13%): IR 1695 cm^{-1} (C=O); NMR δ 2.40 (s), 7.75 (m). 1-Fluoro-1-iodo-1-phenyl-2-propanone (95%): IR 1723 cm^{-1} (C=O); NMR δ 2.30 (d, J_{FCH_3} = 4), 7.40 (m). 2-Fluoro-2-iodo-1-phenyl-1-propanone (35%): IR 1696 cm^{-1} (C=O); NMR δ 2.54 (d, J_{FCH_3} = 20), 7.78 (m). 1-Bromo-1-iodo-1-phenyl-2-propanone (98%) [IR 1720 cm^{-1} (C=O); NMR δ 2.30 (s), 7.60 (m)] and 2-bromo-2-iodo-1-phenyl-1-propanone (68%) [IR 1690 cm^{-1} (C=O); NMR δ 2.35 (s), 7.60 (m)] were also prepared by bromination of the corresponding iodo-compounds with NBS in the general manner.

Registry No.—**1a** semicarbazone, 63017-11-8; **1a** (−)-menthydrazone epimer I, 63017-12-9; **1a** (−)-menthydrazone epimer II, 63017-13-0; **1c**, 63017-14-1; **1c** (−)-menthydrazone epimer I, 63017-15-2; **2c** (−)-menthydrazone epimer II, 63017-16-3; **2b′**, 63017-17-4; **3a** (−)-menthydrazone epimer I, 63017-18-5; **3a** (−)-menthydrazone epimer II, 63017-19-6; **3c**, 63017-20-9; 1,3-difluoro-2-butanone, 63058-87-7; **4b′**, 703-17-3; **6a′** semicarbazone, 63017-21-0; **6a′** (−)menthydrazone epimer I, 63017-22-1; **6a** (−)-menthydrazone epimer II, 63017-23-2; **10a** (−)-menthydrazone epimer I, 63017-24-3; **10a** (−)-menthydrazone epimer II, 63017-25-4; 2 chloro-1-phenyl-2-propen-1-one, 19233-44-4; 3-chloro-1-fluoro-1-phenyl-2-propanone, 63017-26-5; 3-chloro-1-bromo-1-fluoro-1-phenyl-2-propanone, 63017-27-6; 2,2-dichloro-1-phenyl-1-propanone, 57169-51-4; 3-iodo-2-butanone, 30719-18-7; 3-bromo-2-butanone, 814-75-5; 3-iodo-2-butanone (−)-menthydrazone epimer I, 63017-28-7; 3-iodo-2-butanone (−)-menthydrazone epimer II, 63017-29-8; 3-iodo-2-butanone semicarbazone, 63017-30-1; 3-brono-3-iodo-2-butanone, 63017-31-2; 3-bromo-3-iodo-2-butanone (−)-menthydrazone epimer I, 63017-32-3; 3-bromo-3-iodo-2-butanone (−)-menthydrazone epimer II, 63067-33-4; 3-chloro-3-iodo-2-butanone, 63017-34-5; 3-chloro-3-iodo-2-butanone (−)-menthydrazone epimer I, 63058-88-8; 3-chloro-3-iodo-2-butanone (−)-menthydrazone epimer II, 63017-35-6; 3-chloro-3-iodo-2-butanone semicarbazone, 63107-36-7; 3-fluoro-3-iodo-2-butanone, 63017-37-8; 3-fluoro-3-iodo-2-butanone (−)-menthydrazone epimer I, 63017-38-9; 3-fluoro-3-iodo-2-butanone (−)-menthydrazone epimer II, 63017-39-0; 1-iodo-1-phenyl-2-propanone, 63017-40-3; 2-iodo-1-phenyl-1-propanone, 6084-15-7; 1-chloro-1-iodo-1-phenyl-2-propanone, 63017-41-4; 2-chloro-2-iodo-1-phenyl-1-propanone, 63017-42-5; 1-fluoro-1-iodo-1-phenyl-2-propanone, 63017-43-6; 2-fluoro-2-iodo-1-phenyl-1-propanone, 63017-44-7; 1-bromo-1-iodo-1-phenyl-2-propanone, 63017-45-8; 2-bromo-2-iodo-1-phenyl-1-propanone, 63017-46-9.

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Steric Effects. 9. Substituents at Oxygen in Carbonyl Compounds

Marvin Charton

Department of Chemistry, Pratt Institute, Brooklyn, New York 11205

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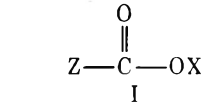
Twenty-nine sets of basic hydrolyses rate constants for alkyl acetates, formates, propionates, and benzoates; four sets of acid-catalyzed hydrolysis rate constants of alkyl acetates; one set of rate constants for the vapor-phase esterification of acetic acid with alcohols; and one set of rate constants for the reaction of 4-nitrobenzoyl chloride with alcohols were correlated by the modified Taft equation using υ_X, υ_{CH_2X}, and υ_{OX} constants. Best results were obtained with the υ_{OX} constants which were defined in this work. Forty values of υ_{OX} are given. The successful correlation with υ_{CH_2X} verified the validity of the equation $\upsilon_{Z_1X} = \upsilon_{Z_2X} + c$. The magnitude of ψ as a function of the structure of the substrate is described.

In many data sets of reaction rates of carbonyl compounds, the effect of substitution at an oxygen atom has been studied. In particular, rates of ester hydrolysis of I, where Z is a constant substituent and X is permitted to vary, have been examined. The first attempt at handling steric effects of the X group is due to Taft,[1] who proposed E_S values for these



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groups and pointed out[2] that E_{SX} and E_{SZ} may differ significantly from each other when X = Z. In this work, effects of R in the set RCH_2OAc were correlated with the Taft equation

$$\log (k/k^0) = \delta E_S \qquad (1)$$

using E_{SZ} values. Results were good for a set of eight substituents, although two of the substituents had to be excluded from the set. It seemed to us of interest to extend our previous investigation[3–10] to this topic. For this purpose, we examined

Table I. Data Used in the Correlations

1. kr, ROBz + OH^- in 56% w/w MeAc–H_2O at 25 °C[a]
   Me, 9.022; Et, 2.891; Pr, 1.932; Bu, 1.667; $BuCH_2CH_2$, 1.274; $Bu(CH_2)_4$, 1.263; *i*-Pr, 0.4644; *i*-Bu, 1.429; *s*-Bu, 0.2259; *t*-Bu, 0.01327; *i*-$PrCH_2CH_2$, 1.200; MePrCH, 0.1487; Me_2EtC, 0.005024;[b] c-C_5H_9, 0.3972; c-C_6H_{11}, 0.2679
2. kr, ROBz, + OH^- in 60% v/v dioxane–H_2O at 35 °C[c]
   Me, 1.74; Et, 0.553; Pr, 0.379; *i*-Pr, 0.0919; Bu, 0.289; *i*-Bu, 0.240; *s*-Bu, 0.0468; *i*-$PrCH_2CH_2$, 0.234; Et_2CH, 0.0162
3. kr, ROAc + OH^- in 40% v/v dioxane–H_2O at 35 °C[d]
   Me, 19.3; Et, 8.90; Pr, 6.75; *i*-Pr, 1.84; Bu, 5.38; *i*-Bu, 3.95; *s*-Bu, 0.954; *t*-Bu, 0.103;
4. kr, ROAc + OH^- in 62% w/w MeAc–H_2O at 0 °C[e]
   Me, 0.910; Et, 0.405; *i*-Pr, 0.0628; *i*-Bu, 0.147
5. kr, ROAc + OH^- in 62% w/w MeAc–H_2O at 10 °C[e]
   Me, 2.08; Et, 0.908; *i*-Pr, 0.1395; *i*-Bu, 0.314
6. kr, ROAc + OH^- in 62% w/w MeAc–H_2O at 20 °C[e]
   Me, 3.96; Et, 1.75; *i*-Pr, 0.289; *i*-Bu, 0.676
7. $10^4 kr$, ROAc + H_3O^+ in 62% w/w MeAc–H_2O at 30.1 °C[e]
   Me, 52.0; Et, 42.6; *i*-Pr, 20.0; *i*-Bu, 30.9; *t*-Bu, 8.00
8. $10^4 kr$, ROAc + H_3O^+ in 62% w/w MeAc–H_2O at 40 °C[e]
   Me, 120.0; Et, 98.5; *i*-Pr, 47.1; *i*-Bu, 71.6; *t*-Bu, 27.0
9. $10^2 kr$, ROAc + OH^- in 70% v/v MeAc–H_2O at 20 °C[f]
   Me, 8.47; Et, 3.56; Pr, 2.02; *i*-Pr, 0.530; *i*-Bu, 1.41; Bu, 1.74; *s*-Bu, 0.231
10. $10^2 kr$, ROAc + OH^- in 70% v/v MeAc–H_2O at 24.7 °C[f]
    Me, 10.8; Et, 4.66; Pr, 2.70; *i*-Pr, 0.706; *i*-Bu, 1.82; Bu, 2.30; *s*-Bu, 0.327; *t*-Bu, 0.0265; c-C_6H_{11}, 0.456
11. $10^2 kr$, ROAc + OH^- in 70% v/v MeAc–H_2O at 35 °C[f]
    Et, 8.22; Pr, 5.07; *i*-Pr, 1.40; *i*-Bu, 3.55; Bu, 4.39; *s*-Bu, 0.682; *t*-Bu, 0.0593; c-C_6H_{11}, 0.884
12. $10^2 kr$, ROAc + OH^- in 70% v/v MeAc–H_2O at 44.7 °C[f]
    Et, 13.5; Pr, 8.80; *i*-Pr, 2.53; *i*-Bu, 6.28; Bu, 7.66; *s*-Bu, 1.27; *t*-Bu, 0.112; c-C_6H_{11}, 1.78
13. $10^2 kr$, RO_2CEt + OH^- in 70% v/v MeAc–H_2O at 20 °C[f]
    Me, 4.93; Et, 1.65; *i*-Pr, 0.201; Bu, 0.760
14. $10^2 kr$, RO_2CEt + OH^- in 70% v/v MeAc–H_2O at 24.7 °C[f]
    Me, 6.41; Et, 2.21; *i*-Pr, 0.298; Bu, 0.989
15. $10^2 kr$, RO_2CEt + OH^- in 70% v/v MeAc–H_2O at 35 °C[f]
    Me, 10.9; Et, 4.08; *i*-Pr, 0.604; Bu, 1.88
16. $10^2 kr$, RO_2CEt + OH^- in 70% v/v MeAc–H_2O at 44.7 °C[f]
    Me 17.5; Et, 6.84; *i*-Pr, 1.14; Bu. 3.51
17. kr, RO_2CH + OH^- in H_2O at 5 °C[g]
    Me, 696; Et, 509; Pr, 483; Bu, 456; *i*-Pr, 239
18. kr, RO_2CH + OH^- in H_2O at 15 °C[g]
    Me, 1240; Et, 902; Pr, 844; Bu, 789; *i*-Pr, 413
19. kr, RO_2CH + OH^- in H_2O at 25 °C[g]
    Me, 2200; Et, 1540; Pr, 1370; Bu, 1310; *i*-Pr, 655
20. kr, RO_2CH + OH^- in H_2O at 35 °C[g]
    Me, 3730; Et, 2440; Pr, 2170; Bu, 1840; *i*-Pr, 1040
21. kr, ROH + AcOH over silica–alumina catalyst at 250 °C[h]
    Me, 6.6; Et, 6.3; Pr, 8.0; Bu, 8.2; *i*-Bu, 7.8; *i*-Pr, 5.5; *s*-Bu, 8.3; *t*-Bu, 14.0
22. $10^3 kr$, ROH + 4-$O_2NC_6H_4COCl$ in Et_2O at 25 °C[i]
    Me, 184; Et, 84.5; Pr, 65.9; *i*-Pr, 10.1; Bu, 70.3; *s*-Bu, 7.35; *t*-Bu, 2.70; *i*-Bu, 30.8; $BuCH_2$, 79; $BuCH_2CH_2$, 85; $Bu(CH_2)_3$, 69; *s*-$BuCH_2$, 36; *i*-$PrCH_2CH_2$, 73; *i*-$PrCH_2CH_2CH_2$, 68; MePrCH, 5.9; MeBuCH, 6.5; Et_2CH, 3.6; Pr_2CH, 2.7
23. $10^5 kr$, ROAc + H_3O^+ in 75% v/v MeAc–H_2O at 35 °C catalyzed by HCl[j]
    Me, 13.0; Et, 12.0; Bu, 9.65; c-C_5H_9, 4.35; PrMeCH, 3.59; $BuCH_2$, 8.78; c-C_6H_{11}, 3.79; $BuCH_2CH_2$, 7.60; $Bu(CH_2)_4$, 6.65
24. $10^5 kr$, ROAc + H_3O^+ in 75% v/v MeAc–H_2O at 35 °C catalyzed by resin acid[j]
    Me, 6.45; Et, 3.34; Bu, 1.12; c-C_5H_9, 0.612; PrMeCH, 0.308; $BuCH_2$, 0.663; c-C_6H_{11}, 0.478; $BuCH_2CH_2$ 0.420; $Bu(CH_2)_4$, 0.083
25. kr, ROAc + OH^- in H_2O at 20.0 °C, average values[k]
    Me, 8.09; Et, 4.85; *i*-Pr, 1.29; Bu, 4.05; $BuCH_2$, 3.63; *i*-$PrCH_2CH_2$, 3.17
26. kr, ROAc + OH^- in H_2O at 30.0 °C, average values[k]
    Me, 16.0; Et, 9.04; *i*-Pr, 3.40; Bu, 7.41; $BuCH_2$, 6.82; *i*-$PrCH_2CH_2$, 6.49
27. kr, ROAc + OH^- in H_2O at 20 °C and 2000 atm[k]
    Bu, 6.1; *i*-Bu, 5.7; *i*-Pr, 2.08; $BuCH_2$, 6.0
28. kr, ROAc + OH^- in H_2O at 20 °C and 5000 atm[k]
    Et, 15.9; Bu, 14.1; *i*-Bu, 12.3; *i*-Pr, 5.2
29. kr, ROAc + OH^- in H_2O at 20 °C and 8000 atm[k]
    Et, 31.0; Bu, 25.7; *i*-Bu, 28.3; *i*-Pr, 11.4; $BuCH_2$, 25.2
30. $10^3 kr$, ROAc + OH^- in 70% v/v dioxane–H_2O at 20 °C[l]
    Me, 54; Et, 35; *s*-$BuCH_2$, 12.5; *i*-$PrMeCHCH_2$, 10; *t*-$BuCH_2$, 8.6; $EtMe_2CCH_2$, 6.0; *i*-$PrEtCHCH_2$, 5.3; Et_2CHCH_2, 5.1; $BuEtCHCH_2$, 5.1; *t*-$BuEtCHCH_2$, 1.7; Et_3CCH_2, 1.5; c-$C_3H_5CH_2$, 31; c-$C_4H_7CH_2$, 23; c-$C_5H_9CH_2$, 16; c-$C_6H_{11}CH_2$, 10.
31. $10^3 kr$, ROAc + OH^- in 70% v/v dioxane–H_2O at 30 °C[l]
    Et, 66; *s*-$BuCH_2$, 27; *t*-$BuCH_2$, 17; c-$C_6H_{11}CH_2$, 23; *i*-Pr, 12.4; *t*-Bu, 0.8
32. kr, ROAc + OH^- in H_2O at 0.0 °C[m]
    Pr, 1.01; *i*-Pr, 0.313; Bu, 0.925; *i*-Bu, 0.870; *s*-Bu, 0.206; *t*-Bu, 0.0158; *i*-$PrCH_2CH_2$, 0.899
33. kr, ROAc + OH^- in H_2O at 10.0 °C[m]
    Pr, 2.15; *i*-Pr, 0.640; Bu, 1.94; *i*-Bu, 1.76; *s*-Bu, 0.419; *t*-Bu, 0.0368; *i*-$PrCH_2CH_2$, 1.80
34. kr, ROAc + OH^- in H_2O at 20.0 °C[m]
    Me, 7.84; Et, 4.57; Pr, 4.23; *i*-Pr, 1.26; Bu, 3.33; *i*-Bu, 3.54; *s*-Bu, 0.816; *t*-Bu, 0.0809; *i*-$PrCH_2CH_2$, 3.61; Et_2CH, 0.340; Me_2EtC, 0.0374
35. kr, ROAc + OH^- in H_2O at 30.0 °C[m]
    Pr, 8.09; *i*-Pr, 2.50; Bu, 7.58; *i*-Bu, 6.75; *s*-Bu, 1.55; *t*-Bu, 0.166; *i*-$PrCH_2CH_2$, 6.72

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the correlation of rate constants for 29 sets of base-catalyzed hydrolysis and four sets of acid-catalyzed hydrolysis of esters of the type I with the modified Taft equation,

$$\log k_{OX} = \upsilon_X + h \qquad (2)$$

Also studied were a set of rate constants for the reaction of XOH with AcOH, and a set of rate constants for the reaction of XOH with 4-$O_2NC_6H_4COCl$. The data used in the correlations are presented in Table I. The υ constants required for the correlations are from our previous work.[3,9] For results of the correlations with eq 2, see the paragraph at the end of the paper. In this work only substituents OX with X = alkyl have been examined. Alkyl substituents even in basic hydrolysis seem to be free of variable electrical effects, as we have shown for esters in which X is constant and Z is alkyl.[4] As further evidence, consider the σ_I and σ_R constants of alkoxy substituents. For values of these, see the paragraph at the end of this paper.

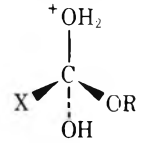
Results of the correlations with eq 2 are as follows: nine sets gave excellent (>99.5% CL), one gave very good (99.0% CL),

Table II. Calculated Values of υ_{OMe}

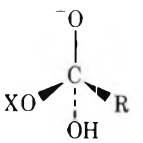
υ_{OMe}	Set	Ref
0.43	2	*a*
0.30	6	*b*
0.30	2A	*c*

[a] M. Charton, *J. Org. Chem.*, **40**, 407 (1975). [b] Reference 7. [c] Reference 10.

nine gave good (97.5% CL), eight gave fair (95.0% CL), and one gave poor correlation (90.0% CL). Seven sets did not give significant results (<90.0% CL). As the large majority (28 out of 35) of the sets studied gave significant results, it seems reasonable to conclude that the data studied involve predominantly steric effects. The υ_X values do not seem to be the best steric parameter for representing the data, however. If we examine the tetrahedral intermediate for the basic ester hydrolysis reactions which constitute most of the sets studied (1–6, 9–20, 25–35) and compare it with the tetrahedral intermediate from which υ_X values are defined, II and III, respectively, we observe that as R remains constant X varies in II and



II



III

OX in III. What is required then is a set of υ_{OX} values. Such values are unavailable. The correlations obtained with υ_X did not seem to us to be good enough to use as the basis for the definition of υ_{OX} values. We have therefore examined the following approach to the problem. Consider a substituent to be composed of two parts, Z and X, where Z joins X and the skeletal group G to which the substituent is attached. Now let us assume that for some substituent Z_1X we can write the steric parameter υ as,

$$\upsilon_{Z_1X} = f_{Z_1} + f_X \tag{3}$$

while for some other substituent, Z_2X we can write

$$\upsilon_{Z_2X} = f_{Z_2} + f_X \tag{4}$$

Then,

$$\upsilon_{Z_1X} = \upsilon_{Z_2X} + f_{Z_1} - f_{Z_2} \tag{5}$$

If we consider two sets of substituents, one with constant Z_1 and the other with constant Z_2,

$$\upsilon_{Z_1X} = \upsilon_{Z_2X} + c \tag{6}$$

Then from eq 7, with $Z_1 = CH_2$ and $Z_2 = O$

$$\upsilon_{OX} = \upsilon_{CH_2X} + c \tag{7}$$

We have therefore correlated the data in Table I with the equation

$$\log k_{OX} = \psi\upsilon_{CH_2X} + h \tag{8}$$

For the results of the correlations with eq 8, see the paragraph at the end of this paper. Nineteen sets gave excellent (>99.5% CL), four gave very good (99.0% CL), four gave good (97.5% CL), and six gave poor correlation (90% CL). One set did not give significant results (<90.0% CL). Obviously, the results obtained from correlation with eq 8 are very much better than those obtained with eq 2. Ideally, however, we would like to have a set of υ_{OX} values. It is essential to be able to employ these υ_{OX} values together with the other υ values we have determined, so that data sets containing many different substituent types can be correlated with the modified Taft equation. It is particularly important, therefore, that the υ_{OX} values be on the same scale as the υ values we have previously reported. If this is not done, then the utility of the υ_{OX} steric parameters would be limited to sets including only OX groups, and the parameters would be much less useful. We may now proceed to define such a set of values. For this purpose, we must choose a reference set of data, a value for some OX substituent, and a value of ψ for the reference set. For a reference set, we have chosen set 10, rate constants for the basic hydrolysis of alkyl acetates in 70% v/v MeAc–H_2O at 24.7 °C. This set was chosen because it gave an excellent correlation with eq 8 and included many of the most common OX groups. We then assigned a value of 0.36 to υ_{OMe}. This value was chosen on the basis that $\upsilon_{OH} = 0.32$, $\upsilon_{CH_2Me} = 0.56$, and $\upsilon_{CH_3} = 0.52$. Then the effect of replacing H with Me in CH_2Me = $\upsilon_{CH_2Me} - \upsilon_{CH_3} = 0.04$. Therefore, the effect of replacing H by Me for OMe should also be 0.04, and $\upsilon_{OMe} - \upsilon_{OH} = 0.04$. Then, it follows that υ_{OMe} should be about 0.36. Values of υ_{OMe} obtained from other correlations in previous investigations are shown in Table II. The average value of υ_{OMe} obtained is 0.34, in good agreement with the value of 0.36 we have chosen. The value of ψ chosen is the value obtained for the correlation set 10 with eq 8 in order to place the υ_{OX} values on the same scale

Table III. υ_{OX} Values

OX	υ	Source	OX	υ	Source
OMe	0.36	definition	OCH_2CMe_2Et	0.78	31
OEt	0.48	10	OCH_2CHEt-*i*-Pr	0.76	31
OPr	0.56	10	OCH_2CHEt_2	0.71	31
O-*i*-Pr	0.75	10	$OCH_2CHEtBu$	0.76	31
O-*i*-Bu	0.62	10	OCH_2CHEt-*t*-Bu	0.96	31
OBu	0.58	10	OCH_2CEt_3	0.97	31
O-*s*-Bu	0.86	10	OCH_2-c-C_3H_5	0.48	31
O-*t*-Bu	1.22	10	OCH_2-c-C_4H_7	0.52	31
O-c-C_6H_{11}	0.81	10	OCH_2-c-C_5H_9	0.58	31
OCH_2CH_2Bu	0.61	1	OCH_2-c-C_6H_{11}	0.65	31
$O(CH_2)_4Bu$	0.61	1	OCHMe-*i*-Pr	0.91	31
OCH_2CH_2-*i*-Pr	0.62	1	OCHEt-*i*-Pr	1.18	31
OCH_2MePr	0.90	1	OCHMe-*t*-Bu	1.19	31
$OCMe_2Et$	1.35	1	$OCHiBu_2$	1.28	31
O-c-C_5H_9	0.77	1	OCH_2CH_2-*t*-Bu	0.53	30
$OCHEt_2$	1.00	2	OCH_2CHMe-*t*-Bu	0.66	30
OCH_2Bu	0.58	26	OCH_2CMeEt_2	0.82	30
OCH_2-*s*-Bu	0.62	31	OCH_2CH-*i*-Pr_2	0.89	30
OCH_2CHMe-*i*-Pr	0.64	31	$OCEt_2Me$	1.52	34
OCH_2-*t*-Bu	0.70	31	$OCPrMe_2$	1.39	34

Table IV. Values of ψ, h, and $100r^2$ Obtained from Correlation with Equation 10

Set	$-\psi$	h	$100r^2$	Set	$-\psi$	h	$100r^2$
1	3.25	2.10	99.8	19	1.31	3.83	96.4
2	3.08	1.29	99.2	20	1.40	4.08	98.6
3	2.65	2.26	99.8	21	−0.369	0.667	87.6
4	3.00	1.04	100.	22	2.17	2.98	88.5
5	3.04	1.41	99.9	23	1.22	1.61	94.1
6	2.92	1.65	100.	24.	2.31	1.50	87.2
7	0.967	2.07	99.2	25	1.93	1.65	93.9
8	0.767	2.33	96.4	26	1.64	1.79	97.6
9	3.11	2.05	99.9	27	2.78	2.42	96.6
11	2.92	2.33	99.9	28	1.84	2.16	87.6
12	2.84	2.53	99.9	29	1.61	2.33	80.8
13	3.54	1.94	99.8	30	2.61	2.71	98.2
14	3.40	2.00	99.6	31	2.58	3.05	100.
15	3.22	2.17	99.8	32	2.78	1.62	99.2
16	3.02	2.31	99.8	33	2.71	1.89	99.4
17	1.15	3.28	94.1	34	2.46	1.96	98.4
18	1.19	3.44	94.9	35	2.61	2.41	99.6

Table V. Comparison of Steric Effects upon Acidic and Basic Catalyzed Hydrolysis

Set	Solvent	T, °C	ψ_A
	Acidic		
7	62% w/w MeAc–H_2O	30.1	−0.967
23	75% v/v MeAc–H_2O	35	−1.22
	Basic		ψ_B
6	62% w/w MeAc–H_2O	20	−2.92
11	70% v/v MeAc–H_2O	35	−2.92

as the υ_X and υ_{CH_2X} values. We may now obtain the defining equation for υ_{OX} values from set 10.

$$\upsilon_{OX} = -0.329 \log k_{OX} + 0.701 \quad (9)$$

Values of υ_{OX} obtained from set 10, and from other sets, are set forth in Table III. Data for the remaining 34 sets were then correlated with the equation

$$\log k_{OX} = \psi\upsilon_{OX} + h \quad (10)$$

Values of ψ, h, and $100r^2$ (which represents the percent of the data accounted for by the correlation) are reported in Table IV. For other statistics, see the paragraph at the end of this paper. All the 34 sets gave significant correlations.

The correlations obtained for sets 7, 8, 23, and 24 suggest that in these sets involving acid-catalyzed hydrolysis of alkyl acetates the compounds in the set are reacting by the same mechanism. If this were not the case, excellent correlations would not be obtained.

To verify eq 7, we have correlated υ_{OX} with υ_{CH_2X} by means of the equation

$$\upsilon_{OX} = m\upsilon_{CH_2X} + c \quad (11)$$

The results are: m, 0.959; c, −0.100; r, 0.967; F, 159.1 (99.9% CL); s_{est}, 0.0562; s_m, 0.0760 (99.9% CL); s_c, 0.0627 (80.0% CL); n, 13. As is predicted by eq 7, m is not significantly different from 1. We conclude that eq 7 is verified.

It is of interest to compare the magnitude of the steric effect upon the basic hydrolysis of alkyl acetates with that upon the acidic hydrolysis. This may be done by comparing ψ values under reaction conditions which are as similar as possible. Such comparisons are made in Tables V and VI. The results show clearly that acid-catalyzed hydrolysis exhibits a much smaller steric effect than basc-catalyzed hydrolysis. The ψ values of sets 4, 5, and 6 show that the dependence of ψ on temperature is slight. Thus, comparison between sets 6 and 7 is justified. It is unlikely that the difference in solvent between sets 23 and 11 would interfere with comparison between values for these sets. The large difference between ψ_A and ψ_B found for hydrolysis of RCO_2X contrasts with the much smaller difference found for hydrolysis of XCO_2R (X is variable, R is constant). If we compare values of ψ for the hydrolysis of RCO_2X with ψ values for other carbonyl reactions as is done in Table VI, we observe that the ψ values for basic ester hydrolysis of alkyl acetates and ethyl carboxylates are about 0.35 unit apart in 70% v/v MeAc–H_2O, whereas the ψ values for acid hydrolysis in this medium differ by 0.76. The greater difference in ψ for alkyl acetate hydrolyses as compared with ethyl carboxylate hydrolyses is then largely due to the comparatively small value of ψ for the acid hydrolyses of alkyl acetates.

Comparing ψ values for basic hydrolysis of alkyl formates and acetates in water, the alkyl formates have a much smaller value in accord with the fact that the tetrahedral intermediate for their hydrolysis has a constant H atom, whereas that for the hydrolysis of alkyl acetates has a constant Me group. The ψ value for the basic hydrolysis of the amides is between that for the acetates and that for the formates. This is in accord

Table VI. Comparison of ψ Values under Similar Reaction Conditions

Substrate	Reagent	Solvent	T, °C	ψ	Source
MeC(=O)OX	H_3O^+	75% v/v MeAc–H_2O	35	−1.22	*a*
XC(=O)OEt	H_3O^+	70% v/v MeAc–H_2O	35	−1.98	*b*
MeC(=O)OX	OH^-	70% v/v MeAc–H_2O	35	−2.92	*c*
XC(=O)OEt	OH^-	70% v/v MeAc–H_2O	35	−2.57	*d*
MeC(=O)OX	OH^-	H_2O	30.0	−2.61	*e*
HC(=O)OX	OH^-	H_2O	35	−1.40	*f*
$XC(=O)NH_2$	OH^-	H_2O	75	−1.87	*g*

[a] This work, set 23. [b] Reference 3, set 8. [c] This work, set 11. [d] Reference 4, set 2. [e] This work, set 35. [f] This work, set 20. [g] Reference 8, set 7.

with its tetrahedral intermediate, which has a constant NH_2 group.

A comparison of ψ values for sets 3, 11, 31, and 35 shows that the effect of solvent on the ψ value for the basic hydrolysis of alkyl acetates is small.

At the suggestion of a referee, we have examined the correlation of data for the alkaline hydrolysis of ZCO_2X in 40% aqueous dioxane at 35 °C with the equation

$$\log k = \psi_1 \upsilon_Z + \psi_2 \upsilon_{OX} + h \quad (12)$$

The data used were a combination of set 3 from Table I and set 5 from ref 4. The results of the correlation with eq 12 are: multiple correlation coefficient, 0.995; F test for significance of regression, 64.30 (99.9% CL); s_{est}, 0.0609; s_{ψ_1}, 0.0805 (99.9% CL); s_{ψ_2}, 0.0741 (00.0% CL); s_h, 0.0822 (99.9% CL); partial correlation coefficient of υ_Z on υ_{OX}, 0.479 (90.0% CL); ψ_1, −2.06; ψ_2, −2.54; h, 3.23; number of points in set. 15; range in log k, 2.27. Thus, the rates of hydrolysis of esters substituted in both the acyl and alkoxy moieties can be successfully treated by means of eq 12.

The success of this work in evaluating υ_{OX} constants which are on the same scale as, and can therefore be used in the same correlation as, υ constants for alkyl, halogen, haloalkyl, oxyalkyl, and other groups is not yet completely established. We hope to demonstrate in future work that the υ_{OX} values reported here are indeed applicable to data sets containing a mixture of substituent types.

Supplementary Material Available: the results of the correlations with eq 7 and 8 and values of σ_I and σ_R for OR groups and complete statistics for the correlations of the data in Table I with eq 10 (5 pages). Ordering information is given on any current masthead page.

Registry No.—Acetic acid, 64-19-7; 4-nitrobenzoyl chloride, 122-04-3.

References and Notes

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Steric Effects. 10. Substituents at Nitrogen in Carbonyl Compounds

Marvin Charton

Department of Chemistry, Pratt Institute, Brooklyn, New York 11205

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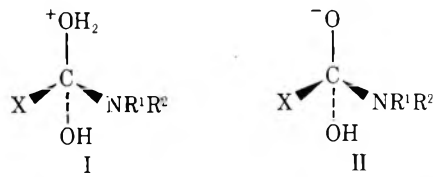
Twelve sets of carbonyl addition reactions including rate constants for acidic and basic hydrolysis of N-substituted amides, rate constants for the reaction of methyl acetate with alkylamines, and rate constants for the reaction of piperonal with alkylamines were correlated with the modified Taft equation using $\upsilon_{CHX^1X^2}$ constants; 16 sets of data were correlated with $\upsilon_{NX^1X^2}$ constants. Very good results were obtained. The $\upsilon_{NX^1X^2}$ constants were defined in this work. Eighteen values of $\upsilon_{NX^{12}}$ are given. The results verify the validity and generality of the equation $\upsilon_{Z_1X^1X^2} = \upsilon_{Z_2X^1X^2} + c$. The variation of ψ with structure is discussed for a variety of acid-catalyzed and base-catalyzed hydrolyses of carbonyl derivatives.

In the preceding paper of this series,[1] steric substituent constants were developed for alkoxy groups. These constants were applicable to addition reactions of carbonyl compounds. In this work we consider the application of the techniques we have developed to the definition of steric substituent constants for alkylamino and dialkylamino substituents. Let us consider substituent effects upon rates of acid and alkaline hydrolysis of N-substituted amides. The tetrahedral intermediates involved in the acid and alkaline hydrolysis are I and II, respectively. The X group represents a constant substituent; the NR^1R^2 group varies. We have shown that the electrical effects of alkyl groups in base-catalyzed ester hydrolysis reactions are constant,[2] as are electrical effects of alkoxy groups.[1] It seems likely that the electrical effects of alkylamino and dialkylamino groups are also constant in addition reactions of the carbonyl group. In support of this contention, the σ_m and σ_p substituent constants of NHX groups are given by the equations[3]



$$\sigma_{m\text{-NHX}} = 1.11\ \sigma_{m\text{-X}} - 0.187 \quad (1)$$

$$\sigma_{p\text{-NHX}} = 1.33\ \sigma_{m\text{-X}} - 0.476 \quad (2)$$

According to Taft

$$\sigma_{INHX} = (3\ \sigma_{m\text{-NHX}} - \sigma_{p\text{-NHX}})/2 \quad (3)$$

and

$$\sigma_{RNHX} = \sigma_{p\text{-NHX}} - \sigma_{INHX} \quad (4)$$

From eq 1, 2, and 3

$$\sigma_{INHX} = (3.33\ \sigma_{m\text{-X}} - 0.561 - 1.33\sigma_{m\text{-X}} + 0.476)/2 \quad (5)$$

$$= (2\sigma_{m=X} - 0.085)/2 = \sigma_{m\text{-X}} - 0.043 \quad (6)$$

Now, according to Taft,[4]

$$\sigma_{m\text{-X}} = \sigma_{IX} + \sigma_{RX}/3 \quad (7)$$

We are interested in the case in which X is alkyl. For values of σ_I and σ_R for alkyl groups, see the paragraph at the end of this paper. The average value of σ_I is -0.01 ± 0.02. Since the error in the σ_I values is probably 0.05, we conclude that σ_I values for alkyl groups are constant. Examination of the σ_R values for alkyl groups shows that they average 0.16 ± 0.03; the error in σ_R is not less than 0.05; therefore these values are again constant. Then from eq 7, σ_m for alkyl groups is con-

Table I. Data Used in the Correlations

1. *kr*, AcNHX + H_3O^+ in H_2O at 65 °C[a]
   Me, 2.23; Et, 1.40; Pr, 1.14; *i*-Pr, 0.437; Bu, 1.12; *i*-Bu, 0.808; *s*-Bu, 0.261; *i*-$PrCH_2CH_2$, 1.44; $BuCH_2CH_2$, 1.12; c-C_6H_{11}, 0.472; $PhCH_2$, 1.28
2. *kr*, AcNHX + H_3O^+ in H_2O at 75 °C[a]
   Me, 5.74; Et, 3.83; Pr, 2.82; *i*-Pr, 1.11; Bu, 2.98; *i*-Bu, 2.09; *s*-Bu, 0.684; *i*-$PrCH_2CH_2$, 2.84; $BuCH_2CH_2$, 2.78; c-C_6H_{11}, 1.24; $PhCH_2$, 3.17
3. *kr*, AcNHX + H_3O^+ in H_2O at 85 °C[a]
   Me, 13.0; Et, 9.53; Pr, 6.77; *i*-Pr, 2.84; Bu, 6.93; *i*-$PrCH_2CH_2$, 6.72; $BuCH_2CH_2$, 6.53; c-C_6H_{11}, 2.98; $PhCH_2$, 7.61
4. *kr*, AcNHX + H_3O^+ in H_2O at 95 °C[a]
   Me, 26.3; Et, 21.2; Pr, 15.3; *i*-Pr, 6.71; Bu, 14.8; *i*-Bu, 10.8; *s*-Bu, 3.96; *i*-$PrCH_2CH_2$, 15.0; $BuCH_2CH_2$, 14.9; c-C_6H_{11}, 7.59; $PhCH_2$, 19.3
5. *kr*, $AcNX^1X^2$ + H_3O^+ in 1.0 N aq HCl at 75 °C[b]
   H, H, 511; Me, H, 25.5; Et, H, 14.0; Ph, H, 11.9; *i*-Pr, H, 5.40; Bu, H, 10.1; *i*-Bu, H, 8.09; Me_2, 22.6; Me, Et, 6.10; Et_2, 1.36; Pr_2, 0.68
6. *kr*, AcNHX + H_3O^+ in 1.0 N aq HCl at 80 °C[b]
   Et, 22.2; Pr, 17.2; Bu, 15.6; *i*-Bu, 11.3
7. *kr*, AcNHX + H_3O^+ in 1.0 N aq HCl at 85 °C[b]
   Me, 59.0; Et, 32.7; Pr, 23.2; Bu, 24.1; *i*-Bu, 17.5
9. *kr*, AcNHX + OH^- in 1.0 N aq NaOH at 60 °C[b]
   Me, 6.78; Et, 3.83; Pr, 2.24
10. *kr*, AcNHX + OH^- in 1.0 N aq NaOH at 65 °C[b]
    Me, 10.1; Et, 5.42; Pr, 3.37; *i*-Pr, 1.05; Bu, 2.83
11. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 70 °C[b]
    Et, H, 7.72; Pr, H, 4.50; Bu, H, 3.58; Me, Et, 4.25; Et_2, 0.51
12. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 75 °C[b]
    H, H, 112; Me, H, 21.5; Et, H, 10.8; Pr, H, 6.62; *i*-Pr, H, 2.20; Bu, H, 6.17; *i*-Bu, H, 3.85; Me_2, 31.1; Me, Et, 5.90; Et_2, 0.70; Pr_2, 0.40
14. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 85 °C[b]
    Me, Et, 1.12; Et_2, 1.49; Pr_2, 0.75
15. *kr*, $AcNX^1X^2$ + OH^- in 1.0 N aq NaOH at 90 °C[b]
    Me, Et, 15.0; Et_2, 2.12; Pr_2, 0.87
16. 10^4*kr*, MeOAc + XNH_2 in dioxane 5 M in $(CH_2OH)_2$[c]
    Me, 853; Et, 111; Bu, 106; $BuCH_2$, 98.7; Pr, 87.9; *i*-Bu, 43.5; *i*-Pr, 4.22; *s*-Bu, 2.27
17. 10^2*kr*, piperonal + XNH_2 in MeOH at 0.00 °C[d]
    Me, 1.92; Et, 0.952; Pr, 1.04; *i*-Pr, 0.267; Bu, 1.15; *i*-Bu, 1.13; *s*-Bu, 0.292; *t*-Bu, 0.0267
18. 10^2*kr*, piperonal + XNH_2 in MeOH at 24.97 °C[d]
    Me, 5.55; Et, 2.88; Pr, 3.15; *i*-Pr, 0.895; Bu, 3.37; *i*-Bu, 3.16; *s*-Bu, 0.940; *t*-Bu, 0.115
19. 10^2*kr*, piperonal + XNH_2 in MeOH at 45.00 °C[d]
    Me, 11.4; Et, 6.00; Pr, 6.40; *i*-Pr, 1.98; Bu, 6.83; *i*-Bu, 6.23; *s*-Bu, 2.00; *t*-Bu, 0.299

[a] P. D. Bolton, J. Ellis, R. D. Frier, and P. C. Nancarrow, *Aust. J. Chem.*, **25**, 303 (1972). [b] T. Yamana, Y. Mizukami, A. Tsuji, Y. Tasuda, and K. Masuda, *Chem. Pharm. Bull.*, **20**, 881 (1972). [c] E. M. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950). [d] R. I. Hill and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284 (1956).

Table II. Values of $\upsilon_{NX^1X^2}$

NX^1X^2	$\upsilon_{NX^1X^2}$	Set[a]	NX^1X^2	$\upsilon_{NX^1X^2}$	Set[a]
NHMe	0.39	*b*	NEt_2	1.37	5
NHEt	0.59	5	NPr_2	1.60	5
NHPr	0.64	5	NH-*s*-Bu	1.12	2
NH-*i*-Pr	0.91	5	$NHCH_2CH_2$-*i*-Pr	0.65	2
NHBu	0.70	5	$NHCH_2CH_2Bu$	0.66	2
NH-*i*-Bu	0.77	5	NH-c-C_6H_{11}	0.92	2
NMe_2	0.43	5	$NHCH_2Ph$	0.62	2
NMeEt	0.87	5	N-*i*-Pr_2	2.01	14
$NHCH_2Bu$	0.64	16	NH-*t*-Bu	1.83	19

[a] Set from which $\upsilon_{NX^1X^2}$ was calculated. [b] By definition.

Table III. Values of ψ, h, and $100r^2$ Obtained from Correlation with Equation 11

Set	$-\psi$	h	$100r^2$	Set	$-\psi$	h	$100r^2$
1	1.37	0.952	97.0	11	1.37	1.63	92.0
2	1.34	1.33	94.5	12A	1.50	1.90	94.5
3	1.30	1.68	95.8	14	1.63	2.45	99.6
4	1.21	1.97	96.6	15	1.69	2.65	100.
6	1.54	2.24	96.8	16	3.69	4.35	94.7
7	1.37	2.30	96.6	17	1.31	0.854	94.7
9	1.73	1.52	90.4	18	1.19	1.25	95.3
10	1.92	1.79	98.4	19	1.12	1.52	84.0

stant. It follows then, for eq 6, that σ_{INHX} is constant. From eq 2 we conclude that $\sigma_{p\text{-}NHX}$ is constant, and therefore from eq 4 that σ_{RNHX} is constant. Thus, the electrical effects of alkylamino groups are independent of the nature of the alkyl group. As to the electrical effect of dialkylamino groups as compared with alkylamino groups, we would expect them to behave in a similar manner. The evidence for this is more tenuous, however. A number of successful correlations have been reported in which the value $\sigma_I = 0.10$ has been used for both MHMe and NMe_2.[5] Using the σ_p values given by McDaniel and Brown[6] σ_R values of −0.94 and −0.93 are obtained for NHMe and $NHMe_2$. Thus, at least in the case of the dimethylamino group the electrical effects are comparable to those of alkylamino groups.

The arguments we have presented for the constancy of the electrical effects of alkylamino and dialkylamino groups lead to the inexorable conclusion that the only effect of these substituents on carbonyl addition reactions will be steric.

In order to correlate data for carbonyl addition reactions involving variable NR^1R^2 groups, steric substituent constants for these groups are required. Such constants are not available. We have shown, however,[1] that a substituent may be written in the form ZX, where Z joins X and the skeletal group to which X is attached. Then, for two sets of substituents, one with constant Z_1 and the other with constant Z_2, the equation

$$\upsilon_{Z_1X} = \upsilon_{Z_2X} + c \tag{8}$$

is obeyed, where the υ values are steric substituent constants. We propose to extend this equation to

$$\upsilon_{Z_1X^1X^2} = \upsilon_{Z_2X^1X^2} + c \tag{9}$$

where $Z_1 = N$, $Z_2 = CH$.

Thus, rate data for sets of carbonyl addition reactions involving variable NR^1R^2 groups have been correlated with the modified Taft equation in the form[1]

$$\log k_{NX^1X^2} = \upsilon_{CHX^1X^2} + h' \tag{10}$$

The data used in the correlations are set forth in Table I. The values required are from our previous work.[7] For results of the correlations with eq 10, see the paragraph at the end of this paper. Sets 6, 7, 9, 14, and 15 were excluded from the correlations because the substituents in these sets have at most only two significantly different υ_{CH_2R} values.

The results for set 5 were considerably improved by the exclusion of the value for X^1X^2 = H, H (set 5A). The further exclusion of the value for $X^1X^2 = Me_2$ improved the results somewhat. The results for set 12 were not significantly improved by exclusion of the value for X^1X^2 = H, H (set 12A). Further exclusion of the value for $X^1X^2 = Me_2$ gives better results (set 12B).

Of the 12 sets correlated with eq 10, ten sets gave excellent

Table IV. Correlations of $\upsilon_{NX^1X^2}$ with $\upsilon_{CHX^1X^2}$ [a]

Set	m	c	r	F	s_{est}	s_m	s_c	n
A	1.21	−0.218	0.918	80.82	0.164	0.134	0.127	17
B	1.05	−0.107	0.943	112.3	0.112	0.0991	0.0905	16
C	1.03	−0.0691	0.964	169.3	0.0887	0.0789	0.0728	15

[a] All correlations were significant at the 99.9% confidence level (CL).

Table V. Comparison of ψ Values

Substrate	Reagent	T, °C	ψ	υ^k	Source
MeC(=O)NHX	H_3O^+	75	−1.34	0.52	*a*
MeC(=O)NX^{1}X^2	H_3O^+	75	−1.30	0.52	*b*
MeC(=O)NX^{1}X^2	OH^-	75	−1.50	0.52	*c*
MeC(=O)OX	OH^-	30	−2.61	0.52	*d*
HC(=O)OX	OH^-	35	−1.40	0	*e*
XC(=O)NH$_2$	OH^-	75	−1.87	0.32	*f*
XC(=O)NH$_2$	H_3O^+	75	−2.07	0.32	*g*
	H_3O^+	30	−1.53	0.71[l]	*h*
	OH^-	30	−1.50	0.71[l]	*i*
XC(=O)NHOH	H_3O^+	50.5	−2.16	0.48[m]	*j*

All reactions were studied in water. [a] This work, set 2. [b] This work, by definition. [c] This work, set 12A. [d] Reference 1, set 35. [e] Reference 1, set 20. [f] Reference 8, set 7. [g] Reference 8, set 4A. [h] Reference 8, set 12A. [i] Reference 8, set 27A. [j] Reference 8, set 28A. [k] υ of constant substituent in substrate. [l] υ for c-C_5H_9. [m] Calculated from $\upsilon_{NX^1X^2} = 1.03, \upsilon_{CHX^1X^2} = 0.0691$.

(>99.5% CL), one gave good (97.5% CL), and one gave fair correlation (95.0% CL). Thus the validity of eq 9 is again substantiated. Our results now make it possible to define υ constants for alkylamino groups. As was the case in our previous definition of υ_{OX} groups, we are interested in defining $\upsilon_{NX^1X^2}$ groups which can be used together with the other υ values we have previously calculated in order to make possible the application of the modified Taft equation to sets containing a wide range of substituent type. It is therefore vital that the $\upsilon_{NX^1X^2}$ values be on the same scale as our other υ constants. Otherwise, the $\upsilon_{NX^1X^2}$ constants would only be applicable to sets in which the sole substituent type is NX^1X^2. In order to do this we must choose a reference set. As a reference set we have chosen the rate constants for acidic hydrolysis of N-substituted amides in 1.0 N aqueous HCl at 75 °C (set 5). This set was chosen because it gave an excellent correlation with eq 10 and included a large number of substituents. A value of 0.39 was then assigned to the NHMe group. This value was obtained by means of the same type of argument we used in the previous work in this series[1] in assigning a value to the OMe group. Ideally, we would have liked to simply use the value $\upsilon_{NH_2} = 0.35$, but the rate constant for the NH_2 group does not fit the correlation obtained with eq 10. The value of ψ chosen for set 5 is the value obtained from correlation of set 5B with eq 10. In choosing this value for ψ we are putting the $\upsilon_{NX^1X^2}$ values on the same scale as the other υ values. This is shown by writing the modified Taft equation for the use of true $\upsilon_{NX^1X^2}$ values

$$\log k_{NX^1X^2} = \psi\upsilon_{NX^1X^2} + h \quad (11)$$

and then writing eq 9 for $\upsilon_{NX^1X^2}$ and $\upsilon_{CHX^1X^2}$

$$\upsilon_{NX^1X^2} = \upsilon_{CHX^1X^2} + c \quad (12)$$

Now substituting in eq 11, we obtain

$$\log k_{NX^1X^2} = \psi(\upsilon_{CHX^1X^2} + c) + h \quad (13)$$

$$= \psi\upsilon_{CHX^1X^2} + \psi c + h \quad (14)$$

which is equivalent to eq 10 with $h' = \psi c + h$

We may now obtain the equation for defining $\upsilon_{NX^1X^2}$ constants from set 5B.

$$\upsilon_{NX^1X^2} = -0.769 \log k_{NX^1X^2} + 1.47 \quad (15)$$

Values of $\upsilon_{NX^1X^2}$ obtained from set 5B and other sets are reported in Table II. Data for all sets other than set 5 were then correlated with eq 11. Values of ψ, h, and $100r^2$ (which represents the percent of the data accounted for by the correlation) are reported in Table III. For other statistics see the paragraph at the end of this paper. One set did not correlate. As the two sets which gave the poorest results had only three points, it is not surprising that good correlations were not obtained. Overall, the results are very good, and support the utility of the $\upsilon_{NX^1X^2}$ constants.

To verify eq 12, we have correlated the $\upsilon_{NX^1X^2}$ values with $\upsilon_{CHX^1X^2}$ values. The results of these correlations are set forth in Table IV. The equation used is

$$\upsilon_{NX^1X^2} = m\upsilon_{CHX^1X^2} + c \quad (16)$$

Set A includes all available $\upsilon_{NX^1X^2}$ values. The value for X^1X^2 = H, *t*-Bu is excluded from Set B. Further exclusion of the value $X^1X^2 = Me_2$ results in set C. All three sets give excellent correlation. Best results are obtained with set C, however. Furthermore, with set C the value of m obtained is not significantly different from the value of 1 predicted by eq 12. The results obtained support the validity of eq 12 and together with our previous results for OX groups support the generality of eq 9. It is now possible to estimate values of $\upsilon_{NX^1X^2}$ from values of $\upsilon_{CHX^1X^2}$.

It is of interest to compare the magnitude of the steric effect upon the basic hydrolysis of N-substituted amides with that upon the acidic hydrolysis of amides under similar reaction conditions. This can be done by comparing the ψ values for sets 5B and 12A. The values are −1.30 and −1.50, respectively. The application of the "Student's *t*" test shows that the two values are not significantly different. This is in accord with our findings for the hydrolysis of amides substituted in the acyl moiety.[8] By contrast, the hydrolysis of alkyl acetates and benzoates showed a distinct difference in steric effects between acid-catalyzed and base-catalyzed reactions,[1] as did the hydrolysis of esters substituted in the acyl moiety.[2,7]

We have also compared the magnitude of the steric effect for N-substituted amide hydrolysis with that for other carbonyl addition reactions under similar reaction conditions. Values of ψ are given in Table V. Although the values of ψ are at different temperatures, the results obtained in this work and previous work[1,8] suggest that this will not cause large differences in ψ. We had previously suggested that the ψ values might depend on the size of the constant substituent in the substrate. Plots of ψ values for acid-catalyzed hydrolyses and for base hydrolyses against the υ values of the constant substituent in the substrate show no discernable relationship between ψ and υ. The ψ values lie in the range −1.30 to −2.16 for acidic hydrolysis and −1.40 to −2.61 for basic hydrolysis. Possibly, the value of ψ will depend on the extent to which the transition state resembles the tetrahedral intermediate. Further data are required before any conclusion can be reached.

At the suggestion of a referee we have examined the corre-

lation of data for the acid hydrolysis of ZCONHX in water at 75 °C with

$$\log k = \psi_1 \upsilon_Z + \psi_2 \upsilon_{NHX} + h \quad (17)$$

The data used were a combination of set 2 in Table I and set 4 of ref 8. Results of the correlation are: multiple correlation coefficient, 0.969; F test for significance of regression, 176.8 (99.9% CL); s_{est}, 0.126; s_{ψ_1}, 0.109 (99.9% CL); s_{ψ_2}, 0.128 (99.9% CL); s_h, 0.125 (99.9% CL); partial correlation coefficient of υ_Z on υ_{NHX}, 0.497 (98.0% CL); $\psi_1 = -1.93$; $\psi_2 = -1.82$; $h = 2.73$; number of points in the set, 26; range in log k, 1.84. The high confidence level for the correlation of υ_Z on υ_{NHX} indicates that the separation of steric effects is less than is desirable. It seems probable, however, that rates of hydrolysis of amides substituted in both the acyl and amino moieties can be successfully correlated by eq 17.

Supplementary Material Available. The results of the correlations with eq 10, values of σ_I and σ_R for alkyl groups, and complete statistics for the correlation of the data in Table I with eq 11 (3 pages). Ordering information is given on any current masthead page.

Registry No.—Methyl acetate, 79-20-9; piperonal, 120-57-0.

References and Notes

(1) M. Charton, *J. Org. Chem.*, preceding article in this issue.
(2) M. Charton, *J. Am. Chem. Soc.*, **97**, 3691 (1975).
(3) M. Charton, *J. Org. Chem.*, **28**, 3121 (1963).
(4) R. W. Taft, *J. Phys. Chem.*, **64**, 1805 (1960).
(5) M. Charton, *J. Org. Chem.*, **31**, 2991 (1966); M. Charton and B. I. Charton, *J. Chem. Soc. B*, *43* (1967); M. Charton, *J. Org. Chem.*, **34**, 1887 (1969); **36**, 266 (1971).
(6) Footnote *b*, Table I.
(7) M. Charton, *J. Am. Chem. Soc.*, **97**, 1552 (1975); M. Charton, *J. Org. Chem.*, **41**, 2217 (1976).
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Chemistry of Nitrosoureas. Decomposition of 1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-Bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea

Robert B. Brundrett* and Michael Colvin

The Oncology Center, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

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1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea were synthesized and decomposed in buffered water. The products were analyzed by GC and GC/MS. The stereochemistry of the product 3-chloro-2-butanols and 2-chloro-2-butenes indicates that a significant fraction of these products are formed via reactions of 3-chloro-2-butyldiazo hydroxide with S_N2 and E2 stereochemistry, as well as by S_N1 and E1 reactions involving the secondary 3-chloro-2-butyl carbonium ion. Since primary carbonium ions are higher energy species than secondary ones, we predict that the decomposition of the antitumor agent 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) to 2-chloroethanol and vinyl chloride occurs predominantly by way of S_N2 and E2 reactions of 2-chloroethyldiazo hydroxide and not by way of S_N1 and E1 reactions involving the primary 2-chloroethyl carbonium ion.

BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea] is a useful agent for the treatment of certain malignant diseases. The major products of the decomposition of BCNU in buffered aqueous solution (pH 7.4) are vinyl chloride, acetaldehyde, 1,2-dichloroethane, and 2-chloroethanol.[1] Recently, we reported the synthesis and decomposition of specifically deuterated BCNUs.[2] The results excluded the intermediacy of diazochloroethane and the vinyl carbonium ion and were consistent with the intermediacy of the 2-chloroethyl carbonium ion. However, the results did not definitively distinguish between the S_N1–E1 path through the 2-chloroethyl carbonium ion and the S_N2–E2 path in which the various reactions and rearrangements occur concerted with the loss of nitrogen from the 2-chloroethyldiazo hydroxide. Because the decomposition of BCNU to 2-chloroethanol involves a primary carbon atom, there is no stereochemistry by which an S_N1 process could be distinguished from an S_N2 process. We report here the synthesis and decomposition of the substituted BCNU derivatives 1,3-bis(*threo*-3-chloro-2-butyl)-1-nitrosourea and 1,3-bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea in which there is stereochemistry to follow.

Chemistry. 1,3-Bis(*erythro*-3-chloro-2-butyl)-1-nitrosourea (*erythro*-BCBNU, **5**) was synthesized as shown in Scheme I. 1,3-Bis(*threo*-3-chloro-2-butyl)-1-nitrosourea (*threo*-BCBNU) was synthesized by the same route, only starting from *cis*-2-butene. The unnitrosated ureas can exist as a mixture of a meso compound and a *dl* pair and the nitrosated ureas as a mixture of two *dl* pairs, but these facts do not affect any of the stereochemistry in this paper. The first three steps of the syntheses are known stereospecific reactions[3] and the last step does not involve making or breaking any bonds to carbon atoms. The remaining step, the reaction of dimethylaziridine with phosgene, is expected to go with one inversion by analogy with other aziridine ring openings.[4] This

Scheme I

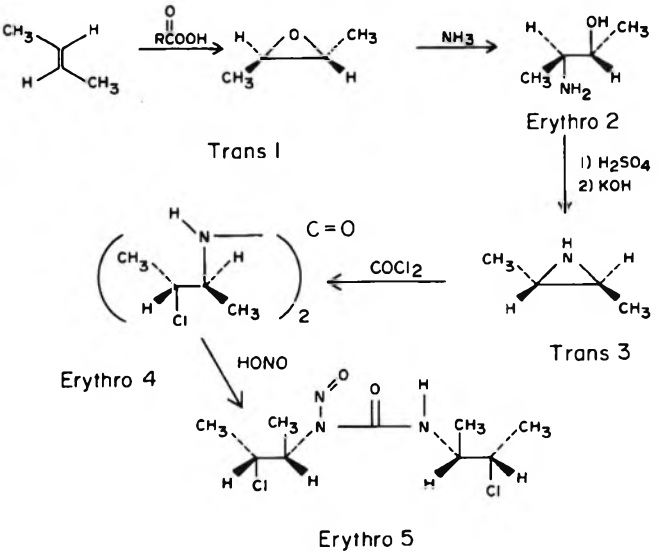
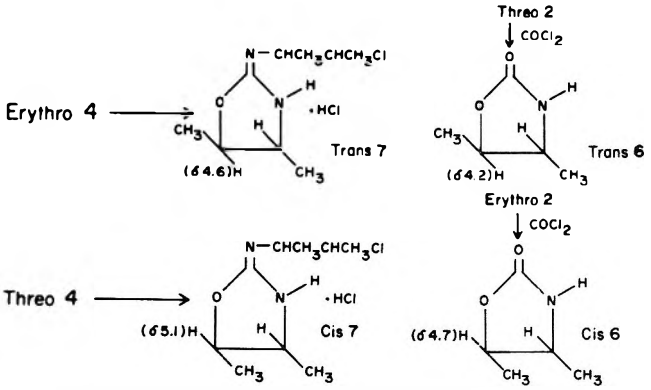


Table I. Products from BCBNU Decomposition

Product	Yield from BCBNU %[a] erythro	threo	GC retention time, min
Isobutyraldehyde	16	7	2.4
Butanone	43	29	3.8
1-Buten-3-ol	8	10	5.6
trans-2-Chloro-2-butene	3	17	7.0
cis-2-Chloro-2-butene	6	2	8.6
2-Buten-1-ol	6	7	12.0
threo-3-Chloro-2-butanol[b]	12	10	18.8
erythro-3-Chloro-2-butanol[c]	6	18	20.0

[a] Mole percent of identified products. Total product recovery was 80% of theoretical. [b] MS *m/e* (% base): 45 (100), 27 (18), 29 (12), 43 (11), 55 (7), 57 (5). [c] MS *m/e* (% base): 45 (100), 27 (12), 43 (10), 29 (8), 55 (5), 57 (4).

Scheme II



expectation was checked by converting the ureas to the oxazolines (Scheme II). If this reaction goes with one inversion, the *erythro*-urea should give the *trans*-oxazoline and the *threo*-urea should give the *cis*-oxazoline. That the ureas gave the expected oxazolines was determined by comparing the NMRs to those of *cis*- and *trans*-4,5-dimethyloxazolidone. The *cis*-oxazolidone and the oxazoline from *threo*-4 both have the absorption of the C-5 hydrogen farthest downfield.

Results

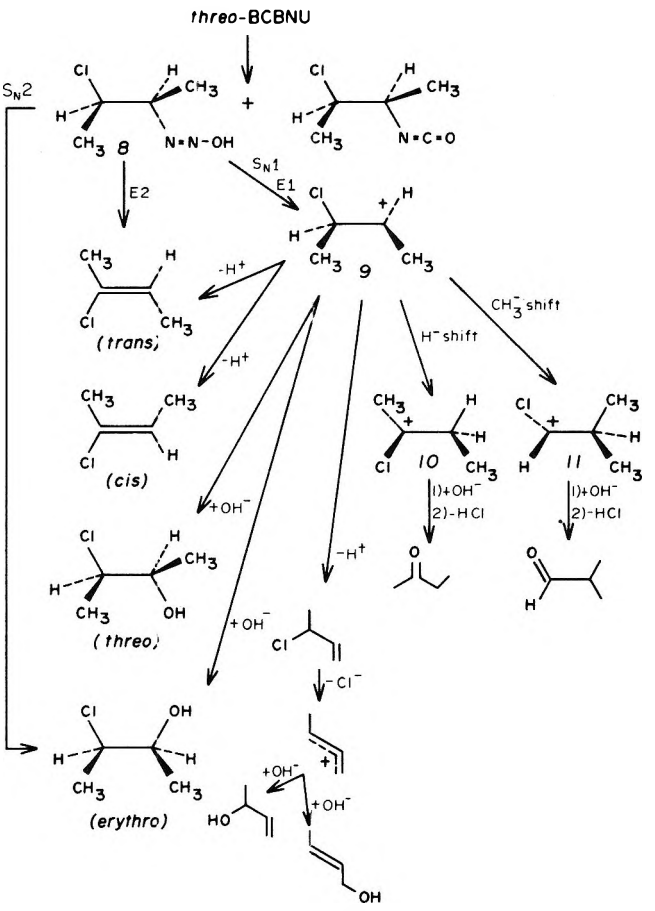
threo- and *erythro*-BCBNU were allowed to decompose at 37 °C in phosphate-buffered water (pH 7.4) in a gas-tight vial, and the products were analyzed by both GC and GC/MS. The products were identified by comparison of the GC retention times and the mass spectra to authentic standards. The results are shown in Table I. Of the eight products identified, four contain stereochemical information—*cis*- and *trans*-2-chloro-2-butene, and *threo*- and *erythro*-3-chloro-2-butanol. *erythro*-BCBNU gives predominantly *threo*-3-chloro-2-butanol and *cis*-2-chloro-2-butene, while *threo*-BCBNU gives predominantly the *erythro*-butanol and the *trans*-butene.

Discussion

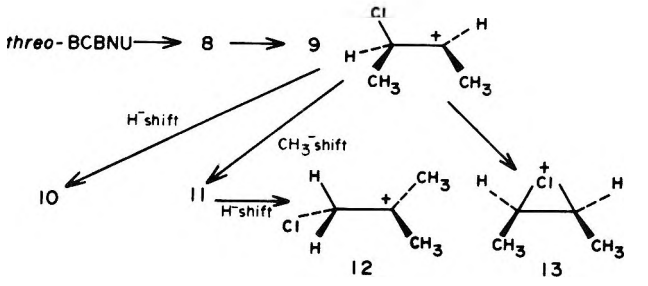
The products from the decomposition of the two BCBNUs can be explained by the mechanism shown in Scheme III for *threo*-BCBNU (the analogous mechanism explains the decomposition of the erythro isomer). In this mechanism, BCBNU decomposes to a isocyanate and a diazo hydroxide. The isocyanate half, by analogy to BCNU,[5] probably forms a mixture of 3-chloro-2-butylamine and bis(3-chloro-2-butyl)urea. These compounds are not volatile enough to pass through the GC column used. The products seen arise from the diazo hydroxide half of the BCBNU molecule.

In the mechanism shown in Scheme III, the 3-chloro-2-butanol arises in part (ca. ⅔) by an S_N1 reaction which gives

Scheme III



Scheme IV



equal amounts of the threo and erythro alcohols and in part (ca. ⅓) by an S_N2 mechanism which gives the inverted erythro alcohol (the predominant stereoisomer formed). The stereochemistry of the chlorobutanols can also be explained by a rapid stepwise mechanism. In this mechanism the diazo hydroxide decomposes to a nitrogen separated ion pair which can either collapse to predominantly retained alcohol or react with a solvent molecule (on the back side, since the front side is blocked by the nitrogen) to give mostly inverted alcohol. To prevent total racemization, this second step must occur faster than the ion can rotate and expose its front side to solvent.

Some of the alcohol may arise via a cyclic chloronium ion (13, Scheme IV) not considered in Scheme III. If this ion is formed by collapse of chlorine trans to the nitrogen either concerted with the loss of nitrogen or so rapidly after the loss of nitrogen that the newly formed carbonium ion cannot rotate, the chloronium ion will be formed with one inversion. The opening of this ion by water will occur with one inversion to give, overall, the retained threo alcohol. Some participation by the chloronium ion 13 is likely, since in the decomposition of BCNU 10% of the chloroethanol comes from a chloronium ion.[2] At the extreme of minimum chloronium ion participation, the threo alcohol will be derived primarily via an S_N1

mechanism as outlined in Scheme III. At the extreme of maximum chloronium ion participation, all of the threo alcohol would arise via **13** and no S_N1 mechanism would be operative. Here an S_N2 mechanism would account for all of the erythro alcohol produced which is about ⅔ of the total chlorobutanol. Thus, the amount of actual inversion is probably greater than the ⅓ indicated.

The 3-chloro-2-butanols are unstable at 37 °C in the buffer used for the nitrosourea decomposition. The two isomers decompose at about the same rate with about 25% of each reacted after 4 days. The major product is 2,3-epoxybutane with smaller amounts of 2,3-butanediol, 2-butanone, and isobutyraldehyde also formed. 2,3-Epoxybutane and 2,3-butanediol are minor products in the nitrosourea decomposition mixture. Because the threo and erythro isomers decompose at about the same rate, the final threo/erythro ratio observed should reflect the relative amounts of the two isomers actually formed.

The 2-chloro-2-butene arises in part by an E1 mechanism which gives a mixture of *cis*- and *trans*-butenes and in part by a reaction with E2 stereochemistry which gives the *trans*-butene (the predominant stereoisomer formed). This reaction could involve the loss of the β hydrogen trans to the nitrogen either concerted with the loss of the nitrogen (E2 mechanism) or so rapidly after the loss of nitrogen that the newly formed ion cannot undergo an internal ratation. The predominant formation of the *trans*-butene is not due simple to relative stability of the products, because *erythro*-BCBNU gives predominantly the *cis*-butene. The standard used to identify the 2-chloro-2-butenes was a mixture of nearly equal amounts of the cis and trans isomers. To make sure the first isomer off of the GC column was the lower boiling trans isomer, the mixture was fractionally distilled. The distillate was found to be enriched in the first isomer, the pot residue was enriched in the second isomer off the GC column. For the purpose of quantitating products, the two isomers were assumed to have equal detectability by flame ionization. The two isomers are unstable at 37 °C in the buffer used. Equal amounts of the isomers (~50%) are reacted after 4 days. No product could be identified. Because the cis and trans isomers decompose at about the same rate, the final cis/trans ratio observed should reflect the relative amounts of the two isomers actually formed.

The allylic alcohols, 1-buten-3-ol and 2-buten-1-ol, are formed by hydrolysis of the 3-chloro-1-butene which is the other possible elimination product. This elimination is probably a mixture of an E1 reaction and a reaction with E2 stereochemistry as is the elimination to form the 2-chloro-2-butenes. The hydrolysis of 3-chloro-1-butene under the conditions of the decomposition gives the two alcohols in the same ratio as the nitrosourea decomposition. The two butenols are stable at 37 °C in the buffer used.

The butanone is formed by a hydride shift followed by a reaction of hydroxide with the resulting 2-chloro-2-butyl carbonium ion and loss of hydrochloric acid. The isobutyraldehyde is formed by a methyl shift followed by reaction of hydroxide with the resulting 1-chloro-2-methyl-1-propyl carbonium ion and loss of HCl. Both of these rearrangements probably involve primarily the migration of a group trans to the nitrogen and occur either concerted with the loss of nitrogen or so rapidly after the loss of nitrogen that the newly formed carbonium ion cannot rotate. Both isobutyraldehyde and butanone are stable at 37 °C in the buffer used.

Some of the chlorobutyl carbonium ions which may be involved in the decomposition of BCBNU are shown in Scheme IV. Theroretical calculations predict that the order of stability is **12** (lowest energy), **13, 10, 9,** and **11** (highest energy).[6] Ionization of 2,3-dichlorobutane in "magic acid," which should initially give ion **9,** gives a 40:60 mixture of **12** and **10**.[7] Ion **11** is most probably an intermediate in the transformation of **9** to **12,** In the decomposition of BCBNU, products were seen from **10** (2-butanone) and **11** (isobutyraldehyde), but none were seen from **12** (2-chloromethyl-2-propanol). The failure to observe products from ion **12** indicates that the capture of ion **11** by water is much faster than the rearrangement of **11** to **12.** If the capture of ion **11** by water is much faster than its rearrangement to **12** (the energetically most favorable rearrangement in Scheme IV), then the other carbonium-ion rearrangements may also be unable to compete with capture by water. Since products are seen from the rearranged ions **10** and **11,** these rearrangements may be occurring concerted with the loss of nitrogen from 8 rather than from the free ion **9.** The concertedness of these rearrangements may also be indicated by the fact that products are seen from ion **11.** Since the theoretical calculations predict that the rearrangement of **9** to **11** is endothermic,[6] this reaction should not be able to compete with the exothermic rearrangement of **9** to **10**.[6] Thus, the products formed are probably controlled primarily by the conformation of the molecule and its solvent shell at the time the nitrogen leaves rather than by relative nucleophilicities, migratory aptitudes, and product stabilities. For a more detailed discussion of the possible role of nitrogen separated ion triplets and concerted vs. rapid stepwise reaction mechanisms one should see the excellent reviews of deamination by White[8] and by Moss.[9]

The mechanism proposed to explain the products seen from the decomposition of the two BCBNU isomers is similar to that for the decomposition of BCNU. Both mechanisms involve substitutions, eliminations, and rearrangements, reactions which are typical of carbonium ions. However, the stereochemistry of the products shows that a significant fraction of the substitution reaction to give 3-chloro-2-butanol is S_N2 in nature and that there is significant E2 character in the elimination reaction to give 2-chloro-2-butene. The carbonium ion produced by BCBNU is secondary and hence a more energetically favorable species than the primary carbonium ion that BCNU would produce. Therefore,the decomposition of BCNU would be expected to involve S_N2–E2 reactions to a much greater extent. The deamination of optically active 1-deuteriobutylamine, a reaction involving a primary carbon, gives predominant inversion of configuration.[10] For these reasons, we postulate that the decomposition of BCNU is predominantly S_N2–E2 in character.

A knowledge of the exact nature of this decomposition is important because the cytotoxic activity of the clinically useful antitumor agent, BCNU, is apparently due to its ability to alkylate with a 2-chloroethyl group. In several recent publications, evidence has been presented that indicates the antitumor effects of the nitrosoureas are due to the alkylating properties of the molecule.[11] In particular, it has been shown that cytosine is alkylated by BCNU and the products are consistent with alkylation with 2-chloroethyl groups.[12] We have recently presented evidence that alkylating species generated from BCNU are either the 2-chloroethyl carbonium ion, the cyclic chloronium ion, and/or 2-chloroethyldiazo hydroxide.[2] The predominant inversion of configuration found in these studies of the decomposition of BCBNU leads us to postulate that the alkylating reaction of BCNU is predominantly S_N2 in character. Thus, the ultimate cytotoxic alkylating species generated by BCNU is probably 2-chloroethyldiazo hydroxide with a short but finite lifetime inside the target cell.

Experimental Section

NMR spectra were obtained on a Varian A-60 instrument. Gas chromatography was performed on a Varian 2700 instrument. Gas chromatography/mass spectrometry was performed on a DuPont 491 instrument.

2,3-Epoxybutane (1). The cis isomer was prepared from *cis*-2-

butene and the trans isomer from *trans*-2-butene by epoxidation with *m*-chloroperbenzoic acid following the procedure of Pasto and Cumbo.[3a] *cis*-**1**: bp 60 °C (lit.[3a] 56–59 °C); NMR ($CDCl_3$) δ 3.0 (2 H, m), 1.2 (6 H, d). *trans*-**1**: bp 54 °C (lit.[3a] 52–53 °C); NMR ($CDCl_3$) δ 2.7 (2 H, m), 1.3 (6 H, d).

3-Amino-2-butanol (2). The threo isomer was prepared from *cis*-**1** and the erythro isomer was prepared from *trans*-**1** by reaction with excess aqueous ammonia following the procedure of Dickey, Fickett, and Lucas.[3b] *threo*-**2**: bp 77 °C at 30 mm (lit.[3b] 69–70 °C at 20 mm); NMR (Me_2SO-d_6) δ 3.3 (1 H, pentet), 2.7 (3 H, br s), 2.5 (1 H, pentet), 1.0 (6 H, t). *erythro*-**1**: bp 82 °C at 30 mm (lit.[3b] 75–75.5 °C at 20 mm); NMR (Me_2SO-d_6) δ 3.4 (1 H, m), 2.7 (3 H, br s), 2.5 (1 H, m), 0.9 (6 H, two d's).

2,3-Dimethylaziridine (3). The cis isomer was prepared from *threo*-**2** and the trans isomer was prepared from *erythro*-**2** by reacting the hydrogen sulfate ester with base following the procedure of Dickey, Fickett, and Lucas.[3b] *cis*-**3**: bp 83 °C (lit.[13] 81.1–81.5 at 739 mm); NMR ($CDCl_3$) δ 2.0 (2 H, m), 1.1 (6 H, d), 0.5 (1 H, br s). *trans*-**3**: bp 75 °C (lit.[13] 73.8–73.9 at 739 mm); NMR ($CDCl_3$) δ 1.6 (2 H, m), 1.2 (6 H, d), 0.3 (1 H, br s).

1,3-Bis(3-chloro-2-butyl)urea (4). The threo isomer was prepared from *cis*-**3** and the erythro isomer was prepared from *trans*-**3**. A solution of the 2,3-dimethylaziridine (3.6 g, 0.05 mol) in acetone (25 mL) was added slowly to a solution of phosgene (2.5 g, 0.025 mol) in acetone (60 mL) at 0 °C. The mixture was allowed to stir at 25 °C overnight, and then the solvent was removed under vacuum. Chromatography (ethyl acetate on alumina) and crystallization gave a 50% yield of product. *threo*-**4**: mp 135–137 °C (from benzene); NMR ($CDCl_3$) δ 5.5 (2 H, br d), 4.2 (4 H, m), 1.5 (6 H, d), 1.2 (6 H, d); MS M^+ 240, 242, and 244, $M^+ - HCl$ 204 and 206, $M^+ - ClCHCH_3$ 177 and 179. *erythro*-**4**: mp 110–112 °C (from hexanes); NMR ($CDCl_3$) 5.6 (2 H, br d), 4.2 (4 H, m), 1.5 (6 H, d), 1.1 (6 H, d); MS M^+ 240, 242, and 244, $M^+ - HCl$ 204 and 206, $M^+ - ClCHCH_3$ 177 and 179.

1,3-Bis(3-chloro-2-butyl)-1-nitrosourea (5). The threo isomer was prepared from *threo*-**4** and the erythro isomer was prepared from *erythro*-**4**. To a solution of 1,3-bis(3-chloro-2-butyl)urea (240 mg, 1 mmol) in formic acid (3 mL) at 0 °C was added dropwise with stirring a solution of sodium nitrite (140 mg, 2 mmol) in water (1 mL). After stirring for 1 h, the mixture was dissolved in ether, and the ether solution was washed three times with iced water and dried. Removal of the ether gave a 90% yield of product as a yellow oil. *erythro*-**5**: NMR ($CDCl_3$) δ 7.2 (1 H, br s), 5.2–4.0 (4 H, m), 1.4 (12 H, m). *threo*-**5**: NMR ($CDCl_3$) δ 7.0 (1 H, br s), 5.3–3.9 (4 H, m), 1.4 (12 H, m).

4,5-Dimethyloxazolidone (6). The cis isomer was prepared from *erythro*-**2** and the trans isomer was prepared from *threo*-**2**. Phosgene was bubbled slowly through a vigorously stirred mixture of 3-amino-2-butanol (1.5 g, 0.017 mol), powdered NaOH (2.0 g, 0.05 mol), powdered anhydrous sodium sulfate (4.0 g), and methylene chloride (100 mL) until the liquid phase remained acidic to wet litmus for 5 min after the phosgene adition was stopped (~1 h). The mixture was filtered and the solvent removed under vacuum. Chromatography (ethyl acetate on silica gel) separated a more mobile impurity to give a 60% yield of the product as a colorless oil. *cis*-**6**: NMR ($CDCl_3$) δ 6.9 (1 H, br s), 4.7 (1 H, pentet), 4.0 (1 H, pentet), 1.3 (3 H, d), 1.1 (3 H, d); MS M^+ 115, $M^+ - CO$ 87. *trans*-**6**: NMR ($CDCl_3$) δ 6.9 (1 H, br s), 4.2 (1 H, pentet), 3.5 (1 H, pentet), 1.4 (3 H, d), 1.3 (3 H, d); MS M^+ 115, $M^+ - CO$ 87.

2-(3-Chloro-2-butylimino)-4,5-dimethyl-2-oxazoline Hydrochloride (7). This synthesis is based on the synthesis of 2-(2-chloroethylamino)-2-oxazoline from 1,3-bis(2-chloroethyl)urea.[14] 1,3-Bis(3-chloro-2-butyl)urea (240 mg, 1 mmol) was refluxed with water (10 mL) until all solid has dissolved. The solvent was removed, the residue dissolved in D_2O (1 mL), and the solvent again removed under vacuum to give a white solid. **7** from *threo*-**4**: NMR (D_2O) δ 5.1 (1 H, m), 4.6 (exchangeable H, s), 4.4–3.2 (3 H, m), 1.2 (12 H, m). **7** from *erythro*-**4**: NMR (D_2O) δ 4.6 (1 H, m), 4.5 (exchangeable H, s), 4.4–3.5 (3 H, m), 1.2 (12 H, m).

3-Chloro-2-butanol (8). The erythro alcohol was prepared from *trans*-**1** and the threo alcohol was prepared from *cis*-**1** by reaction with aqueous HCl following the method of Lucas and Gould.[15] *erythro*-**8**: bp 136 °C (lit.[12] 135.4 °C at 748 mm). *threo*-**8**: bp 132 °C (lit.[12] 130.8 °C at 748 mm).

Decompositions. A mixture of nitrosourea (13.5 mg, 0.05 mmol) and 0.1 *m* phosphate buffer at pH 7.4 (1 mL) was shaken at 37 °C for 4 days in a gas-tight vial fitted with a Teflon-lined septum. Then methylene chloride (1 mL) was injected into the vial, and both the aqueous and organic layers were analyzed by GC using a 6-ft glass column packed with 0.4% Carbowax 1500 on Carbopack A. The column temperature was kept at 50 °C for 7 min and then raised at a rate of 4 °C/min.

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Registry No.—*cis*-**1**, 1758-33-4; *trans*-**1**, 21490-63-1; *erythro*-**2**, 40285-24-3; *threo*-**2**, 40285-23-2; *cis*-**3**, 930-19-8; *trans*-**3**, 930-20-1; **4**, 63548-65-2; **5**, 63548-66-3; *cis*-**6**, 19190-97-7; *trans*-**6**, 19190-96-6; **7**, 63609-37-0; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6.

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An Electron Spin Resonance Spectroscopic Study of Aminocarbonyl Nitroxides. Long-Range Hyperfine Splitting of Amino Substituents and Conformational Preferences around the C_α–N(O) Bond in Aminocarbonyl Tosylmethyl Nitroxides

Rense M. Tel and Jan B. F. N. Engberts*

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

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A series of aminocarbonyl tosylmethyl nitroxides **2a–f** was generated from the corresponding *N*-hydroxyurea derivatives. Their ESR spectral features are discussed and compared with those of some simple aminocarbonyl nitroxides (**4a–e**). Usually coupling with only one nitrogen atom is observed despite noticeable hyperfine interaction with the amino substituents (H, alkyl) across the carbonyl group. The ESR spectra of **2a–f** show pronounced line-width alternation effects which are rationalized in terms of slow rotation around the C_α–N(O) bond. For **2c**, the two energetically equivalent conformations could be frozen out at −45 °C ($\Delta G^{\ddagger}$ = 6.2 kcal mol^{-1}). In these conformations, the S–C_α bond is nearly eclipsed with the half-filled $2p_z$ orbital on the nitroxide nitrogen atom.

Recent NMR studies have shown that in the preferred solution conformation of *N,N'*-[bis(α-tosylbenzyl)]urea (**1**) the tosyl methyl protons are positioned above (or below) the most remote benzyl aromatic ring.[1] A subsequent x-ray investigation of **1** revealed that a similar folded conformation is present in the crystal.[2] Unfortunately, the instability and low solubility of **1** precluded NMR investigation of the conformational flexibility over a range of temperatures. We therefore resorted to a faster spectroscopic technique, i.e., electron spin resonance spectroscopy (ESR), to assess the conformational mobility around the C_α–N bond in some structurally related ureas. Here we report the preparation (in situ) of a series of aminocarbonyl tosylmethyl nitroxides **2** and

$[p\text{-}CH_3C_6H_4SO_2CH(C_6H_5)NH]_2C{=}O$

1

$R_1R_2NC(=O)-\dot{N}(O)-CH_2SO_2C_6H_4CH_3\text{-}p$

2

an analysis of their ESR spectral features as a function of temperature. We find that the ESR spectra exhibit pronounced line width alternation (LWA) effects even at ambient temperatures which we have rationalized in terms of slow rotation around the C_α–N(O) bond on the ESR time scale. In one case, definite conclusions could be drawn about the favored conformation as well as about the barrier to rotation.

Results and Discussion

ESR Spectra of Aminocarbonyl Nitroxides. The aminocarbonyl tosylmethyl nitroxides[3] **2a–f** were prepared via the route shown in Scheme I. The one-step synthesis of the *N*-hydroxy-*N'*-(tosylmethyl)ureas **3a–f** from the corresponding *N*-hydroxyureas constitutes a further extension of the versatile Mannich-type condensation reaction of sulfinic acids with aldehydes and amino compounds to afford N-substituted α-aminosulfones.[4,5] Unfortunately, no N,N'-disubstituted *N*-hydroxyureas could be prepared by this method.[6]

ESR parameters for the nitroxides **2a–f** are collected in Table I. The magnitudes of the nitrogen hyperfine splitting constants (hfsc's) and of the *g* values are consistent with those reported previously for some aminocarbonyl nitroxides.[7–10] Further support for the structural assignment is found in the internal consistency of the A_N and A_H values within the series and in comparison of the hfsc's of **2a–f** with those of the simple aminocarbonyl nitroxides **4a–e** (Table I) which were obtained from the reaction of authentic *N*-hydroxyurea derivatives with

Scheme I

$$p\text{-}CH_3C_6H_4SO_2H + CH_2O + HN(OH)CONR_1R_2$$

$$\xrightarrow[HCOOH]{-H_2O} p\text{-}CH_3C_6H_4SO_2CH_2N(OH)CONR_1R_2 \xrightarrow{PbO_2} \textbf{2a-f}$$

3a–f

R_1, R_2: see Table I

PbO_2. Since the structural features of aminocarbonyl nitroxides have received little attention thus far, the hfsc's of **2a–f** and of **4a–e** will be discussed in some detail. First, we note that the A_N values are somewhat higher than those of acyl alkyl nitroxides, reflecting cross-conjugation of the lone pairs of both nitrogen atoms with the carbonyl moiety. Second, and more interestingly, the ESR spectra clearly reveal hyperfine interaction with the amino substituents (R_1, R_2) across the carbonyl function.[11] Furthermore, in all cases only the ESR spectrum of one of the several possible rotamers, originating from hindered rotation around the N–C(O) bond is observed. We have assigned the $A^H_{R_1}$ and $A^H_{R_2}$ splittings (Table I) on the basis of the following assumptions. (1) The favored conformation of *N*-hydroxyurea in which the oxygen atoms adopt a trans position (in view of steric reasons and confirmed by the crystal structure of *N*-hydroxyurea[12,13]) is retained in the aminocarbonyl nitroxides. (2) If one of the amino substituents is hydrogen, we propose that the second more bulky substituent will preferentially reside in trans position to the nitroxide oxygen. (3) In view of the small A_H values observed for **2b, 2d, 2f, 4b, 4d,** and **4e,** we suggest that the amino substituents of **2a, 2e,** and **4a** which exhibit the highest splittings will occupy a trans position with respect to the nitroxide oxygen atom.

The ESR spectra of **2b, 2c, 4b,** and **4c** do not show hfs by the phenyl protons. Since the line width is smaller than 0.2 G, hyperfine interaction with the second nitrogen atom can also be excluded. The same situation holds for **2a, 2d, 2f, 4a, 4d,** and **4e** and can be quite adequately explained in terms of the small magnetic moment of nitrogen relative to that of hydrogen. Only for **2e** a small hfsc of the second nitrogen atom (A_N2 = 0.30 G) could be resolved (Figure 1). This may well be a consequence of the electron-releasing ability of the dimethylamino substituent which will tend to increase the spin density at the amino nitrogen atom.[14] The significance of this factor is illustrated by the relatively large magnitude of the N^1 hfsc of **2e** as compared with that of **2c.**

Line Width Alternation (LWA). At room temperature,

Table I. Hyperfine Splitting Constants[a] and g Values for the Aminocarbonyl Nitroxides $R_1R_2NCON(O)R_3$ (2 and 4)

Nitroxide	Registry no.	R_1	R_2	R_3	A_N	$A^H_{CH_2}$	A^H_{NH}	$A^H_{R_1}$	$A^H_{R_2}$	g[b]
2a	63216-22-8	H	H	*p*-$CH_3C_6H_4$-SO_2CH_2	8.8 (8.6)	5.4 (5.4)		0.75 (0.70)	0.32 (0.17)	2.0066
2b	63216-23-9	H	C_6H_5	*p*-$CH_3C_6H_4$-SO_2CH_2	8.9 (9.0)	5.4 (5.4)		0.4 (0.4)		
2c	63216-24-0	C_6H_5	C_6H_5	*p*-$CH_3C_6H_4$-SO_2CH_2	8.1 (8.1)	5.0 (5.0)				
2d	63216-25-1	H	CH_3	*p*-$CH_3C_6H_4$-SO_2CH_2	9.0 (9.0)	5.5 (5.5)		0.80 (0.80)[c]	0.40 (0.40)	2.0064
2e	63216-26-2	CH_3	CH_3	*p*-$CH_3C_6H_4$-SO_2CH_2	9.2 (9.1)[d]	5.4 (5.3)		0.9 (0.96)	0.3 (0.32)	
2f	63216-27-3	H	$C_6H_5CH_2$	*p*-$CH_3C_6H_4$-SO_2CH_2	8.9 (9.0)	5.5 (5.5)		0.4 (0.37)[e]	0.5 (0.57)	
4a	19224-51-2	H	H	H	8.0		11.7	0.73	0.32	2.0066
4b	63216-28-4	H	C_6H_5	H	8.0 (8.0)		11.5 (11.6)	0.45		
4c	63216-29-5	C_6H_5	C_6H_5	H	7.1		10.8			
4d	63216-30-8	H	CH_3	H	8.2		11.7	0.8[c]	*f*	2.0068
4e	63216-31-9	H	$C_6H_5CH_2$	H	8.2		11.7	0.5	0.5	

[a] Hfsc's (in G) in 1,4-dioxane as the solvent; the hfsc's between parentheses are for CH_2Cl_2 as the solvent. [b] Estimated accuracy: ±0.0002. [c] A_{CH_3}. [d] The hfsc for the second nitrogen is 0.30 G. [e] A_{CH_2}. [f] Not resolved.

the ESR spectra of **2a–f** show alternating line width effects. For example, the ESR spectrum of **2c** at 35 °C exhibits broadening of the $m_I = \pm 0.5$ lines, while the outside lines of the triplets are sharp (Figure 2). Upon lowering of the temperature, the central lines further broaden, and at −10 °C these lines are so broad that they cannot be detected. At still lower temperatures, new lines appear, and at −45 °C the spectrum is consistent with two nonequivalent hydrogen hyperfine splittings of 3.0 and 6.9 G, respectively. Such LWA is indicative for a slow interconversion process between two conformations in which the methylene protons are nonequivalent. Since the two forms are equally populated, the equation $A_{H_\beta} = 0.5(A_{H_{\beta 1}} + A_{H_{\beta 2}})$ should hold, a condition which is very well fulfilled (Table I).

We propose that the exchange process finds its origin in slow rotation around the C_α–N(O) bond in **2a–f**. Similar LWA effects have been observed for some structurally related radicals, including arylsulfonylmethyl benzoyl nitroxides[6] and phenyloxycarbonyl tosylmethyl nitroxide.[15] Assuming planar geometry around the nitroxide nitrogen and employing the Heller–McConnell relation (eq 1 in which ρ_N is the spin density in the $2p_z$ orbital on nitrogen, θ the dihedral angle between the axis of the nitrogen $2p_z$ orbital and the C–H_β bond, and B_0 and B_1 parameters related to spin polarization and hyperconjugation, respectively) with $B_0 = 0$ and $\rho_N B_1 = 16$ G,[16] we can calculate the dihedral angles θ for the preferred conformations around the C_α–N(O) bond.

$$A_{H_\beta} = \rho_N(B_0 + B_1 \langle \cos^2 \theta \rangle) \quad (1)$$

The results are depicted in Figure 3. Apparently, the nitroxide radical favors conformations in which the S–C_α bond is nearly eclipsed with the half-filled $2p_z$ orbital on the nitroxide nitrogen atom. A similar eclipsing phenomenon has been proposed for a series of arylsulfonylmethyl alkoxy nitroxides[17] mainly on basis of substituent effects on A_N. At present we cannot decide between the several factors which may contribute to the conformational preferences for **2a–f**, but only note that the phenomenon is quite frequently observed for radicals of the type X-C-Y· (X = heteroatom, Y = radical site).[18] Interestingly, a comparable conformational preference has been found for **1** in the solid state.[2] For this molecule empirical potential-energy calculations strongly suggest that both nonbonded repulsive and attractive interactions significantly contribute to the conformational preferences,[2] but more detailed interpretations must await further investigation.

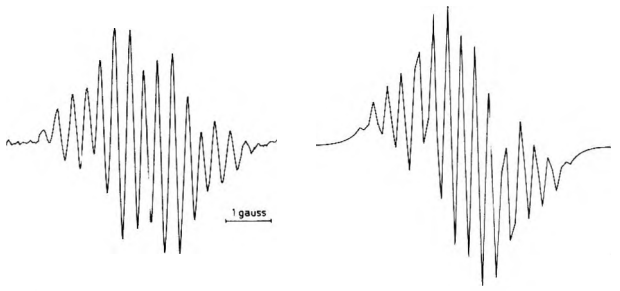

Figure 1. Low-field nitrogen line of **2e**: observed (left), computer simulated (right).

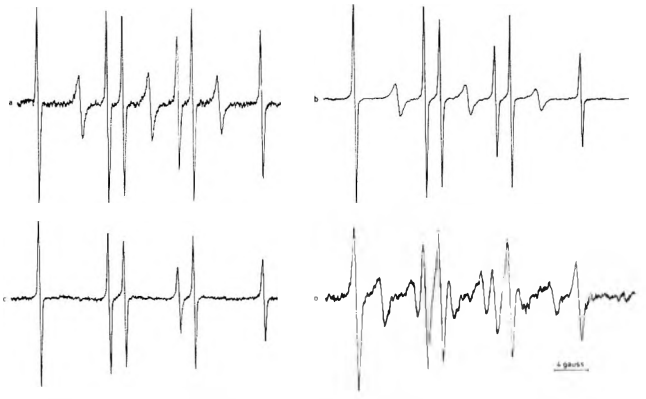

Figure 2. ESR spectra of **2c**: (a) at +35 °C, (b) at +20 °C, (c) at −10 °C, (d) at −45 °C.

From the line widths of the lines in the ESR spectrum of **2c** at −45 °C, the lifetime τ of the preferred conformations could be evaluated by using eq 2.[19] Herein Γ = line width at −45 °C, Γ_0 = line width in the absence of exchange, γ_e = magnetogyric ratio of the electron, and τ = lifetime of the conformation.

$$\Gamma = \Gamma_0 + 1/2\tau\gamma_e \quad (2)$$

We find $\tau = 9.47 \times 10^{-8}$ s and, since $k = (2\tau)^{-1}$ (k = rate constant for exchange), the barrier to rotation[20] is $\Delta G^{\ddagger} = 6.2$ kcal mol^{-1}.

Experimental Section

Elemental analyses were carried out in the Analytical Department of this laboratory under the supervision of Mr. A. F. Hamminga. Melting points were determined using a Mettler FP2 melting-point

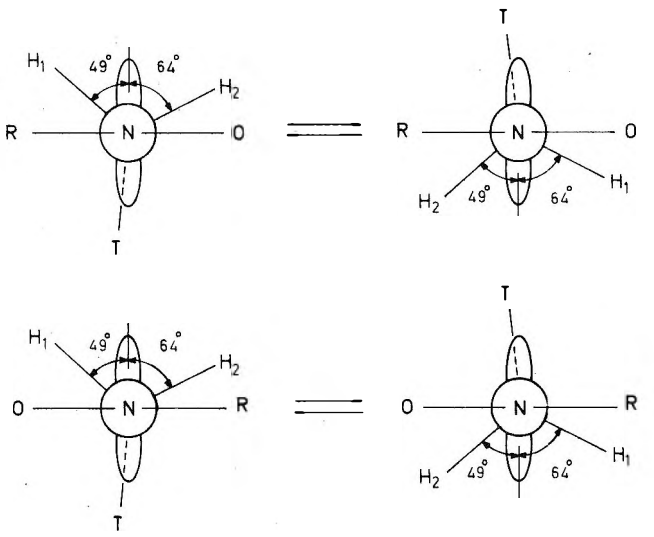

Figure 3. Newman projections of the two sets of equilibrium conformations of **2c** at −45 °C. T = tosyl.

apparatus with a Mettler FP21 microscope attachment. NMR spectra were recorded on a Varian Model A-60 spectrometer using Me_2SO-d_6 as the solvent and Me_4Si ($\delta = 0$) as an internal standard. IR spectra were measured on a Perkin-Elmer grating spectrophotometer, Model 125. The ESR spectra were recorded on a Varian E-4 apparatus fitted with a Varian A-1268 variable temperature controller. All solutions used for ESR experiments were purged with nitrogen for 30 min in order to remove dissolved oxygen. The g values (±0.0002) were measured using α,α'-diphenyl-β-picrylhydrazyl as a reference compound ($g = 2.0037$). The ESR spectrum of nitroxide **2e** was satisfactorily simulated by using the hfsc's listed in Table I.

Hydroxylamine,[21] *N*-hydroxyurea,[22] *N*-hydroxy-*N'*-phenylurea,[23] benzyl carbamate,[24] benzyl isocyanate,[25] *N*-benzyl-*N'*-hydroxyurea,[26] and *N,N*-dimethyl-*N'*-hydroxyurea[27] were prepared by known procedures. *N*-Hydroxy-*N'*-methylurea was obtained by a procedure analogous to that for *N*-benzyl-*N'*-hydroxyurea.[26] *N,N*-Diphenyl-*N'*-hydroxyurea was synthesized by a method analogous to that described for *N,N*-diethyl-*N'*-hydroxyurea.[27] Commercially available sodium *p*-toluenesulfinate and formaldehyde (36% aqueous solution) were employed. The new compounds **3** were purified by crystallization from 70% ethanol at temperatures below 50 °C.

***N*-Hydroxy-*N*-(tosylmethyl)urea (3a).** Formaldehyde (0.022 mol) and 2 mL of formic acid were added to a solution of sodium *p*-toluenesulfinate (3.56 g, 0.02 mol) and *N*-hydroxyurea (1.52 g, 0.02 mol) in 3 mL of water (pH ~3). After 5 min the first crystals separated and after 1 h the yield of **3a** was 94%: mp 134–135 °C; NMR δ 2.39 (s, 3 H), 4.90 (s, 2 H), 6.51 (s, 2 H), 7.61 (m, 4 H), 9.81 (s, 1 H) ppm; IR (KBr) 3495, 3380, 3180, 1675, 1560, 1315, 1145 cm^{-1}. Anal. Calcd for $C_9H_{12}N_2O_4S$: C, 44.26; H, 4.95; N, 11.46; S, 13.12. Found: C, 44.20; H, 4.84; N, 11.49; S, 13.01.

***N*-Hydroxy-*N*-(tosylmethyl)-*N'*-phenylurea (3b).** Formaldehyde (0.022 mol) and formic acid (2 mL) were added to a suspension of sodium *p*-toluenesulfinate (3.56 g, 0.02 mol) and *N*-hydroxy-*N'*-phenylurea (3.04 g, 0.02 mol) in 35 mL of water and 15 mL of ethanol (pH ~3). The suspension was stirred for 10 min. After 1 h the yield of crystalline **3b** was 75%. A sample had mp 134–135 °C (dec); NMR δ 2.37 (s, 3 H), 5.03 (s, 2 H), 7.3 (m, 6 H), 7.62 (m, 4 H), 9.06 (s, 1 H) ppm; IR (KBr) 3365, 3200, 1670, 1550, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.23; H, 5.03; N, 8.75; S, 10.01. Found: C, 56.16; H, 5.04; N, 9.28; S, 9.42.

***N,N*-Diphenyl-*N'*-hydroxy-*N'*-(tosylmethyl)urea (3c).** Prepared by a procedure analogous to that for **3b.** After stirring for 30 min, the yield was 57%: mp 143–144.5 °C (dec); NMR δ 2.39 (s, 3 H), 5.00 (s, 2 H), 7.2 (m, 10 H), 7.62 (m, 4 H), 9.45 (s, 1 H) ppm; IR (KBr) 3200, 1635, 1585, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_4S$: C, 63.61; H, 5.09; N, 7.07; S, 8.09. Found: C, 63.48; H, 5.10; N, 7.02; S, 8.04.

***N*-Hydroxy-*N*-(tosylmethyl)-*N'*-methylurea (3d)** was obtained using a procedure analogous to that for **3a,** but using 50 mL of 1:1 (v/v) EtOH–H_2O as the solvent. The yield was 85% and a sample had mp 129–130 °C (dec); NMR δ 2.39 (s, 3 H), 2.57 (d, $J = 5$ Hz, 3 H), 4.91 (s, 2 H), 7.00 (q, 1 H), 7.60 (m, 4 H), 9.77 (s, 1 H) ppm; IR (KBr) 3465, 3165, 1660, 1525, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.46; N, 10.85; S, 12.41. Found: C, 46.32; H, 5.32; N, 11.15; S, 12.05.

***N,N*-Dimethyl-*N'*-hydroxy-*N'*-(tosylmethyl)urea (3e).** A solution of sodium *p*-toluenesulfinate (3.56 g, 0.02 mol) in 25 mL of water was mixed with a solution of *N,N*-dimethyl-*N'*-hydroxyurea (2.1 g, 0.02 mol) in 20 mL of dioxane. Then formaldehyde (0.022 mol) and formic acid (3 mL) were added. After 2 h the first crystals of **3e** separated and after one night the yield was 53%. A sample of **3e** showed mp 132–133 °C (dec); NMR δ 2.40 (s, 3 H), 2.80 (s, 6 H), 4.86 (s, 2 H), 7.60 (m, 4 H), 9.75 (s, 1 H) ppm; IR (KBr) 3360, 1650, 1500, 1320, 1140 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.78. Found: C, 48.50; H, 5.96; N, 10.29; S, 11.78.

***N*-Benzyl-*N'*-hydroxy-*N'*-(tosylmethyl)urea (3f)** was prepared using a procedure analogous to that for **3a** using 70 mL of 1:1 (v/v) EtOH–H_2O as the solvent. The yield was 91%: mp 127–128 °C (dec); NMR δ 2.39 (s, 3 H), 4.20 (d, $J = 6$ Hz, 2 H), 4.93 (s, 2 H), 7.24 (s, 5 H), 7.59 (m, 4 H), 9.86 (s, 1 H) ppm; IR (KBr) 3400, 3195, 1645, 1525, 1320, 1145 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.57; H, 5.46; N, 8.97; S, 9.02.

Registry No.—**3a,** 63216-32-0; **3b,** 63216-33-1; **3c,** 63216-34-2; **3d,** 63216-35-3; **3e,** 63216-36-4; **3f,** 63216-37-5; formaldehyde, 50-00-0; sodium *p*-toluenesulfinate, 824-79-3; *N*-hydroxyurea, 127-07-1; *N*-hydroxy-*N'*-phenylurea, 7335-35-5; *N,N*-diphenyl-*N'*-hydroxyurea, 53731-89-8; *N*-hydroxy-*N'*-methylurea, 7433-46-7; *N,N*-dimethyl-*N'*-hydroxyurea, 52253-32-4; *N*-benzyl-*N'*-hydroxyurea, 24966-37-8.

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Kinetics and Mechanism of the Hydrolysis of 2-Phenyl-1,3,2-benzodiazaborole

T. Okuyama,* K. Takimoto, and T. Fueno

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

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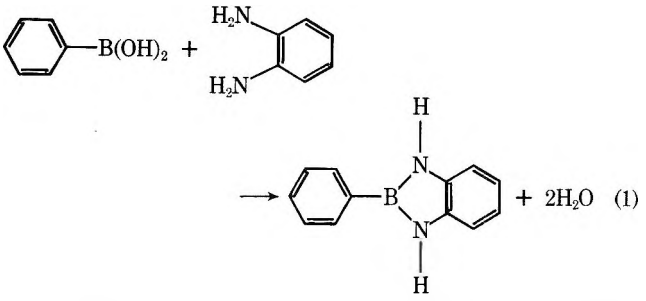
Rates of hydrolysis of 2-phenyl-1,3,2-benzodiazaborole and its substituted derivatives have been measured in 25% aqueous acetonitrile in the pH range of 4–11. The reaction was catalyzed by both general acids and bases. The kinetic solvent isotope effects $k_H/k_D > 1$ were obtained except for hydronium-ion catalysis ($k_{H_3O^+}/k_{D_3O^+} = 0.55$). The Hammett ρ values for various catalytic constants were found to be positive in sign (0.81–1.76) again with the single exception of the H_3O^+ catalysis ($\rho = -0.68$). A possible reaction mechanism has been presented.

Boronic acids as well as boric acid easily form complexes or adducts with bifunctional oxygen or nitrogen compounds.[1] Among many other examples, benzeneboronic acid and o-phenylenediamine react to give a stable heterocyclic adduct, 2-phenyl-1,3,2-benzodiazaborole, under appropriate conditions.[2] Dewar et al.[3] showed that the stability of this adduct arises from its heteroaromaticity and noted its reluctance in hydrolysis. On the other hand, this type of boron compounds attract the interest of medicinal chemists for their possible use in cancer therapy.[2,4] Hydrolytic properties at the physiological pH are essential for this use.[4]



However, detailed investigations on the hydrolysis of this type of compounds are scanty. The only report on such studies is concerned with in situ formation and hydrolysis of cyclic esters of boric acid and salicylamide and related compounds.[5] Semiquantitative hydrolysis rates were measured with boric acid esters[6,7] and aminoboranes.[8]

In the present investigation, hydrolysis of 2-phenyl-1,3,2-benzodiazaborole (**1a**) and its substituted derivatives (**1b–1g**) to the corresponding benzeneboronic acid and o-phenylenediamine has kinetically been studied in the pH range of 4–11.

Experimental Section

Materials. 2-Phenyl-1,3,2-benzodiazaborole **1a** and its derivatives **1b–1g** were prepared according to the literature[2] by the condensation of an appropriate areneboronic acid[9] with an ortho-aromatic diamine in xylene or toluene. The crude products were recrystallized twice from toluene: mp **1a**, 207–208 °C (lit.[9] 212–214 °C); **1b**, 245–246 °C (lit.[9] 242–243 °C); **1c**, 235–237 °C; **1d**, 222–223.5 °C (lit.[9] 219–221 °C); **1e**, 157–159 °C; **1f**, 221–223 °C (lit.[9] 224–225 °C); **1g**, 182–184 °C (lit.[9] 183–184 °C). Elemental analyses of all the substrates showed satisfactory results.

Acetonitrile was distilled from P_2O_5. Inorganic salts of reagent grade were used without further purification. Organic buffers were distilled or recrystallized before use. Freshly boiled, glass-distilled water was used for all rate determinations.

Kinetics. All measurements were carried out at 30 ± 0.1 °C in 25% aqueous acetonitrile (v/v), ionic strength being maintained at 0.10 by the addition of KCl. To prepare buffer solutions, necessary amounts of a buffer and KCl (to bring the ionic strength to 0.10) were placed in a volumetric flask, to which 0.24 part of acetonitrile was added. Then, water was added to fill the flask at room temperature. Three milliliters of the buffer solution was equilibrated at constant temperature in a stoppered quartz cuvette inserted in a water-jacketted cell holder. Into the buffer solution was injected 30 μL of a stock solution of **1** in anhydrous acetonitrile with the use of a microsyringe. After thorough mixing, the reaction was monitored by the decrease of the absorption of the substrate (~295 nm), using a Shimadzu spectrophotometer UV-200 with an automatic cell-positioner assembly. Pseudo-first-order plots were linear up to more than 90% reaction over the entire pH range studied.

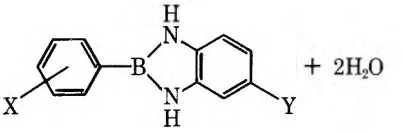
Rates of the fast reactions in hydrochloric acid were determined with a stopped-flow spectrophotometer, Union RA-1100. The stock solution of **1a** in this case was an unbuffered 25% aqueous THF solution, in which the half-time of **1a** was no shorter than 30 min.

The pH values of buffer solutions and reaction mixtures were determined with a Hitachi-Horiba pH meter CTE F-5 calibrated with aqueous standard buffers[10] supplied by the Nakarai Chemicals, Inc.

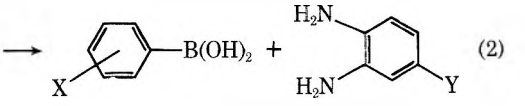
Solvent Isotope Effects. Deuterium oxide (99.75%) as well as DCl and NaOD solutions in D_2O (99%) was supplied by E. Merck, Darmstadt. Anhydrous K_2CO_3 and CH_3COONa were used for buffer preparations. The pD values are given as approximate values with use of the glass electrode correction formula of Fife and Bruice.[12]

Results

For slow reactions of the unsubstitued substrate **1a**, scannings of the ultraviolet spectra of the reaction mixture were carried out at appropriate time intervals. Absorbance decreased in the whole wavelength region scanned, 230–320 nm, to result in a final spectrum which completely agreed with that of the equimolar mixture of benzeneboronic acid and *o*-phenylenediamine. Undoubtedly, the overall reaction proceeds according to eq 2.



1a, X = H, Y = H
b, X = *p*-OCH_3, Y = H
c, X = *p*-CH_3, Y = H
d, X = *p*-Cl, Y = H
e, X = *m*-Cl, Y = H
f, X = H, Y = CH_3
g, X = H, Y = Cl



The reaction was then followed spectrophotometrically at the wavelength of maximum absorbance change (~295 nm). First-order plots were linear over 90% conversions for all the runs studied. Rate constants were determined at 30 °C with varying buffer concentrations in aqueous solution containing 25% (v/v) acetonitrile at a constant ionic strength of 0.10. Observed rate constants k_{obsd} were linearly dependent on the total buffer concentrations [B];

$$k_{obsd} = k_0 + k_B[B] \quad (3)$$

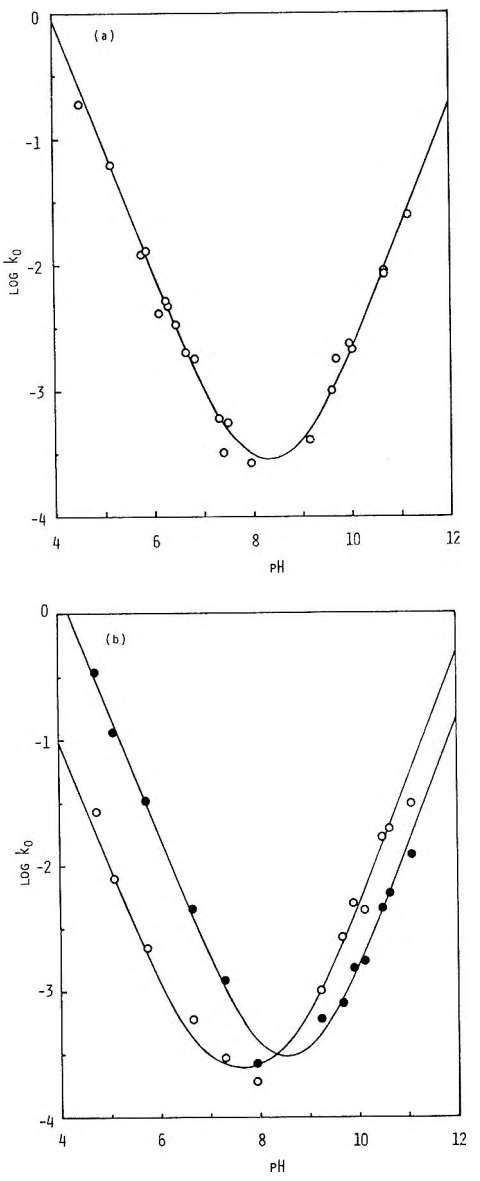


Figure 1. pH–rate profiles for the hydrolysis of diazaboroles: (a) **1a**, (b) **1f** (○) and **1g** (●).

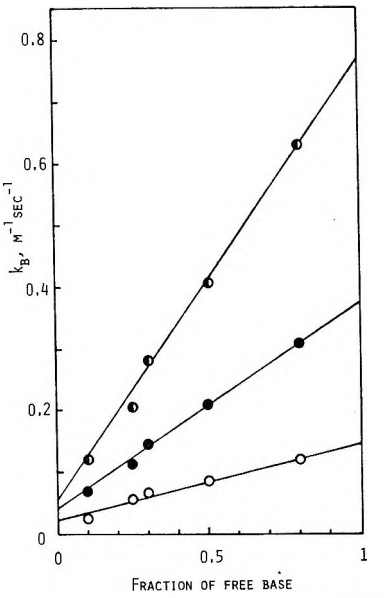


Figure 2. Buffer-dependent rate constants in imidazole buffers for the hydrolysis of **1a** (○), **1d** (●), and **1e** (◐).

Table I. Rate Constants for the Hydrolysis of Diazaboroles at 30 °C

Diazaborole	$10^{-3}\,k_{H_3O^+}$, $M^{-1}\,s^{-1}$	k_{OH^-},[a] $M^{-1}\,s^{-1}$
1a	8.85[b]	42.7[c]
1b	10.7	23.8
1c	10.1	26.5
1d	5.31	66.7
1e	4.04	102
1f	17.5	29.3
1g	0.99	97.5
ρ[d]	−0.68 ± 0.08	0.99 ± 0.05

[a] Calculated with $K_w = 0.471 \times 10^{-14}$ M^2 except for **1a**. [b] $k_{H_3O^+} = (8.65 \pm 0.32) \times 10^3$ $M^{-1}\,s^{-1}$ at [HCl] = 0.005 M. [c] Obtained from the hydrolysis in NaOH solutions ([NaOH] = 0.001–0.004 M). Standard deviation = ±0.2 $M^{-1}\,s^{-1}$. [d] The Hammett ρ constant obtained from the rate constants for **1a–1e**.

where k_0 is the first-order rate constant extrapolated to zero buffer concentration.

The intrinsic rate constants k_0 showed a pH dependence of the inverse bell shape; both the acid catalysis from acidic to neutral pH and the base catalysis at alkaline pH were observed. Examples of the pH–rate profiles are shown in Figure 1.

$$k_0 = k_{H_3O^+}[H_3O^+] + K_w k_{OH^-}/[H_3O^+] + k_{H_2O}$$
$$= k_{H_3O^+}[H_3O^+] + k_{OH^-}[OH^-] + k_{H_2O} \quad (4)$$

Rate constants obtained are given in Table I. The rate constant k_{OH^-} was calculated from the $K_w k_{OH^-}$ value obtained from the pH–rate profile. The ionic product K_w of the medium was estimated by the comparison of k_{OH^-} determined separately for **1a** in NaOH solution with the $K_w k_{OH^-}$ value: $K_w = 0.47 \times 10^{-14}$. The K_w value estimated here is reasonable for 25% aqueous acetonitrile at 30 °C. A mixed organic aqueous solvent would have a K_w value considerably smaller than that for pure water.[13] The water-catalysis term was necessary to reproduce the pH–rate profile of a shallow bottom. The k_{H_2O} value was essentially the same for all the substrates studied here: $k_{H_2O} = 2 \times 10^{-4}\,s^{-1}$.

Buffer-dependent rate constants k_B were partitioned into the acid and base catalytic constants, k_{HA} and k_{A^-}, by their plots against the fraction of conjugate base of the buffer, as shown in Figure 2.

$$k_B = (k_{HA}[HA] + k_{A^-}[A^-])/([HA] + [A^-]) \quad (5)$$

For most buffers the k_{HA} and k_{A^-} terms were negligible respectively in the higher and lower pH regions. Only near the neutral pH (phosphate and imidazole buffers) both k_{HA} and k_{A^-} terms were observed. Catalytic constants obtained are summarized in Table II.

The correlation of base catalytic constants with the pK_a of the conjugate acid is shown in Figure 3 for **1a**. These Bronsted plots show a considerable scatter from the line (the slope β = 0.3). But we find no systematic deviations which imply the operation of possible nucleophilic catalysis. The scatter may have arisen simply because of the variety of catalyst structures.

The substituent effects on the catalytic constants were analyzed by the Hammett $\rho\sigma$ relationship for substrates **1a–1e**. Linearities of the relationship are shown in Figure 4, as examples, for (a) the hydronium and hydroxide ion catalyses and (b) the imidazole buffer catalyses. The reaction

Table II. Catalytic Constants, k_{HA} and k_{A^-} (M^{-1} s^{-1}), for the Hydrolysis of Diazaboroles at 30 °C

Registry no.	Acid or base	1a[b]	1b[b]	1c[b]	1d[b]	1e[b]	1f[b]	1g[b]	ρ[a]
75-04-7	$EtNH_2$	2.58							
109-89-7	Et_2NH	3.31							
121-44-8	Et_3N	1.57							
3812-32-6	CO_3^{2-}	1.09	0.497	0.593	1.82	3.02	0.562	2.89	1.22 ± 0.06
920-66-1	$(CF_3)_2CHOH$	1.92	1.02	1.20	4.79	8.08	1.45	8.18	1.45 ± 0.09
15390-83-7	$B(OH)_4^-$	0.0916	0.0418	0.0552	0.177	0.259			1.24 ± 0.01
280-57-9		3.78							
110-91-8		1.09	0.509	0.622	2.34	3.54			1.35 ± 0.04
77-86-1	Tris	0.172	0.0735	0.0912	0.361	0.634			1.48 ± 0.04
14066-19-4	HPO_4^-	0.0844	0.0412	0.0467	0.185	0.301	0.0752	0.222	1.40 ± 0.07
288-32-4	Imidazole	0.148	0.0590	0.0750	0.375	0.770			1.76 ± 0.07
7803-49-8	NH_2OH	0.0998							
14066-20-7	$H_2PO_4^-$	0.0447	0.0254	0.0278	0.0732	0.108	0.0233	0.0592	1.01 ± 0.06
17009-90-4	Imidazolium	0.0240	0.0182	0.0198	0.0427	0.0580			0.81 ± 0.08
64-19-7	CH_3CO_2H	0.19							

[a] The Hammett ρ constant obtained from the catalytic constants for 1a–1e. [b] Registry no.: 1a, 2479-64-3; 1b, 24341-80-8; 1c, 63181-66-8; 1d, 5747-25-1; 1e, 5785-83-1; 1f, 28249-53-8; 1g, 63181-67-9.

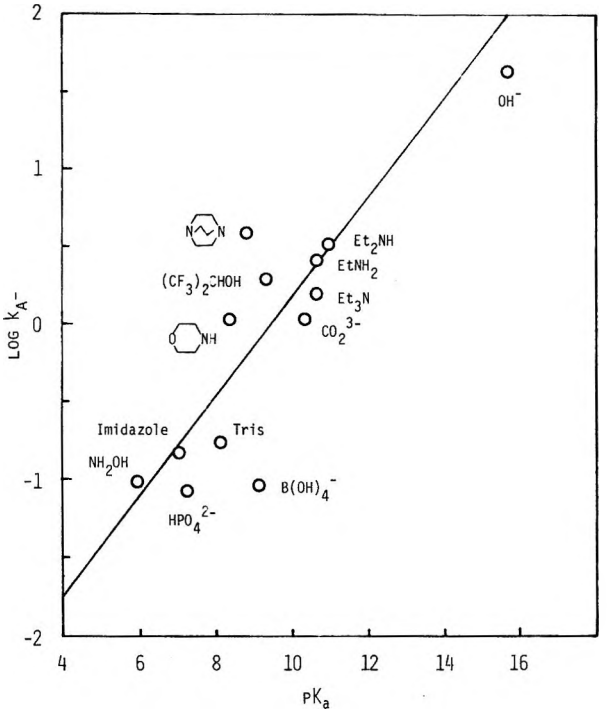


Figure 3. The Bronsted plots for general base catalysis in the hydrolysis of **1a**.

constants ρ are summarized in Tables I and II. The ρ values are positive (0.81–1.76) in sign except for the hydronium-ion catalysis ($\rho = -0.68$).

The effects of a 5 substituent can be seen in the results with **1a, 1f,** and **1g.** They are positive in the sense of the Hammet ρ value (reactivity increasing with the increasing electron attraction of a 5 substituent) except for H_3O^+ catalysis. Because of the structural complexity and a small number of substituents examined, the effects cannot be treated quantitatively.

Solvent kinetic isotope effects in the hydrolysis of **1a** were examined at both acid and alkaline pH. The kinetic results in deuterium media are given in Table III. The results in hydrochloric acid and sodium hydroxide solutions give the isotope effects,

$$k_{H_3O^+}/k_{D_3O^+} = 0.55 \pm 0.05$$

and

$$k_{OH^-}/k_{OD^-} = 1.40 \pm 0.02$$

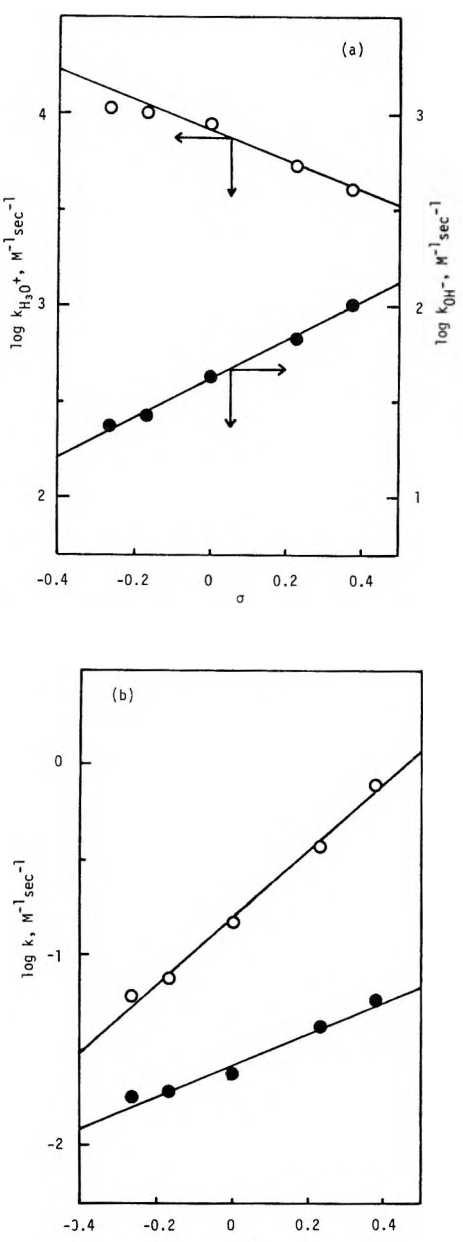


Figure 4. Hammett's $\rho\sigma$ relations: (a) $k_{H_3O^+}$ (○) and k_{OH^-} (●), (b) k_{A^-} (○) and k_{HA} (●) in imidazole buffers.

Table III. Kinetic Data for the Hydrolysis of 1a in D_2O

Buffer	DA/A⁻	pD	[Buffer], M	k_0, s^{-1}	k_B, M^{-1} s^{-1}
Acetate	1.104	5.58 ± 0.02	0.02–0.10	$(3.99 \pm 0.02) \times 10^{-2}$	$(4.57 \pm 0.38) \times 10^{-2}$
Carbonate	1.669	11.07 ± 0.03	0.008–0.042	$(3.06 \pm 0.21) \times 10^{-3}$	$(2.21 \pm 0.08) \times 10^{-1}$
DCl			0.005		$(1.56 \pm 0.09) \times 10^{4}$
NaOD			0.002–0.004		$(3.04 \pm 0.02) \times 10^{1}$

Since in the acetate and carbonate buffers the base and acid catalyses are respectively negligible,

$$k_{AcOD} = 8.7 \times 10^{-2}\ M^{-1}\ s^{-1}$$

and

$$(k_{CO_3^{2-}})^D = 0.59\ M^{-1}\ s^{-1}$$

That is, the isotope effects on buffer catalyses are

$$k_{AcOH}/k_{AcOD} = 2.2$$

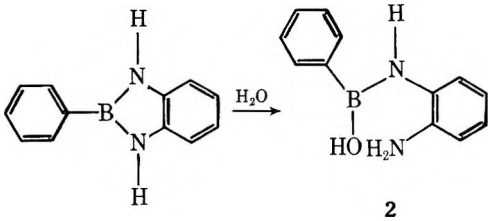
and

$$(k_{CO_3^{2-}})^H/(k_{CO_3^{2-}})^D = 1.85$$

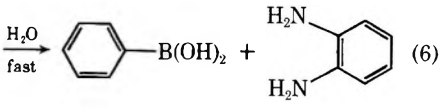
Although the pD values given for the deuterium buffer solutions are only approximate,[12] the k_0 values obtained are reasonable in view of the close agreement with those estimated from the $k_{H_3O^+}$ and k_{OD^-} values.

Discussion

Hydrolysis of **1** must proceed in a stepwise manner through an intermediate formation of the acyclic aminoborinic acid **2**. The intermediate **2** must be hydrolyzed much more easily



1 **2**

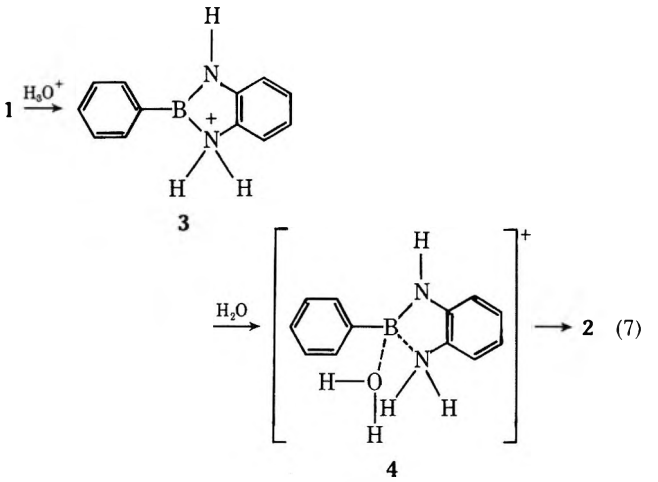


(6)

than the starting diazaborole **1** of cyclic structure.[3,8] We observed no sign of accumulation of such an intermediate. Thus, in discussing the reaction mechanism in kinetic terms, we have only to consider the first step of eq 6.

Kinetics of the hydrolysis is relatively simple with acid catalysis at lower pH and base catalysis at higher pH. Acidic and basic centers of the diazaborole are a priori boron and nitrogen atoms, respectively. The acid and base catalyses should correspondingly operate at the nitrogen and boron atoms of the diazaborole. A mechanism involving nucleophilic catalysis may be excluded as mentioned above.

Hydronium-Ion Catalysis. Hydronium-ion catalyzed hydrolysis with $k_{H_3O^+}/k_{D_3O^+} < 1$ must take place through preequilibrium protonation.[14] A mechanism involving the rate-determining proton transfer would have resulted in $k_{H_3O^+}/k_{D_3O^+} > 1$. The observed substituent effects must be composites of those on the first protonation equilibrium and those on the rate-determining attack of H_2O toward the protonated diazaborole, **3**. The negative ρ value observed indicates that the effect on the preequilibrium step is the

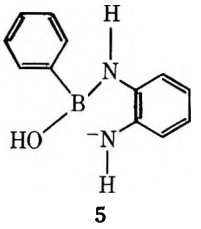


3 **4**

(7)

greater. The transition state (**4**) of the second step must be structurally nearer to its initial state (**3**).

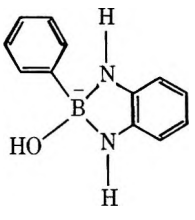
Base Catalysis. Base-catalyzed hydrolysis takes place with normal isotope effects of $(k_{A^-})^H/(k_{A^-})^D > 1$. A mechanism



5

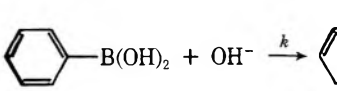
involving simultaneous B–O bond formation and B–N bond cleavage is unlikely because of the instability of the nitrogen anion intermediate **5**.

The intermediacy of a tetrahedral anion like **6** is more likely. The tetrahedral intermediate of type **6** is similar to the con-



6

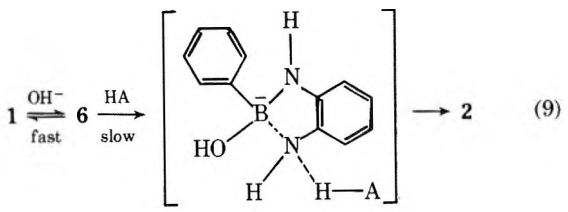
jugate base form of boric[15] and boronic acids.[16] The rate of the hydroxide addition (eq 8) was measured for benzeneboronic acid by the temperature-jump technique; $k = 4.75 \times 10^7\ M^{-1}\ s^{-1}$ in 0.10 M aqueous KCl at 35 °C.[17] The rate constant for



(8)

the reaction of **1** with OH^- to form **6** would also be of the order of $10^7\ M^{-1}\ s^{-1}$. At least, it would never be as small as the k_{OH^-} value ($42.7\ M^{-1}\ s^{-1}$) observed here. Furthermore, the solvent isotope effects on rate-determining "hydroxide-destroying" reactions are usually ranged from 0.6 to 0.8.[18] Our present

results ($k_{OH^-}/k_{OD^-} = 1.4$) evidently fall outside this isotope-effect range. Thus, the rate-determining step is likely to be the decay of the tetrahedral intermediate **6** (eq 9). The rate-

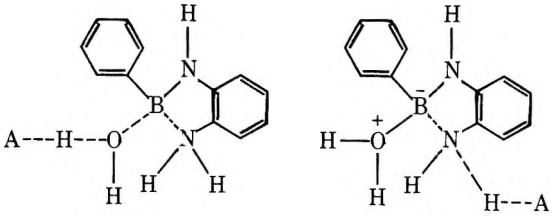


7

determining step involves proton transfer to give rise to the isotope effects $(k_{A^-})^H/(k_{A^-})^D > 1$. A buffer conjugate acid (HA) operates as a general acid. In the hydroxide-ion catalysis, HA should be H_2O.

The ρ values observed (0.99–1.76) are reasonable as the sums of those for the first equilibrium (ρ_1) and those for the rate-determining step (ρ_2). The ρ_1 values would not be much different from the value observed for the equilibrium of benzeneboronic acid ($\rho_1 = 2.00$[17]), while the ρ_2 values would no doubt be negative in sign.

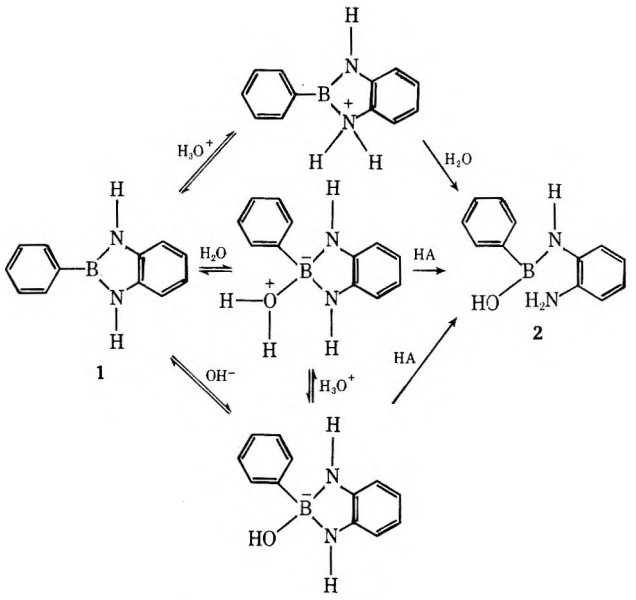
General Acid Catalysis. The mechanism of general acid-catalyzed hydrolysis, where $k_H/k_D > 1$ and $\rho > 0$, seems not to be straightforward. The mechanism must be an extraporation of that of either hydronium ion or base catalysis. In eq 7 the rate-determining water attack may be facilitated by a general base A^- or in eq 9 the intermediate **6** may be in an O-protonated form. That is, the transition state structurally



8 9

resembles 8 or **9**. The isotope effects observed ($k_{AcOH}/k_{AcOD} = 2.2$) seem to be compatible with both these mechanisms. The substituent effects would be close to those for eq 7 and 9; $\rho < 0$ and $\rho > 0$, respectively. Thus, the mechanism similar to eq 9, where **6** is protonated at the O atom and the transition state resembles **9**, seems to be more probable for the general acid-catalyzed hydrolysis.

In conclusion, the mechanism of the hydrolysis is summarized below. The acid and base catalyses occur cooperatively,



but not concertedly, and the hydrolysis undergo easily in the whole pH range in aqueous solutions.

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Response of Nitro-Activated Benzene and Five-Membered Heteroaromatic Systems to the Nucleophilic Reagent. Kinetics of *p*-Tolylthio Denitration in Methanol

Paolo Mencarelli and Franco Stegel*

Centro C.N.R. di Studio sui Meccanismi di Reazione, c/o Istituto di Chimica Organica dell'Università di Roma, 00185 Roma, Italy

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The rates of *p*-tolylthio denitration of 1-methyl-2,5-dinitropyrrole, 2,5-dinitrofuran, 2,5-dinitrothiophene, and 1,4-dinitrobenzene have been measured in methanol at 25 °C. The reactivity order observed differs from that observed in the piperidino denitration of the same substrates for the inversion of the reactivity between the pyrrole and benzene derivatives. A possible cause is suggested for this inversion.

The relative reactivities of 1-methyl-2,5-dinitropyrrole (**1**), 2,5-dinitrofuran (**2**), and 2,5-dinitrothiophene (**3**) in the reaction of piperidino denitration have recently been determined[1] and compared with the reactivity of 1,4-dinitrobenzene (**4**). The results were characterized by the reactivity sequence **2** > **3** > **4** > **1**, where the reactivity of the pyrrole derivative was only slightly lower than that of the benzenoid substrate.

Besides the presence of activating substituents and the nature of the leaving group, the nature of the nucleophilic reagent is known to affect the relative rates of nucleophilic aromatic substitutions of different substrates.[2]

We wish to report here on the relative reactivities of substrates **1**–**4** in the substitution with the *p*-toluenethiolate ion, a charged nucleophilic reagent much more reactive than piperidine. As a consequence of the change of nucleophile, we find an interesting alteration of the reactivity sequence previously observed.

Experimental Section

Melting points are uncorrected. Microanalytical, UV–visible, NMR, and MS characterizations of the products were made as described in ref 1.

Materials. Substrates **1**–**4** were available from previous work.[1] Methanol was purified from magnesium; sodium methoxide was prepared and titrated as previously described.[3] *p*-Toluenethiol (Fluka purum) was sublimated under reduced pressure; its purity was checked by TLC.

The **kinetics** of 2,5-dinitrothiophene were followed spectrophotometrically at the wavelength corresponding to the absorption maximum of the reaction product. Since the absorption maxima of the reaction products of the other substrates fall in the region where the *p*-toluenethiolate ion shows a somewhat intense absorption, the kinetics of these compounds were followed at a longer wavelength (390 nm), where this inconvenience is less important. The substitutions of the pyrrole and benzene compounds were followed in the thermostated compartment of a Beckman DB-GT spectrophotometer; owing to the higher reactivity of the furan and thiophene derivatives, a Durrum D-110 stopped-flow spectrophotometer was used for the reactions of these substrates. The range of concentrations of the substrates was 0.5–1 × 10^{-4} M. The thiolate solutions were obtained by mixing a slight excess of thiol with a methanol solution containing a known amount of methoxide ion and by taking up to volume. The concentrations of the thiolate ion were in the range 1–10 × 10^{-3} M and were corrected, when required, for the thermal expansion of the solvent.

1-Methyl-2-nitro-5-(*p*-tolylthio)pyrrole. Sodium methoxide in methanol was slowly added, at room temperature, to a methanol solution (10 mL) containing equivalent amounts of 1-methyl-2,5-dinitropyrrole and *p*-toluenethiol (3.2 × 10^{-4} M). After 2 h the solvent was removed, and the residue was washed with water and purified by chromatography on silica gel with petroleum ether and benzene 1:1: mp (ligroin) 84.5–85.5 °C; λ_{max} (CH_3OH) 354 nm; M^+ at *m/e* 248; δ (in CCl_4) 2.30 (s, 3 H), 3.90 (s, 3 H), 6.38 (d, 1 H, J = 4.0 Hz), 6.95 (br s, 4 H), 7.06 (d, 1 H, J = 4.0 Hz); yield, 75%.

Anal. Calcd: C, 58.05; H, 4.87; N, 11.28; S, 12.91. Found: C, 58.18; H, 4.95; N, 11.12; S, 13.01.

2-Nitro-5-(*p*-tolylthio)furan. **2** (0.20 g, 0.13 × 10^{-3} mol), dissolved in 10 mL of MeOH, was slowly added to a methanol solution containing 1.4 × 10^{-3} mol of both toluenethiol and sodium methoxide. A TLC analysis at the end of the addition showed the formation of one product only and the absence of **2**. After removal of the solvent under reduced pressure, the organic material was immediately dissolved in benzene and purified from traces of unreacted thiol by chromatography on silica gel with benzene. The product was recrystallized from hexane: mp 39.5–40.5 °C; λ_{max} (CH_3OH) 358 nm; M^+ at *m/e* 235; δ (in CD_3COCD_3) 2.35 (s, 3 H), 6.92 (d, 1 H, J = 3.6 Hz), 7.1–7.5 (m, 4 H), 7.58 (d, 1 H, J = 3.6 Hz); yield, 67%.

Anal. Calcd: C, 56.16; H, 3.86; N, 5.96. Found: C, 55.7; H, 3.6; N, 5.8.

This product decomposes within a few days on standing, and more rapidly in the presence of bases, to give black tars. It should be stored in the cold, away from light.

2-Nitro-5-(*p*-tolylthio)thiophene. A procedure substantially similar to the one just described was used. The product had a melting point 39–40 °C, significantly different from that previously reported (57 °C).[4] However, the presence in the NMR spectrum of two doublets with the coupling constant typical of 2,5-disubstituted thiophenes[5] leaves no doubt about the structure of the product: M^+ at *m/e* 251; λ_{max} (MeOH) 385 nm; δ (in CCl_4) 2.39 (s, 3 H), 6.87 (d, 1 H, J = 4.2 Hz), 7.0–7.5 (m, 4 H), 7.68 (d, 1 H, J = 4.2 Hz); yield, 41%.

1-Nitro-4-(*p*-tolylthio)benzene. The substitution on **4** was performed under conditions similar to the substitution of **1**; because of the lower reactivity of **4**, the reaction was run with a small excess of thiolate nearly 20 h: mp 78–78.5 °C (lit.[6] 80–81 °C); λ_{max} (MeOH) 341 nm; yield, 62%.

Results and Discussion

Compounds **1**–**4** undergo the *p*-tolylthio denitration reaction in methanol by the action of the conjugate base of *p*-toluenethiol. As expected, in going from the neutral piperidine to an anionic nucleophilic reagent, a strong rate enhancement is observed. However, it must be remarked that the rate increase in the thiolate reaction may be partially offset by the use of methanol, a solvent that is generally slower[7] than acetonitrile in nucleophilic aromatic substitution and is also expected to decrease the reactivity of anionic nucleophiles through the formation of strong hydrogen bonds. A direct comparison of the reactivity of all substrates in both piperidino and arylthio denitration was not feasible in the same solvent, owing to the large reactivity range in the series **1**–**4**; thus, the pyrrole and benzene derivatives (**1** and **4**) are very poorly reactive toward piperidine in methanol, whereas 2,5-dinitrofuran reacts very fast with anionic nucleophiles in acetonitrile.

The formation of the expected thioethers occurs in a straightforward way under both preparative and kinetic conditions, and no side-products were detected by TLC analysis.

The kinetics were run in the presence of an excess of the nucleophilic reagent and were characterized by good pseudo-first-order plots up to 90% in all cases. This is contrasted by the fact that the kinetics of piperidino denitration

Table I. Kinetic Data for the p-Tolylthio Denitration of Compounds 1–4 in Methanol at 25 °C

Compd	Registry no.	k,[a] L mol^{-1} s^{-1}	k_{rel}
1	56350-95-9	2.60	1
2	826-03-9	4.4×10^3	1.7×10^3
3	59434-05-8	4.2×10^2	1.6×10^2
4	100-25-4	2.24×10^{-2}	8.8×10^{-3}

[a] Corrected for statistical factors.

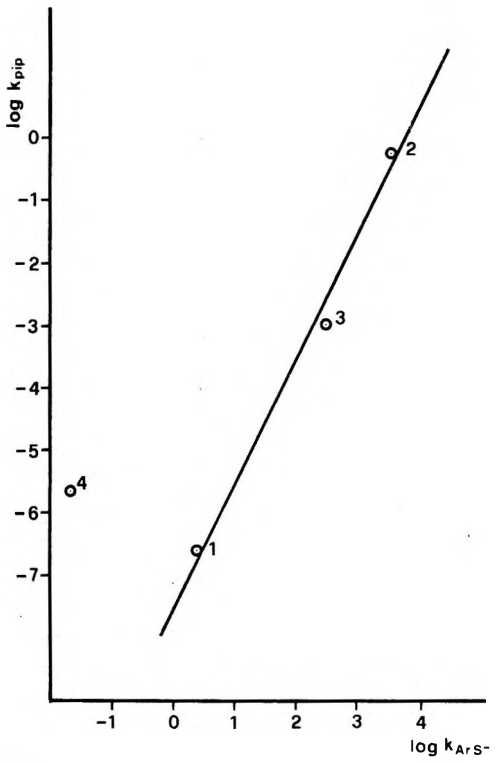

Figure 1. Free-energy correlation between piperidino denitration in CH_3CN (log k_{pip}) and p-tolylthio denitration in CH_3OH (log k_{ArS^-}), at 25 °C, of substrates 1–4.

of the less reactive substrates 1 and 4 did not show such a well-behaved pattern, probably because of the occurrence of side reactions.[1]

Rate data for the p-tolylthio denitration reaction at 25 °C are reported in Table I. They show that in this reaction the reactivity order for the heterocyclic substrates (2 > 3 > 1) is the same as that observed in the piperidino denitration reaction.

In contrast, an interesting inversion of reactivity is obtained for the reactions of the pyrrole and benzene derivatives; thus, while the benzenoid substrate 4 is decidedly more reactive than the pyrrole derivative 1, the less reactive of the heteroaromatic substrates, in the reaction with piperidine (k_1/k_4 = 0.1), the reverse is true for the reaction with the thiolate ion. For this reaction, the reactivity ratio k_1/k_4 is 1.1×10^2, so that the benzenoid substrate is far less reactive in the series 1–4.

It becomes thus evident that, since the reactivity ratio k_1/k_4 is strongly dependent on the nature of the nucleophile, it is not possible to indicate in a general way whether pyrrole derivatives are more or less reactive than similarly substituted benzene derivatives.

It is also worth noting that the reaction of the three heteroaromatic substrates with the more reactive reagent, i.e., the thiolate ion, is less selective than that with piperidine, as shown in the free-energy plot of Figure 1. The straight line

Table II. Comparison of Activation Parameters for the p-Tolylthio[a] and Piperidino Denitration[b] of Compounds 1 and 4 at 25 °C

	p-Toluenethiolate		Piperidine	
Compd	$\Delta H^{\ddagger}$, kcal mol^{-1}	$-\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$-\Delta S^{\ddagger}$, cal mol^{-1} K^{-1}
1	13.7 (±0.5)	10.7 (±1.0)	14.5 (±1)	40 (±2)
4	16.8 (±0.9)	9.7 (±2.9)	11.5 (±0.6)	46 (±2)

[a] Present work. Pertinent kinetic data at different temperatures are reported as follows (k corrected, L mol^{-1} s^{-1}): 1, 1.43 (18.0 °C), 2.60 (25.0 °C), 4.86 (32.7 °C), 7.86 (39.6 °C); 4, 1.14×10^{-2} (18.0 °C), 2.24×10^{-2} (25.0 °C), 4.77×10^{-2} (32.5 °C), 9.56×10^{-2} (40.4 °C). [b] Reference 1.

described by the three heteroaromatic substrates 1–3 has a slope of nearly 2. This correlation indicates that the factors involved in determining the relative reactivities of these substrates are probably the same in both reactions, even if the higher reactivity of the thiolate and, consequently, the lower perturbation expected for the ring in the formation of the transition state may be held responsible for the lower selectivity in the reaction with this reagent.

As expected from the noted inversion of the k_1/k_4 ratio, the benzenoid substrate 4 is located definitely out of the straight line (Figure 1).

It may be not surprising to find a lack of correlation between the data of 1–3 and those of 4, as the absence of the heteroatom and the larger dimensions of the benzene ring are expected to affect the delocalization of the negative charge developing in the benzene compound.

The quantitative significance of these differences in reactivity can be further worked out by comparing the activation parameters for both reactions of the pyrrole and benzene terms (Table II). Unfortunately, the relatively high reactivity of the furan and thiophene derivatives in the thiolate reaction made it impossible to obtain activation data as reliable as those for 1 and 4.

In going from the piperidino to the arylthio denitration the most important changes which seem responsible for the general increase of rate concern the activation entropy, which becomes much less negative. The direction of these changes is consistent with a greater requirement of reorganization of the solvent for the formation of a dipolar transition state from uncharged reagents.

The data in Table II show, on the other hand, that the activation enthalpy is a very important factor in determining the inversion of reactivity between the pyrrole and the benzene derivative. Thus, the reaction of the benzenoid substrate with piperidine is characterized by a $\Delta H^{\ddagger}$ lower than that of the pyrrole substrate, and the reverse is observed for the reaction with the thiolate ion.

In dealing with the reactions of substrates 1–4 with piperidine, it was suggested[1] that some rate-depressing effect could arise in the heteroaromatic substrates from the conjugation of the leaving group with the heteroatom in the ground state. However, in the thiolate reaction this effect must be more than counterbalanced by some other factors, since 1,4-dinitrobenzene is the less reactive in the series, even if the conjugation of the nitro group in this substrate should be particularly weak, owing to the absence of heteroatoms.

In seeking an explanation of this fact, we can observe that a similar situation may be found in the nucleophilic substitution of 4-nitrohalogenobenzenes[8] (and of other similarly activated halogenobenzenes),[9] where the fluorine atom, which is expected to be strongly conjugated with the nitro group, is displaced more rapidly than iodine. It must be noted that this effect is much more intense with CH_3O^- than with CH_3S^-.[10]

This difference in behavior has been accounted for by the higher affinity of the polarizable nucleophilic reagent CH_3S^- for the reaction center bound to the more polarizable iodine atom.[11] The less reactive iodo derivative shows in both reactions a higher activation enthalpy than the fluoro derivative; however, the difference $\Delta\Delta H^{\ddagger} = (\Delta H^{\ddagger}_I - \Delta H^{\ddagger}_F)$ becomes smaller[10] in going from the reaction with CH_3O^- ($\Delta\Delta H^{\ddagger} = 3.9$ kcal/mol) to the reaction with the more polarizable CH_3S^- ($\Delta\Delta H^{\ddagger} = 1.8$ kcal/mol).

Another striking example of the role of the polarizability of the ring-leaving group bond is given by the comparison of reactivity of methoxide and benzenethiolate ions with 2-halobenzothiazoles.[12] In the reaction of otherwise unsubstituted 2-halobenzothiazoles, where the polarizability factor is relatively unimportant, methoxide ion is more reactive than PhS^-; the reverse is true in the reaction of 2-halo-6-nitrobenzothiazoles, where the polarizability of the Hal–C bond becomes stronger, owing to the conjugation with the nitro group.

Therefore, we suggest that the observed inversion of reactivity between the pyrrole and the benzene derivatives may be associated with the polarizability of the leaving groups on the different substrates. In the pyrrole derivative, as well as in the other five-membered heteroaromatic substrates, the bond between the reaction center and the nitro groups should be more polarizable than in 1,4-dinitrobenzene because of the possibility of an extended conjugation between the heteroatom and both nitro groups. The reaction of the benzene compound with the polarizable thiolate ion could not benefit from this possibility, thus becoming slower than the reaction of pyrrole compound **1**. However, at the moment, a detailed evaluation among the heteroaromatic substrates of the role of this factor, as compared to other important factors[1] (electronegativity of the heteroatom, aromaticity of the ring), is not yet feasible.

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Registry No.—Methanol, 67-56-1; *p*-toluenethiol, 106-45-6; 1-methyl-2-nitro-5-(*p*-tolylthio)pyrrole, 63059-30-3; 2-nitro-5-(*p*-tolylthio)furan, 63059-31-4; 2-nitro-5-(*p*-tolylthio)thiophene, 19991-81-2; 1-nitro-4-(*p*-tolylthio)benzene, 22865-48-1.

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Comparative Use of Benzhydrylamine and Chloromethylated Resins in Solid-Phase Synthesis of Carboxamide Terminal Peptides. Synthesis of Oxytocin Derivatives[1,2]

Victor J. Hruby,* Donald A. Upson, and Nirankar S. Agarwal

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

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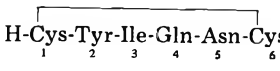
Specifically deuterated derivatives of the peptide hormone oxytocin were synthesized by the solid-phase method of peptide synthesis using either the standard chloromethylated resin or the benzhydrylamine resin as the support for the syntheses, and a comparison of the overall efficiency of the syntheses on the two resins was made. [1-Hemi-DL-[β,β-$^2H_2$]cystine]oxytocin was synthesized using the standard chloromethylated resin, and the two diastereomers were separated and purified by partition chromatography and gel filtration in an overall yield of about 30%. [1-Hemi-DL-[α-$^2H_1$]cystine]oxytocin was prepared using the benzhydrylamine resin to prepare the nonapeptide resin precursor, but otherwise using essentially identical conditions as used for the synthesis on the chloromethylated resin. Again the two diastereomers were separated and purified by partition chromatography and gel filtration. The overall yield of purified diastereomers under the best conditions was about 49%. For the synthesis of the latter compounds, *S*-3,4-dimethylbenzyl protecting groups were used to introduce the cysteine residues. The overall yields of the peptide hormone derivatives prepared on the benzhydrylamine resin were substantially improved if HF reactions were run at lower temperatures (0 °C rather than 25 °C), and if the *S*-3,4-dimethylbenzyl rather than the *S*-benzyl group was used for cysteine protection. Reproducible procedures for preparing benzhydrylamine resins with amino substitution levels of 0.15–0.45 mmol of amino group/g of resin were developed.

Since the introduction of the solid-phase synthesis of peptides by Merrifield,[3] the primary resin support has been chloromethylated polystyrene cross-linked with 1–2% divinylbenzene.[4,5] With this resin, the C-terminal amino acid is attached to the resin to afford a C-terminal resin benzyl ester. Subsequent synthesis of the remaining peptide chain is then accomplished with the resin benzyl ester serving as the C-terminal protecting group. This group is reasonably stable to the usual conditions of solid-phase peptide synthesis, but losses of 1–2% have been observed during each coupling procedure.[6,7] If a carboxamide C-terminal residue is desired, as is the case for many small biologically active peptides, it is generally necessary to first cleave the peptide from the resin as the protected carboxamide terminal derivative and then remove the other protecting groups. The former is usually done by treatment of the peptide resin with ammonia in an-

hydrous methanol[8] using the above resin or the corresponding nitrated resin,[9] or by transesterification followed by ammonolysis.[10] Displacement of the peptide from the resin is not always achieved[11] and even in favorable cases, the peptide is not quantitatively cleaved from the resin by ammonolysis. In addition, the methodology is generally not compatible with aspartic acid and glutamic acid containing peptides. To help circumvent some of these problems, Pietta and Marshall[12] and others[13,14] have used the benzhydrylamine resin for the preparation of carboxamide terminal peptides, and it has found considerable use in peptide synthesis.[4,5] Several alternative resins for solid-phase synthesis of carboxamide terminal peptides have appeared.[15-18] However, little has been done to evaluate the comparative merits of the benzhydrylamine resin or its optimum use in solid-phase peptide synthesis except for the work of Orlowski et al.,[15] using a *p*-methoxybenzhydrylamine resin to prepare di- and tripeptides. We report here the synthesis of derivatives of the nonapeptide hormone oxytocin,



which posseses a C-terminal glycinamide residue, using the benhydrylamine resin and the conventional chloromethylated resin, and compare the syntheses under a variety of conditions. We have found the benzhydrylamine resin more advantageous. In the course of these studies we have also prepared benzhydrylamine resins with reproducible levels of amino substitution, and synthesized a derivative of *S*-3,4-dimethylbenzyl-DL-[α-$^2H_1$]cysteine for use in the synthesis of the oxytocin derivatives on the benzhydrylamine resin.

The solid-phase synthesis on the chloromethylated resin was accomplished by standard procedures used in our laboratory to prepare oxytocin derivatives.[19,20] [1-Hemi-DL-[β,β-$^2H_2$]cystine]oxytocin was prepared, and the diastereomeric hormone derivatives were separated and purified[19,20] by partition chromatography,[21,22] followed by gel filtration chromatography on Sephadex G-25. The overall yield of purified oxytocin derivatives is 30% (see Experimental Section),[23] which is a typical yield obtained by this procedure in the synthesis of oxytocin and derivatives.[8,19,20]

For the solid-phase synthesis on the benzhydrylamine resin, polystyrene resin, 1% cross-linked with divinylbenzene, was converted to the benzhydrylamine resin by a slight modification of procedures previously reported.[14a] The polystyrene cross-linked resin was converted to a phenyl ketone resin, followed by reductive amination using ammonium formate at 150–160 °C for various lengths of time. A highly reproducible level of amino substitution on the resin could be obtained, with the substitution being 0.15 ± 0.02, 0.35 ± 0.04, and 0.45 ± 0.05 mmol of amine/g of resin after 20, 36, and 48 h, respectively. All of these resins retained excellent mechanical and swelling properties for peptide synthesis. In the syntheses of oxytocin derivatives reported here we have used a resin substituted at a level of 0.37 mmol of glycinamide/g of resin. In this way a direct comparison with the chloromethylated resin (in which the substitution level was 0.36 mmol of glycinate/g of resin—see Experimental Section) was made. Amino and peptide resins from the chloromethylated and benzhydrylamine resins showed similar structural and mechanical behavior throughout the syntheses.

For the synthesis on the benzhydrylamine resin, we chose the synthesis of [1-hemi-DL-[α-$^2H_1$]cystine]oxytocin, in which the diastereomeric derivatives were separated from one another and purified by partition chromatography on Sephadex G-25. This permitted a direct comparison of the use of the two different starting resins under essentially identical conditions of purification as well as peptide synthesis. The rationale for preparing partially deuterated peptide hormone derivatives and their uses in biochemical and biophysical studies have been discussed elsewhere.[19,24,25]

The first synthesis on the benzhydrylamine resin followed the same procedures as the synthesis on the chloromethylated resin, except that no benzyl protecting group was used on the hydroxyl group of tyrosine. Previous studies have shown that when peptides with *O*-benzyl protected tyrosine residues are treated with HF, an undesirable side reaction involving alkylation of the tyrosine aromatic nucleus obtains,[26] and we wished to avoid this in our syntheses. The protected specifically deuterated amino acid Boc-*S*-benzyl-DL-[α-$^2H_1$]cysteine[19] was used to introduce the *N*-terminal amino acid residue (see Experimental Section). The peptide resin Boc-DL-[α-$^2H_1$]Cys(Bzl)-Tyr-Ile-Gln-Asn-Cys(DMB)-Pro-Leu-Gly-NH-resin was treated with anhydrous HF containing 10% anisole at 20 °C for 1 h, and the residual *S*-benzyl protecting groups[27] were removed by treatment of the peptide material obtained from the HF treatment with sodium in anhydrous liquid ammonia.[28] The peptide was oxidized with 0.01 N $K_3Fe(CN)_6$[29] under nitrogen.[30] The isomers were separated from each other and from by-products by partition chromatography on Sephadex G-25, followed by gel filtration of the separated diastereomers on Sephadex G-25.[31] The overall yield of purified peptides was 29%, which was essentially the same as was obtained using the chloromethylated resin.

The need to utilize two separate reaction steps to completely remove the *S*-benzyl protecting group led us to investigate the use of the 3,4-dimethylbenzyl group for sulfhydryl protection, since previous studies had shown that the group was completely removed by treatment with HF.[32,33] Again we synthesized [1-hemi-DL-[α-$^2H_1$]cystine]oxytocin and separated and purified the diastereomers. The synthesis of the desired peptide precursor on the benzhydrylamine resin followed the same procedures as before, except that a *S*-3,4-dimethylbenzyl derivative of the specifically deuterated amino acid DL-[α-$^2H_1$]cysteine was prepared and used to incorporate the cysteine residue at position 1 (see Experimental Section).

The protected peptide resin Boc-DL-[α-$^2H_1$]Cys(DMB)-Tyr-Ile-Gln-Asn-Cys(DMB)-Pro-Leu-Gly-NH-resin was treated with HF containing 10% anisole at 0 °C for 60 min. After the usual workup, oxidation, and purification the purified diastereomeric hormone derivatives [1-hemi-L-[α-$^2H_1$]cystine]oxytocin and [1-hemi-D-[α-$^2H_1$]cystine]oxytocin were obtained in an overall yield of 49%. On the other hand, a similar cleavage run at 25 °C in HF for 1 h gave only a 26% overall yield of the two purified diastereomeric peptides and large amounts of by-products.

The hormone derivatives from the various syntheses were assessed for purity and found to be pure by several criteria, including single spots and identical behavior with authentic oxytocin or [1-hemi-D-cystine]oxytocin on TLC using at least three different solvent systems, amino acid analysis, optical rotation, carbon-13 and proton NMR, and by their milk-ejecting activities.[34]

These comparative studies of solid-phase synthesis of oxytocin derivatives using chloromethylated and benzhydrylamine resin suggest that somewhat greater overall yields of oxytocin derivatives (from starting Gly resins to purified peptide hormone derivatives) can be obtained on benzhydrylamine resins than on chloromethylated resins. Under the best synthetic and cleavage conditions for using the benzhydrylamine resin (HF at 0 °C for 60 min, *S*-3,4-dimethylbenzyl protecting groups) our overall yield of purified hormone derivatives was 49%. Very similar yields in the synthesis of oxytocin (55%) have also been obtained on benzhydrylamine resins by Live, Agosta, and Cowburn[35] using similar procedures to those reported here. The overall yields (glycine-

substituted resin to final purified oxytocin derivatives) on chloromethylated resins as reported here (see Experimental Section) and elsewhere[8,19,20] are generally about 30%.

However, it must be pointed out that if the HF cleavage of the protected peptide–benzhydrylamine resin is run at 25 °C rather than 0 °C, or *S*-benzyl groups are used rather than *S*-3,4-dimethylbenzyl groups, the overall yields of pure oxytocin derivatives (26 and 29%, respectively) are about the same as obtained on the chloromethylated resin. Hence, proper choice of HF cleavage conditions and protecting groups are crucial to obtaining any advantages for the benzhydrylamine resin. The exact nature of the side reactions responsible for the decrease in yields in running the HF reaction at 25 °C rather than 0 °C (both reactions were run with the same precursor peptide resin) was not determined, though it undoubtedly involved reactions at the sulfur atom(s) of the cysteine residue(s). This was indicated by the large increase in dimeric and other high molecular weight products observed under the latter condition, and the large decrease in half-cystine content in these side products on amino acid analysis (see Experimental Section).

We have used the Leuckart reductive amination procedure in the preparation of the benzhydrylamine resin, which Orlowski et al.[15] have shown to be the preferred method of synthesis, since it leads to little or no undesirable secondary amine formation. We obtained an overall yield of about ≤9% of the purified oxytocin derivates (an octa- or nonapeptide), which compares well with the overall yields of 65 and 75% for two purified tripeptides which Orlowski et al.[15] obtained using the *p*-methoxybenzhydrylamine resin. Since the length and the properties of the peptides are quite different, it is difficult to compare the relative merits of the two resins. However, the results obtained do suggest that the benzhydrylamine resin (and/or its substituted derivatives) is particularly attractive for the syntheses of carboxamide terminal peptides containing specifically labeled derivatives, such as the ^{2}H compounds reported here, and those containing ^{14}C, ^{3}H, ^{13}C, ^{15}N, ^{125}I, and other labels which are of increasing importance in studies of peptide hormone structure and function, and which often must be incorporated using very precious and expensive amino acid derivatives.

Experimental Section

Thin layer chromatography (TLC) was done on silica gel G glass plates using the following solvent systems: (A) 1-butanol–acetic acid–water (4:1:5, upper phase only); (B) 1-butanol–acetic acid–pyridine–water (15:3:10:12); (C) 1-pentanol–pyridine–water (7:7:6). The peptides were detected on the TLC plates using ultraviolet light, iodine vapors, ninhydrin, and fluorescamine. Capillary melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian T-60 spectrometer or a Bruker WH-90 FT spectrometer. Optical rotation values were measured at the mercury green line (547 nm) using a Zeiss Old 4 polarimeter. Elemental analyses were performed by Spang Microanalytical Laboratory. Amino acid analyses were obtained by the method of Spackman, Stein, and Moore[36] on a Beckman 120C amino acid analyzer after hydrolysis in 6 N HCl for 22–24 h at 110 °C. Partition chromatography purification and separation of oxytocin diastereomers was accomplished on Sephadex G-25 (block polymerizate).[20–22] Following partition chromatography, detection of peptides in eluents was made using UV spectroscopy (280 or 260 nm) or by the Folin–Lowry method.[37] The desired peptides were isolated by addition of deionized water to the organic solvents, followed by rotary evaporation in vacuo at 25–30 °C and lyophilization of the aqueous solution.

Solid-Phase Peptide Synthesis Procedures. Solid-phase peptide syntheses were done using either the Merrifield resin of chloromethylated polystyrene beads cross-linked with 1% divinylbenzene substituted with Boc-glycine[4] or using the benzhydrylamine resin substituted with Boc-glycine (vide infra). The *tert*-butyloxycarbonyl (Boc) group was used for protection of a α-amino groups of amino acids. Protection of side-chain functional groups was *O*-benzyl or no hydroxyl protection for Tyr, and *S*-benzyl (Bzl) or *S*-3,4-dimethylbenzyl (DMB) for cysteine. All protected amino acids were monitored for purity by TLC in at least three solvent systems and by mixed melting points. Asparagine and glutamine were coupled with a four-fold excess of the protected amino acid *p*-nitrophenyl ester and 1-hydroxybenzotriazole as catalyst.[19] In general, *two* coupling steps were used for dicyclohexylcarbodiimide (DCC) mediated coupling of the protected amino acid in methylene chloride (CH_2Cl_2) using a 1.5–3 molar excess of the protected amino acid and a 1.2–2.4 molar excess of DCC in each coupling step. Coupling times generally were for 30 min. A typical synthesis program for coupling an amino acid residue to the growing peptide chain was as previously detailed.[19] All coupling steps were monitored by the ninhydrin method[38] to ensure complete coupling, and coupling reactions were repeated if a positive test (<99% coupling) was indicated.

3,4-Dimethylbenzyl Mercaptan (2). The general procedure of Urquhart et al.[39] for preparing alkyl mercaptans was used. From 30.93 g (0.2 mol) of 3,4-dimethylbenzyl chloride (**1**) and 15.2 g (0.2 mol) of thiourea, 24.9 g (82%) of the title compound was obtained: bp 94 °C (7 mm) [lit.[40] bp 112 °C (14 mm)]; NMR (neat) δ 1.35 (t, 1 H), 1.80 (s, 6 H), 3.20 and 3.22 (d of d, 2 H), 6.62 (s, 3 H).

***S*-3,4-Dimethylbenzyl-DL-[α-$^{2}H_1$]cysteine (5).** The title compound was prepared by a slight modification of published methods.[19,41,42] From 3.04 g (20 mmol) of 3,4-dimethylbenzyl mercaptan (**2**) and 8.37 g (21 mmol) of diethyl α-acetamido-α-dimethylaminomethylmalonate methiodide in 75 mL of ethanol-*d*, 2.64 g (73%) of the title compound was obtained: mp 202–203 °C (lit. mp for protio compound, 184–186 °C;[33] 195–197 °C[32]); TLC in solvent systems A and B gave single spots identical to authentic *S*-3,4-dimethylbenzyl-L-cysteine; NMR (CD_3CO_2D) δ 2.25 (s, 6 H), 3.10 (s, br, 2 H), 3.75 (s, br, 2 H), 4.3–4.7 (α-CH, undetectable), 7.05 (s, 1.2 H—an exchange of about two deuterium atoms into aromatic ring has occurred).

Anal. Calcd for $C_{12}H_{14}D_3NO_2S$: C, 59.48; H, 8.17; N, 5.78. Found: C, 59.15; H, 7.89; N, 6.16.

***N*-Boc-*S*-3,4-Dimethylbenzyl-DL-[α-$^{2}H_1$]cysteine.** The title compound was prepared by the procedure of Schnabel.[43] Treatment of 2.0 g of **5** gave 2.02 g (72%) of the title compound, mp 120.5–121.5 °C. Single uniform spots were obtained on TLC using systems A and B with R_f values identical with those of the L-protio analogue: NMR ($CDCl_3$) δ 1.45 (s, 9 H), 2.20 (s, 6 H), 2.8–2.9 (br s, 2 H), 3.65–3.75 (br s, 2 H), 4.40–4.60 (α-CH undetectable), 7.0 (s, 1.2 H), 11.1 (s, 1 H).

Synthesis of Benzhydrylamine Resin. A highly reproducible synthesis of benzhydrylamine resin[12–14] has been obtained as outlined below. The copolystyrene–1% divinylbenzene phenyl ketone resin was prepared as previously outlined,[14a] except that more extensive washings were performed using EtOH and 50% aqueous EtOH. From 30 g of polystyrene resin cross-linked with 1% divinylbenzene (Biobeads S-X1, 200–400 mesh) there was obtained 33.7 g of pale cream colored phenyl ketone resin, IR (KBr pellet) 1660 cm^{-1}.

The Leuckart reaction was run under similar conditions to those previously reported.[14a] The reactions were run with 5-g portions of the ketone resin for 20, 36, or 48 h at 150–160 °C (oil bath temperature, 170–180 °C). The mixture was cooled and the resin filtered off and washed with four 50-mL portions of H_2O, CH_3OH, and CH_2Cl_2. The resin was dried in vacuo and then hydrolyzed with 80 mL of 12 N HCl in propanoic acid (1:1) at reflux for 5 h. The resin salt was filtered off, washed with four 50-mL portions of H_2O, 50% aqueous EtOH, EtOH, and CH_2Cl_2, and then neutralized with two 50-mL portions of 10% diisopropylethylamine in CH_2Cl_2. After washing thoroughly with CH_2Cl_2 the resin was dried in vacuo, yield ~4.7 g.

In several separate preparations, the degree of amino substitution was found to be reasonably constant by the preceding procedures, being 0.15 ± 0.02 mmol/g of resin after 20 h of reductive amination, 0.35 ± 0.04 mmol/g of resin after 36 h, and 0.45 ± 0.05 mmol/g of resin after 48 h. The degree of substitution was determined by a direct aldimine test[39,40] and by substitution with a Boc amino acid (Gly or Val) to completion (negative ninhydrin test[37]), and then removing the Boc protecting group and measuring the amino acid substitution by the modified[44] aldimine test,[45] or by amino acid analysis.

Solid-Phase Synthesis of [1-Hemi-DL-[β,β-$^{2}H_2$]cystine]oxytocin Using Chloromethylated Resin and Separation of the Diastereomers. The synthesis of the protected nonapeptide precursor to the title compound was accomplished as previously reported.[19] Starting with 3.4 g of Boc-glycine-*O*-resin with a substitution of 0.36 mmol/g of resin (1.23-mmol scale) there was obtained 1.4 g (89%) of crude H-DL-[β,β-$^{2}H_2$]Cys(Bzl)-Tyr(Bzl)-Ile-Gln-Asn-Cys(DMB)-Pro-Leu-Gly-NH_2, mp 220–225 °C. A 325-mg portion of the nonapeptide (0.25 mmol) was deprotected and purified as described previously.[19] The all-L diastereomer (R_f 0.23) [1-hemi-[β,β-$^{2}H_2$]cystine]oxytocin was obtained as a white powder (40 mg, 32%) after gel filtration on Sephadex G-25, $[\alpha]^{22}_{547}$ −22° (c 0.5, 1 N HOAc). Amino

acid analysis: Asp, 1.0; Gly, 1.0; Pro, 0.92; Gly, 1.0; Half-Cys, 2.0; Ile, 1.0; Leu, 1.0; Tyr, 1.0. On TLC a single uniform spot identical with authentic oxytocin was seen in solvent systems A, B, and C. The compound had identical carbon-13 and proton NMR spectral and milk-ejecting[34] activities as previously reported. The diastereomer [1-hemi-D-[β,β-$^2H_2$]cystine]oxytocin (R_f 0.32) was obtained as a white powder (36 mg, 29%) after gel filtration on Sephadex G-25, $[\alpha]^{22}_{547}$ −69° (c 0.5, 1 N HOAc). Amino acid analysis: Asp, 1.0; Glu, 1.0; Pro, 1.0; Gly, 1.0; Half-Cys, 2.0; Ile, 1.0; Leu, 1.0; Tyr, 0.90. On TLC a single uniform spot identical with authentic [1-hemi-D-cystine]oxytocin was seen using solvent systems A, B, and C. The compound had identical milk-ejecting activity[34] and ^{13}C NMR spectra as previously reported. The combined yield of the diastereomers based on starting glycine substituted resin is 29%.

Boc-Glycine–Benzhydrylamine Resin. Benzhydrylamine resin (36 h, 0.38 mmol of amino group/g of resin), prepared as discussed above (8.0 g), was treated with CH_2Cl_2 to swell the resin and filtered. The resin was stirred with 1.39 g (7.9 mmol) of Boc-glycine and 1.63 g (7.9 mmol) of DCC in 70 mL of methylene chloride for 30 min, and then filtered. The resin was washed with three 30-mL portions of CH_2Cl_2, EtOH, and CH_2Cl_2 and gave a negative ninhydrin test.[38] After removal of the Boc protecting group and neutralization, the modified aldimine test established the glycine substitution level to be 0.37 mmol/g of resin.

Synthesis of Boc-DL-[α-$^2H_1$]Cys(DMB)-Tyr-Ile-Gln-Asn-Cys(DMB)-Pro-Leu-Gly-NH-resin. The title compound was synthesized using 2.7 g (1.0 mmol) of the above benzhydrylamine resin and the standard solid-phase methodology. The title compound was obtained as 3.9 g of a pale cream resin.

Synthesis of [1-Hemi-DL-[α-$^2H_1$]cystine]oxytocin Using the *S*-3,4-Dimethylbenzyl Protecting Group and Separation of the Diastereomers. HF Treatment at 0 °C. A 0.98-g portion (0.25 mmol) of the protected peptide resin from above was treated with 20 mL of anhydrous HF (freshly distilled from CoF_3) and 2 mL of anisole at 0 °C for 1 h. The solvents were removed in vacuo at 0 °C. Under nitrogen, the residue was washed with four 30-mL portions of ethyl acetate, and the peptide was extracted from the resin with 10 mL of HOAc, two 20-mL portions of 30% HOAc, and three 30-mL portions of 0.2 N HOAc. The combined extracts were concentrated to about 80 mL in vacuo by rotary evaporation and lyophilized. The white powder (280 mg) was dissolved in 600 mL of 0.1% aqueous acetic acid under nitrogen,[30] oxidized in the usual manner,[29] and the products were separated and purified by partition chromatography on Sephadex G-25 using the solvent system 1-butanol–3.5% aqueous HOAc in 1.5% pyridine (1:1). Analysis of the fractions at 280 nm on a Gilford spectrophotometer showed a small by-product peak at R_f 0.6 (yield 25 mg) and well-resolved peaks for [1-hemi-D-[α-$^2H_1$]cystine]oxytocin (R_f 0.33) and [1-hemi-L-[α-$^2H_1$]cystine]oxytocin (R_f 0.23). The fractions corresponding to each diastereomer were separately pooled and lyophilized, and then each was separately purified by gel filtration chromatography on Sephadex G-25. There was obtained 68 mg (54%) of [1-hemi-[α-$^2H_1$]cystine]oxytocin, $[\alpha]^{24}_{547}$ −21° (c 0.498, 1 N HOAc). TLC in solvent systems A, B, and C gave single uniform spots identical with authentic oxytocin. Amino acid analysis: Asp, 1.0; Glu, 1.0; Pro, 1.0; Gly, 1.0; Half-Cys, 2.0; Ile, 1.0; Leu, 1.0; Tyr, 0.90. The carbon-13 NMR spectrum was identical with that of authentic oxytocin except for the peak corresponding to the C-2 carbon of the half-cystine-1 residue, which was greatly reduced in intensity. The milk-ejecting activity was determined and found to be 480 ± 55 units/mg, identical with authentic oxytocin. Also obtained was 54 mg (43%; the overall combined yield of purified oxytocin derivatives was 49%) of [1-hemi-D-[α-$^2H_1$]cystine]oxytocin, $[\alpha]^{24}_{547}$ −62° (c 0.504, 1 N HOAc). TLC in solvent systems A, B, and C gave single uniform spots, identical with authentic [1-hemi-D-cystine]oxytocin. Amino acid analysis: Asp, 1.0; Glu, 1.0; Pro, 1.0; Gly, 1.0; Half-Cys, 2.0; Ile, 0.93; Leu, 1.0; Tyr, 0.90. The milk-ejecting activity[34] was 35 ± 10 units/mg, identical with other 1-hemi-D-cystine derivatives.[19] Anal. Calcd for $C_{43}H_{65}DN_{12}O_{12}S_2 \cdot CH_3CO_2H$: C, 50.7; H, 6.39; N, 15.3 Found: C, 50.8; H, 6.37; N, 16.2. The entire procedure was repeated with essentially identical results (48% overall yield).

HF Treatment at 25 °C. A 0.98-g portion (0.25 mmol) of the protected peptide resin 1 was treated with 20 mL of anhydrous HF (freshly distilled from CoF_3) and 2 mL of anisole at room temperature (25 °C) for 1 h. The peptide material was extracted, oxidized, and purified by partition chromatography as before. Folin–Lowry analysis of the fractions indicated that a very large component was the by-product peak at R_f 0.60 (yield 72.3 mg) and the poorly resolved diastereomers [1-hemi-D-[α-$^2H_1$]cystine]oxytocin and [1-hemi-[α-$^2H_1$]cystine]oxytocin. The polymer peak gave the following amino acid analysis: Asp, 1.0; Glu, 0.9; Pro, 1.1; Gly, 1.0; Half-Cys, 1.0; Ile, 0.9; Leu, 1.1; Tyr, 0.8; NH_3, 3.1. TLC analysis indicated several components were present. The combined diastereomer peak (145 mg) was resubjected to partition chromatography, and an excellent separation of the diastereomers was obtained with [1-hemi-D-[α-$^2H_1$]cystine]-oxytocin (44 mg) at R_f 0.33 and [1-hemi-L-[α-$^2H_1$]cystine]oxytocin (61 mg) at R_f 0.22. Gel filtration of the 1-hemi-D-cystine diastereomer on Sephadex G-25 gave 26.1 mg (21%) of the pure derivative with a small broad peak of higher molecular weight material preceding it. Gel filtration of the all-L diastereomer on Sephadex G-25 gave 37.6 mg (30%; the overall yield of the two diastereomers was 25.5%) of the pure diastereomer and a significant amount of a broad peak of higher molecular weight material (yield 15.3 mg). Amino acid analysis of the latter peak gave: Asp, 1.0; Glu, 1.0; Pro, 1.1; Gly, 1.0; Half-Cys, 1.6; Ile, 1.0; Leu, 1.2; Tyr, 0.9; NH_3, 3.2. Both of the purified oxytocin diastereomers had identical properties with those prepared above as determined by TLC in solvent systems A, B, and C, amino acid analysis, optical rotation, carbon-13 NMR spectroscopy, and milk-ejecting activity. The procedure was repeated with about the same results (overall yield of 24%).

Synthesis of [1-Hemi-DL-[α-$^2H_1$]cystine]oxytocin on Benzhydrylamine Resin Using the *S*-Benzyl Protecting Group. The synthesis of the protected nonapeptide resin to the title compound was as before using 4.03 g (1.49 mmol) of Boc-Gly-NH resin, except that Boc-*S*-3,4-dimethylbenzylcysteine[19,32,33] was used to introduce the cysteine-6 residue and Boc-*S*-benzyl-DL-[α-$^2H_1$]cysteine[19] was used to introduce the cysteine-1 residue (1.1 and 0.5 equiv at the two coupling steps) to give 6.07 g of Boc-DL-[α-$^2H_1$]Cys(Bzl)-Tyr-Ile-Gln-Asn-Cys(DMB)-Pro-Leu-Gly-NH-resin. A 1.06-g (0.25 mmol) portion of the resin was treated with 20 mL of anhydrous HF and 2 mL of anisole at 20 °C for 1 h, and the crude lyophilized peptide product was obtained as before (334 mg). To remove the remaining *S*-benzyl protecting groups, the crude product was dissolved in 150 mL of anhydrous ammonia (freshly distilled from sodium) and treated with sodium until a blue color persisted for 45 s. The solvents were removed by evaporating under nitrogen and lyophilization. The residue was oxidized and the diastereomers were separated and purified as before to give 34 mg (27%) of [1-hemi-[α-$^2H_1$]cystine]oxytocin, $[\alpha]^{22}_{547}$ −22° (c 0.5, 1 N HOAc). TLC on silica gel plates gave single uniform spots in solvent systems A, B, and C, identical with the compounds as previously prepared. Amino acid analysis: Asp, 1.0; Glu, 1.1; Pro, 0.94; Gly, 1.0; Half-Cys, 1.9; Ile, 1.0; Leu, 1.0; Tyr, 1.0. Also obtained was 39 mg (31%; overall yield of both purified oxytocin derivatives 29%) of [1-hemi-D-[α-$^2H_1$]cystine]oxytocin, $[\alpha]^{22}_{547}$ −63° (c 0.5, 1 N HOAc). TLC on silica gel plates gave single uniform spots in solvent systems A, B, and C identical with the compound as previously prepared. Amino acid analysis: Asp, 1.0; Glu, 1.0; Pro, 1.0; Gly, 1.0; Half-Cys, 2.0; Ile, 0.93; Leu, 1.0; and Tyr, 0.90.

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Registry No.—1, 102-46-5; 2, 4496-95-1; 5, 63527-92-4; thiourea, 62-56-6; diethyl 2-acetamido-α-dimethylaminomethylmalonate methiodide, 7689-61-4; *N*-Boc-*S*-3,4-dimethylbenzyl-DL-[α-$^2H_1$]-cysteine, 63527-93-5; [1-hemi-DL-[β,β-$^2H_2$]cystine]oxytocin, 57866-62-3; H-DL-[β,β-$^2H_2$]Cys(Bzl)-Tyr(Bzl)-Ile-Gln-Asn-Cys-(DMB)-Pro-Leu-Gly-NH_2, 63527-94-6; 1-hemi[β,β-$^2H_2$]cystine]-oxytocin, 57866-63-4; [1-hemi-D-[β,β-$^2H_2$]cystine]oxytocin, 57866-64-5; [1-hemi-DL-[α-$^2H_1$]cystine]oxytocin, 63527-95-7; [1-hemi-L-[α-$^2H_1$]cystine]oxytocin, 63527-96-8; [1-hemi-D-[α-$^2H_1$]cystine]-oxytocin, 63527-97-9; Boc-*S*-3,4-dimethylbenzylcysteine, 41117-66-2; Boc-*S*-benzyl-DL-[α-$^2H_1$]cysteine, 57866-75-8.

References and Notes

(1) Financial support from the U.S. Public Health Service and the National Science Foundation is gratefully acknowledged. Taken in part from the Ph.D. Thesis of Donald A. Upson, University of Arizona, 1975.
(2) All amino acids except glycine are of the L configuration unless otherwise noted. Standard abbreviations for amino acids, protecting groups, and peptides as recommended by the IUPAC–IUB Commission on Biochemical Nomenclature [*J. Biol. Chem.*, **247**, 977 (1972)] are used. Other abbreviations include DCC, dicyclohexylcarbodiimide; DIEA, diisopropylethylamine; TFA, trifluoroacetic acid; DMB, 3,4-dimethylbenzyl.
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A Rapid, Efficient Synthesis of Oxytocin and 8-Arginine-vasopressin. Comparison of Benzyl, *p*-Methoxybenzyl, and *p*-Methylbenzyl as Protecting Groups for Cysteine

David H. Live, William C. Agosta, and David Cowburn*

The Rockefeller University, New York, New York 10021

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Oxytocin and 8-arginine-vasopressin have been synthesized in high yields in a short time using 1.5-fold molar excesses of protected amino acids by means of solid-phase synthesis on a benzhydrylamine resin. Coupling of each residue to the peptide resin was measured by automated picrate monitoring. High-pressure liquid partition chromatography was found to be extremely useful in characterizing products and by-products. Benzyl, *p*-methoxybenzyl, and *p*-methylbenzyl were compared as cysteine protecting groups in the syntheses, with the last two being preferred.

Introduction and Strategy

The neurohypophyseal hormones and their synthetic analogues have been the subject of many studies aimed at elucidating their physiological properties and the correlation between their structures and functions,[1] with oxytocin (I, Figure 1) receiving particular attention in these investigations. We are presently concerned with developing an approach to the unequivocal determination of the conformations and dynamic properties of peptides in solution, principally concentrating our investigations on oxytocin. The technique which we are employing in these investigations is nuclear magnetic resonance (NMR), measuring three-bond homo- and heteronuclear coupling constants from which dihedral angles and their rotational isomerism can be deduced. To extract such data from the spectra, a variety of isotopic isomers is needed. Selective deuteration is required to simplify overlap and coupling in the proton NMR spectra, and selective enrichments in ^{13}C and ^{15}N facilitate the observation of couplings to these less abundant nuclei.[2] Because of the number of isomers needed for a complete study and the expense of enriched precursors, we have undertaken development of methods for the rapid and efficient synthesis of oxytocin. Our strategy for these studies is to synthesize a number of isomers of oxytocin with simultaneous isotopic enrichments in several of the residues. Our synthetic goal is a generally optimized procedure using all the amino acid reagents with maximum

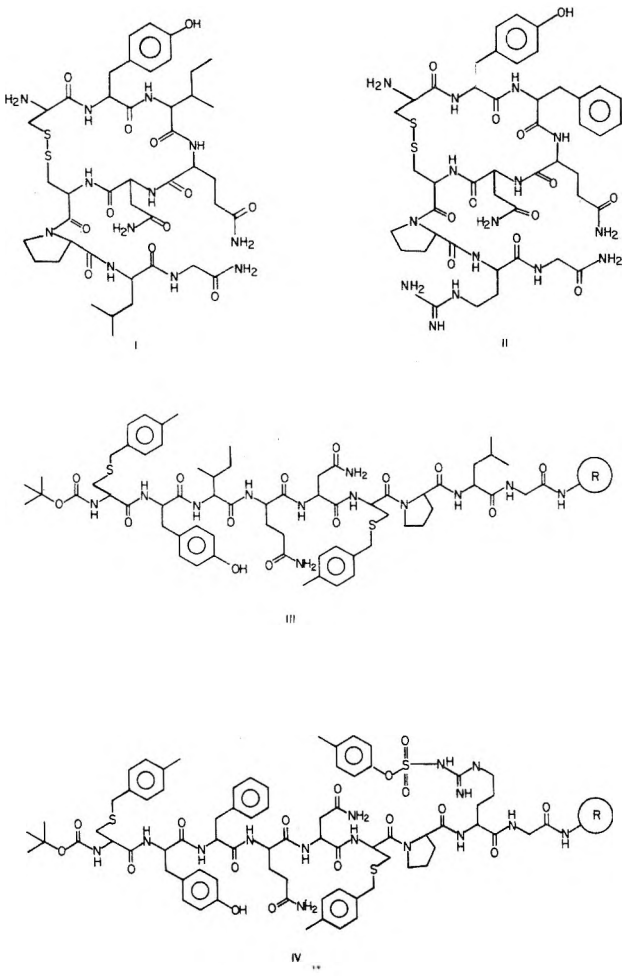

Figure 1. Structures of compounds described.

efficiency, while providing the greatest yield of final product.

Comparisons of previous synthetic routes to oxytocin and some of its analogues can be made on the basis of reported results. Solution peptide synthesis methods and solid-phase methods using chloromethylated resin have given comparable efficiencies on the basis of the quantities of individual amino acid reagents consumed.[3] A comparison of solid-phase syntheses of an oxytocin analogue with benzhydrylamine and with chloromethyl resins indicates that the former resin gave superior results. Treatment of the protected peptide–benzhydrylamine resin with anhydrous hydrogen fluoride yields the desired peptide amide directly,[4] saving time and avoiding losses that might be incurred in the conversion of the terminal carboxyl group to the desired carboxamide, as would be necessary subsequent to cleavage from chloromethyl resin. We have chosen the solid-phase method with benzhydrylamine resin, since it is less time consuming than the other alternatives and should provide a greater yield. A significant additional advantage of the solid-phase approach is the availability of a quantitative nondestructive procedure using picric acid, by which the extent of coupling can be easily monitored spectrophotometrically.[5] This has allowed us to optimize coupling conditions with reasonable effort.

Since several of the amino acids in oxytocin are trifunctional (Cys^1, Tyr^2, Gln^4, Asn^5, Cys^6), it is necessary to consider the effect of protecting groups on the yield of the synthesis. The advantages of side-chain protection in the overall synthesis of the peptide must be balanced against any losses that arise in the derivatization of an isotopically enriched amino acid. Asparagine and glutamine protected at the α-amino group with *tert*-butoxycarbonyl (Boc) and without side-chain protection can be coupled effectively during solid-phase synthesis of an analogous peptide in dimethylformamide (DMF) using dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole monohydrate (HOBzt).[3] Deprotection of protected tyrosine at the conclusion of a synthesis can lead to side reactions,[6] but tyrosine can be used without protecting the phenolic hydroxyl group, particularly in the synthesis of oxytocin, where it is the penultimate residue incorporated.[7] Since isotopic isomers of these three amino acids can be readily synthesized in an unprotected form,[8] we decided to employ them with only α-amino protection in the peptide synthesis.

Cysteine is the only amino acid for which side-chain protection is absolutely necessary in this synthesis. Benzyl (Bzl) and *p*-methoxybenzyl (*p*-MeOBzl) are the sulfhydryl protecting groups most commonly used for this purpose. The more stable benzyl group, though often used in amino acid and peptide synthesis, requires rather vigorous conditions for removal.[9] In our hands these conditions reduced the yield of oxytocin by a factor of 2 compared to that achieved using *p*-MeOBzl protection. However, the *p*-MeOBzl protecting group could not be used successfully in the routes we employed for synthesis of isotopic isomers of cysteine,[8] and conversion from one protecting group to the other after completion of the amino acid synthesis is only about 70% efficient. The *p*-methylbenzyl (*p*-MeBzl) group has been suggested for use in peptide synthesis because it may be removed in hydrogen fluoride under milder conditions.[6] In addition, it has been found to be a good protecting group to use in amino acid synthesis as well.[8] We chose to use the *p*-MeBzl group and found the results of the peptide synthesis to be comparable to those obtained with *p*-MeOBzl protection.

After some investigation we devised a peptide synthetic scheme in which 1.5-fold excesses of amino acid reagents are employed in single couplings for Gly^9, Leu^8, Pro^7, Cys^6, Tyr^2, and Cys^1, and two such couplings are employed for Asn^5, Gln^4, and Ile^3. The only side-chain protection used is the *p*-MeBzl group on both half-cystyl residues. Though the nature and origin of the synthetic by-products are unclear, an important feature of this synthesis is that they are easily separated from the desired product in a single gel filtration, which also serves the purpose of desalting the final products. The overall procedure from the start of the solid-phase synthesis to recovery of chemically pure, fully active product in 55% yield (relative to glycine substitution on the resin) can be carried out in four working days. The final product was characterized by bioassay, amino acid analysis, counter-current distribution, high-pressure liquid chromatography, high-resolution proton NMR, thin-layer chromatography, and optical rotation.

This synthesis of oxytocin has given reproducible results a number of times using labeled and unlabeled precursors. We wished to determine whether the considerations we had applied to increasing efficiency here were readily applicable to the synthesis of another peptide. Therefore, 8-arginine-vasopressin (AVP, II) was prepared in the same manner as oxytocin with minimal changes in procedure. We used tosyl protection for the guanidino group of arginine in addition to *p*-MeBzl on the half-cystyls. From the picrate monitoring data, it appears that satisfactory results are obtained with single 1.5-fold excess couplings for all but Asn^5, Gln^4, and Tyr^2. The final purification of AVP from this synthesis is as easy as that of oxytocin.

Experimental Section

Materials. N^{α}-*tert*-butoxycarbonyl-L-amino acids were obtained from Beckman, Bachem, and Chemical Dynamics Corp., except for Boc-*S*-*p*-methylbenzylcysteine, which was made at The Rockefeller University by Dr. Wesley Cosand. All were checked for purity by

thin-layer chromatography (TLC) (see Analytical Methods). All amino acids (except glycine) were of the L configuration. Methylene chloride (technical, Eastman) was distilled from Na_2CO_3 (anhydrous reagent, Baker). Dimethylformamide (DMF) (spectroquality, MCB) was stored over molecular sieves (4A, Chemical Dynamics) and tested for amines before use in synthesis.[10] Diisopropylethylamine (DIEA) (Aldrich) was distilled after reflux overnight with CaH_2. 1-Butanol (reagent, Baker), acetone (reagent, Baker), and trifluoroacetic acid (TFA) (Halocarbon) were distilled before use. Picric acid (0.1 M) solutions were made up by dissolving picric acid (reagent, MCB) in distilled CH_2Cl_2, stirring with anhydrous Na_2SO_4, and filtering before use.

The following reagents were of reagent grade, if more than one grade was available, and were used as received: acetic acid (Baker); isopropyl alcohol (Baker); ethyl acetate (Baker); dicylohexylcarbodiimide (DCC) (Pierce); 1-hydroxybenzotriazole monohydrate (Aldrich); Sephadex G-15 dextran gel (Pharmacia); ethanol (IMC Chemical Group); fluorescamine (Hoffmann-La Roche); and anhydrous HF (Matheson).

Analytical Methods. Final characterization of oxytocin and AVP was carried out using bioassay, amino acid analysis, counter-current distribution, high-resolution proton NMR, high-pressure liquid chromatography in a system known to resolve oxytocin from 14 replacement and deletion analogues, TLC in three systems, and optical rotation. TLC of peptides was carried out on analytical silica gel G plates (Analtech) with the following solvent systems: (A) 1-butanol–acetic acid–water (4:1:5, upper phase); (B) 1-butanol–acetic acid–pyridine–water (15:3:10:12); (C) ethyl acetate–pyridine–acetic acid–water (5:5:1:3). Material on the plates was visualized by ninhydrin or chlorine–*o*-toluidine reaction. TLC of amino acids was performed on similar plates with chloroform–methanol–acetic acid (85:10:5). Counter-current distribution (CCD), both analytical and preparative, was carried out on a 100-tube CCD apparatus (Post Scientific) with 10 mL of each phase per tube. The solvent system used was 1-butanol–ethanol–0.5% acetic acid in water (4:1:5).[11]

High-pressure liquid chromatography (HPLC) was based on the system of Gruber et al.[12] The equipment we used consisted of a glass linear-gradient maker, a high-pressure pump (Milton Roy), a high-pressure injection valve (Waters), a Partisil-10 ODS prepacked column 0.4 × 25 cm (Whatman), a Spectro/Glo fluorometer (Gilson), and a strip chart recorder (Easterline Angus). A 15–95% acetone–water gradient was run for 75 min at a rate of 0.8 mL/min. Samples were prepared by dissolving them in 0.4 mL of 0.046 M sodium phosphate, pH 7, in a disposable borosilicate test tube, and then adding 0.2 mL of fluorescamine solution (20 mg/100 mL of acetone) with Vortex mixing. A pH 7 standard buffer (Beckman) was found to be a convenient source of the 0.046 M sodium phosphate. After 10 min the sample was diluted up to volume with a solution of 0.03% ammonium formate and 0.01% thiodiglycol. Amino acid analyses were carried out after the procedure of Spackman, Stein, and Moore[13] on a Beckman model MS amino acid analyzer using a 0.9 × 30 cm column of Durrum DC-6A resin. The analyzer had been modified to perform automatically the two buffer changes that are required for a single-column analysis. The Durrum pico-buffer system II was employed. Hydrolysis was carried out in culture tubes, with teflon-lined caps, that were inserted into a heating block. Peptide samples were hydrolyzed in 12 M HCl–acetic acid–liquified phenol[14] (2:1:1) or in 6 M HCl. The latter conditions were used after performic acid treatment of the peptide for conversion of cysteine to cysteic acid.[15] Hydrolyses were carried out for 24 h at 110 °C. When the first conditions were used, the hydrolysate was extracted three times with $CHCl_3$ before drying and then diluted in 0.2 M pH 2.2 citrate buffer for application to the column. In the second case the hydrolysate was dried directly and diluted similarly.

Peptide resin hydrolysis was carried out by two procedures. Either the 12 M HCl–acetic acid–liquified phenol (2:1:1) method described above was used, with the addition that the hydrolysate was filtered before extraction, and the resin was washed with several small portions of 1 M HCl, or 12 M HCl–propionic acid (1:1) at 135 °C for 12 h was used.[16] These latter samples were filtered, and the resin was washed with 1 M HCl as above before drying and subsequent dilution.

Proton NMR spectra were obtained on a Varian HR/NTC TT-220 spectrometer. Optical rotations were measured on a Cary 60 spectropolarimeter, using sucrose as a standard.

***tert*-Boc-*S*-*p*-MeBzl-Cys-Tyr-Ile-Gln-Asn-*S*-*p*-MeBzl-Cys-Pro-Leu-Gly-NH_2 Resin (III).** A 1.0-g sample of benzhydrylamine hydrochloride resin from polystyrene–1% divinylbenzene (Beckman lot no. B1135) was placed in a 75-mL reaction vessel of a Schwartz/Mann peptide synthesizer. Analysis of the resin by Beckman indicated 0.53 mequiv of N/g of resin by elemental analysis and 0.48 mequiv/g available amine via Boc-L-proline coupling, HF cleavage, hydrolysis, and amino acid analysis. We also monitored coupling capacity using HCl–propionic acid hydrolysis of fully coupled glycinamide resin with the result of 0.48 mequiv of available coupling sites/g of resin and using picrate monitoring of the deprotected glycinamide resin, giving 0.50 mequiv/g of resin. Amino acids were dissolved in their appropriate solvents (the Boc derivatives of *p*-MeBzl-cysteine, glycine, proline, leucine, and isoleucine in CH_2Cl_2, asparagine and glutamine in DMF with a twofold molar excess of HOBzt, and tyrosine in 5% DMF in CH_2Cl_2) and placed in the appropriate reservoirs in the synthesizer. The synthesis was initiated at step 7 in Table I and carried through as indicated in Tables I and II until the final coupling of Boc-*p*-MeBzlCys (1.5-fold molar excess, single couplings for Gly, Leu, Pro, Cys, and Tyr, and double couplings for Asn, Gln, and Ile). The monitoring procedure (Table III) was incorporated as desired after step 15 of Table I or step 19 of Table II. The final seven washes of the monitoring sequence were collected automatically, and the absorbance at 362 nm was determined on a Zeiss PMQ II spectrophotometer. The ϵ_{362} for the DIEA–picrate is

Table I. Coupling Scheme for Residues Gly[9], Leu[8], Pro[7], Cys[6], Ile[3], Tyr[2], and Cys[1] [e]

Step	Reagent	Volume, mL	Duration, min	No. of times
1	CH_2Cl_2	25	0.5	5
2	50% TFA–CH_2Cl_2	25	2.0	1
3	50% TFA–CH_2Cl_2	25	30.0[a]	1
4	CH_2Cl_2	25	0.5	5
5	2-Propanol	17	0.5	2
6	CH_2Cl_2	25	0.5	5
7[b]	5% DIEA–CH_2Cl_2	17	2.0	3
8	CH_2Cl_2	25	0.5	5
9[c]	Amino acid–CH_2Cl_2	5	2.0	1
10	DCC–CH_2Cl_2	5	30.0	1
11	CH_2Cl_2	25	0.5	5
12	2-Propanol	17	0.5	2
13	CH_2Cl_2	25	0.5	2
14	2-Propanol	17	0.5	2
15[d]	CH_2Cl_2	25	0.5	5

[a] Deprotection time for Gln[4], before Ile[3] coupling, was 15 min. [b] For the coupling of Gly[9] to the resin the sequence is started at this step. [c] The vessel is not drained after this step. [d] Steps 9–15 were repeated when a second coupling was performed for Ile[3]. [e] Amino acids were *tert*-butoxycarbonyl derivatives in 1.5 M excess in solution except tyrosine, which was dissolved in 5% DMF–CH_2Cl_2. DCC was equimolar with protected amino acids.

Table II. Coupling Scheme for Residues Asn[5] and Gln[4] in Dimethylformamide[c]

Step	Reagent	Volume, mL	Duration, min	No. of times
1–8 are identical to those in Table I				
9	2-Propanol	17	0.5	2
10	CH_2Cl_2	25	0.5	5
11[a]	DMF	17	2.0	3
12[b]	Amino acid HOBzt–DMF	5	2.0	1
13	DCC–DMF	5	120.0	1
14	DMF	17	2.0	1
15	CH_2Cl_2	25	0.5	5
16	2-Propanol	17	0.5	2
17	CH_2Cl_2	25	0.5	2
18	2-Propanol	17	0.5	2
19	CH_2Cl_2	25	0.5	5

[a] When second couplings were used, steps 11–19 were repeated. [b] The vessel is not drained after this step. [c] Amino acids were *tert*-butoxycarbonyl derivatives in 1.5-fold molar excess in DMF solution. HOBzt was used at a twofold molar excess over amino acid concentrations; DCC was equimolar.

Table III. Monitoring Scheme[a]

Step	Reagent	Volume, mL	Duration, min	No. of times
1	DIEA 5% in CH_2Cl_2	17	2.0	3
2	CH_2Cl_2	25	0.5	5
3	2-Propanol	17	0.5	2
4	CH_2Cl_2	25	0.5	5
5	0.1 M picric acid in CH_2Cl_2	17	2.0	3
16	CH_2Cl_2	25	0.5	2
7	2-Propanol	17	0.5	2
8	CH_2Cl_2	25	0.5	5
9	5% DIEA in CH_2Cl_2	17	2.0	3
10	CH_2Cl_2	25	0.5	4

[a] Washes in steps 9 and 10 were collected and their absorbance was measured at 362 nm.

15 000 (Table III).[5] At the conclusion of these steps 1.530 g of air-dried III was recovered (96% yield). Amino acid analysis of III after hydrolysis in the HCl–acetic acid–phenol mixture was Asp 1.00, Glu 1.03, Pro 1.05, Gly 1.10, Ile 0.93, Leu 1.03, and Tyr 0.92. The amino acid analysis showed no loss of chains from the resin during synthesis. Syntheses using between 1 and 2 g of resin have been carried out using the same protocols and with similar proportional yields.

***tert*-Boc-*S*-*p*-MeOBzlCys-Tyr-Ile-Gln-Asn-*S*-*p*-MeOBzlCys-Pro-Leu-Gly-NH_2 Resin (V)** and ***tert*-Boc-*S*-Bzl-Cys-Tyr-Ile-Gln-Asn-*S*-BzlCys-Pro-Leu-Gly-NH_2 Resin (VI)** were prepared similarly to III, except that the appropriately S-derivatized Boc-cysteine was used. Variations in number of couplings or molar excesses of amino acids used made no detectable difference in yield of peptide resins (by weight) or in their amino acid analyses.

Oxytocin (I). A 0.439-g sample of III was placed in a 50-mL Teflon-Kel-F vessel used on an HF apparatus (Toho) described elsewhere.[10] A small Teflon-coated magnetic stirring bar and 1 mL of anisole were added. A frit was secured near the top of the vessel and the vessel was attached to the apparatus. The apparatus was evacuated with an aspirator pump, and the sample vessel was immersed in a dry ice/acetone bath. After 20 min the sample vessel was disconnected from the vacuum and connected to the HF reservoir, and HF was distilled into the vessel until the total liquid volume was approximately 10 mL. (This process takes about 15 min.) The dry-ice bath was then replaced by a water–ice bath (0 °C) with a magnetic stirrer underneath, and the sample vessel was sealed off from the rest of the system. After 75 min the vessel was carefully opened to the aspirator and the HF was allowed to evaporate. Virtually all the HF was gone after 10 or 15 min. After 30 min of aspiration, the line was switched to a mechanical pump and pumping continued for 1 h. The sample remained immersed in a 0 °C bath throughout this time.[17] The system was then filled with Ar or N_2 to atmospheric pressure, and the cleavage vessel was quickly removed and sealed with parafilm.

The material was washed out of the vessel into a coarse fritted funnel with several portions of degassed ethyl acetate totaling about 100 mL. The funnel and the vessel were then placed in a large lyophilizer vessel and evacuated for 30 min to remove remaining ethyl acetate. The cleavage vessel and the resin in the funnel were then washed with several portions of degassed 1 M acetic acid (80 mL total), followed by 160 mL of degassed distilled water in several portions. The solution was then adjusted to pH 8 with 3 M NH_4OH, and 25 mL of 0.01 M potassium ferricyanide solution was added in order to form the disulfide bond of oxytocin. The yellow solution was stirred for about 30 min. The solution was then adjusted to pH 5 with 50% acetic acid, and AG-3 anion-exchange resin (TFA^- form) was added and the mixture stirred for an additional 20 min. The slurry was then filtered, yielding a clear colorless solution, and the resin was washed with a small portion of water. The solution was then lyophilized.

After lyophilization the powder was taken up in about 10 mL of 50% acetic acid and filtered through a millipore filter, yielding a clear, pale yellow solution that was applied to a Sephadex G-15 (2.5 × 70 cm) column previously equilibrated with 50% acetic acid.[18] The column was run at a flow rate of 1 mL/min and 7-mL fractions were collected. Two peaks were eluted as determined by monitoring at 280 nm. Peak 1 retained the yellow color and appeared in fractions 15–18, and peak 2, which was subsequently determined to be pure I, was in fractions 19–26. There was some overlap of the two peaks. Fractions that showed significant amounts of both materials present as judged by TLC were subjected to further purification with CCD. (This was not necessary in the case being described.) Peak 2 yielded 76 mg of material (55% yield) from peptide resin, and peak 1 yielded 30 mg (22% yield). TLC of the peak 1 material in the manner described above in solvent system A gave a poorly resolved series of bands with R_f's between 0.17 and 0.35. The ninhydrin color was purple. Peak 2 gave a yellow spot (by ninhydrin reaction) when TLC was performed using solvent systems A, B, and C. The TLC results agree with those obtained for a sample of oxytocin supplied to us. R_f in system A was 0.34; chlorine–o-toluidine visualization did not reveal any additional spots. Amino acid analyses for these materials are: Asp 1.00, Glu 0.90, Pro 1.07, Gly 1.07, Cys 1.30, Ile 0.77, Leu 1.05, and Tyr 0.78 for peak 1; and Asp 1.00, Glu 1.02, Pro 1.08, Gly 0.97, Cys 1.89, Ile 0.93, Leu 0.99, and Tyr 1.05 for peak 2. The peak 2 material gave only one peak in the appropriate fractions when subjected to CCD.[11] On HPLC the fluorescamine-derivatized peak 2 material appeared as a single peak at a position in agreement with that of a sample of oxytocin supplied to us. The material in peak 1 was retained more strongly on the Partisil ODS column and showed several components, apparently including some oxytocin. This was indicated by the TLC as well. Proton NMR spectra were determined in D_2O and were in complete agreement with previously reported results.[19] Bioassay of peak 2 material for avian vasopressor activity gave a result of 416 ± 19 U/mg, in good agreement with the literature value of 450 ± 30 U/mg,[20] $[\alpha]^{27}_{589}$ − 22° (c 0.48, in acetic acid) [lit.[3c] $[\alpha]^{22.5}_{D}$ − 24° (c 0.5, in acetic acid)].

Cleavage of up to 2 g of resin has been carried out using separate cleavage vessels on the HF apparatus and then combining the material for subsequent workup with no significant effect on overall yield.

I was derived from V in the same way as from III and the results were virtually identical.

I was derived from VI by the same procedure, except that the cleavage vessel was immersed in a bath at 20 °C rather than 0 °C. We detemined by NMR studies of cleaved VI that these conditions were required for complete deprotection of the Bzl groups in this system. Yield of oxytocin (I) was 25% for this workup from VI.

***tert*-Boc-*S*-*p*-MeBzlCys-Tyr-Phe-Gln-Asn-*S*-*p*-MeBzl-Cys-Pro-N^g-TosArg-Gly-NH_2 Resin (IV)** was prepared in the same manner as III with the following differences. Boc-N^g-tosylarginine, dissolved in 5% DMF in CH_2Cl_2, was the second amino acid coupled, and Boc-phenylalanine dissolved in CH_2Cl_2 was the seventh amino acid coupled. A single coupling with 1.5-fold excess of glycine was followed by three 30-min couplings each with 1.5-fold excesses for arginine and proline, two couplings at 1.5-fold excess for *p*-MeBzl-cysteine (the first for 30 min and the second for 60 min), and two 120-min couplings at 1.2-fold excess (due to an instrument adjustment) for asparagine and glutamine. The last three residues were coupled in the manner of the first cysteine. IV (1.06 g) was obtained (92% yield). Picrate monitoring results are in Table V. Amino acid analysis of IV was Asp 1.00, Glu 0.97, Pro 0.89, Gly 1.09, Tyr 0.85, Phe 0.83, and Arg 0.88.

8-Arginine-vasopressin (II) (AVP) was made from IV following the same procedure used for I; 0.72 g of IV yielded 130 mg (52% yield) of II in peak 2 following gel filtration. Peak 1 contained 65 mg (26% yield). TLC analysis of the material in peak 1 showed a broad band between R_f's 0.0 and 0.2 (purple ninhydrin reaction) and a single yellow spot R_f 0.2 for peak 2 material in solvent system A. Peak 2 material gave single yellow spots in systems B and C, and the results in all three systems were consistent with those obtained from a sample of AVP supplied to us. NMR spectra were in agreement with those previously reported.[21] HPLC is illustrated in Figure 2 with the single peak for derivatized G-15 peak 2 material. The result on our material was consistent with that for AVP supplied to us. Rat pressor activity was 496 ± 44 U/mg, in good agreement with the literature value of 487 ± 15 U/mg.[7] Amino acid analysis result for peak 1 material was Asp 1.00, Glu 0.91, Pro 0.98, Gly 1.00, Cys 1.44, Tyr 0.85, Phe 0.84, and Arg 1.07, and for peak 2 Asp 1.00, Glu 0.93, Pro 0.97, Gly 0.99, Cys 1.96, Tyr 0.9, Phe 0.94, and Arg 0.95, $[\alpha]^{27}_{589}$ −23° (c 0.23, in acetic acid) [lit.[7] $[\alpha]^{22}_{D}$ −22° (c 0.22, in acetic acid)].

Results and Discussion

From the results in the Experimental Section it is clear that benzhydrylamine-derivatized polystyrene resin provides an excellent support for solid-phase synthesis of these neurohypophyseal peptide hormones. It offers a more stable peptide–resin linkage which permits the use of fairly vigorous conditions for deprotection of α-amino groups (<0.4% loss of glycine/h on treatment with 50% TFA in CH_2Cl_2), while affording efficient peptide–resin cleavage (>95%) in anhydrous

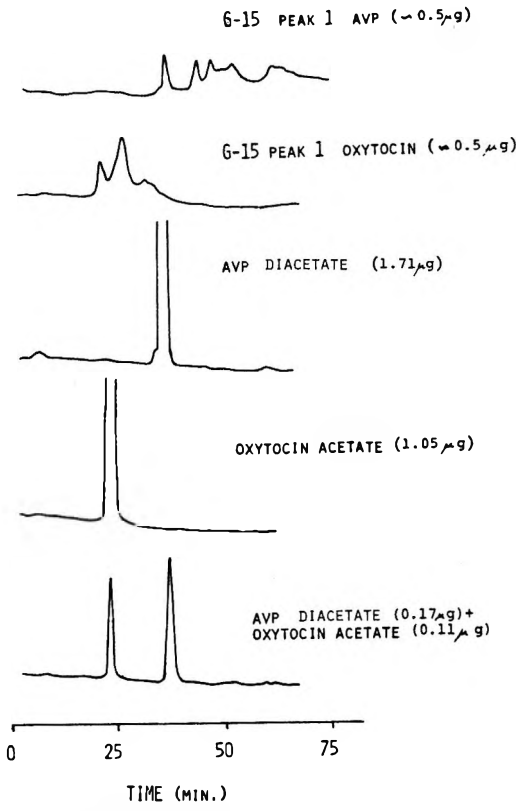

Figure 2. High-pressure liquid chromatography of fluorescamine-derivatized products of oxytocin and 8-arginine-vasopressin syntheses. The by-products of the oxytocin synthesis gave similar chromatograms regardless of protecting group used. The ordinate is intensity of fluorescence, and the traces are displaced, but are on the same scale. The bottom three traces are of G-15 peak 2 material.

hydrogen fluoride at 0 °C for 60 min. Couplings appear to proceed to completion using standard synthetic methods with considerably less than the usual molar excesses of amino acids. This is illustrated by the results of amino acid analyses given in the previous section and by the data in Tables IV and V, where the results of picrate monitoring of the oxytocin and vasopressin syntheses are presented. The data in these tables may be usefully assessed in terms of effective coupling efficiency, that is, the ratio of the percentage completion for a given set of conditions to that after efforts to force completion. Confirmation of the reliability of the effective coupling efficiency can be observed in the similarity of the peptide resin amino acid analyses and synthetic results for syntheses where both 1.5-fold and threefold excesses of amino acid reagents have been used. The appearance in these tables of values significantly less than 100% after both initial 1.5-fold excess couplings as well as after attempts to force the reaction to completion may indicate picrate binding to unreacted free amino termini or to unidentified sites. This background level of picrate eluted after efforts to complete coupling was found to increase with chain length. One possible source of the background would be the appearance of chains with unreactive, but picrate positive, amino group. The increasing level of background during the synthesis is consistent with these chains remaining unreactive throughout the synthesis. Alternatively, some other binding of picrate to the growing peptide chain may be taking place. The trends in the monitoring results for both the oxytocin and vasopressin syntheses were similar, although the background levels for AVP were somewhat higher. We ultimately recovered comparable amounts of material from each synthesis, and this speaks against the possibility that the increased background was due to a larger number of chain terminations. If deletions were

Table IV. Coupling Efficiencies (%) in the Synthesis of Oxytocin

Residue	With 1.5-fold excess single coupling	With threefold excess double coupling	Effective coupling efficiency for single 1.5-fold excess coupling[a]
Gly^9	99.5	99.6	99.9
Leu^8	99.3	99.5	99.8
Pro^7	99.6	99.4	100.2
Cys^6	99.4	99.3	100.1
Asn^5	93.5	99.3	94.2
Gln^4	97.5	98.2	99.3
Ile^3	90.0	98.3	91.6
Tyr^2	97.6	98.0	99.6
Cys^1	97.0	96.8	100.2

[a] Ratios of value in column 2 to those in column 3 (see text), expressed as percentage.

Table V. Coupling Efficiencies (%) in the Synthesis of AVP

Residue	With 1.5-fold excess single coupling	With 1.5-fold excess double coupling	Effective coupling efficiency for single 1.5-fold excess coupling[a]
Gly^9	99.6	99.6	100.0
Arg^8	95.6	96.2 (96.6)[b]	99.4
Pro^7	92.5	94.7 (95.0)[b]	97.4
Cys^6	91.3	92.7	98.5
Asn^5	68.0	93.6	72.6
Gln^4	58.7	90.3	65.0
Phe^3	88.7	89.3	99.3
Tyr^2	80.2	89.5	89.6
Cys^1	93.0	93.7	99.3

[a] Ratios of values in column 2 to those in column 3 (see text), expressed as percentage. [b] A result after third coupling (see text).

present in our purified material, they should probably have appeared as additional peaks in the high-pressure liquid chromatograms.[22] However, no significant additional peaks were present for either oxytocin or AVP. The by-products in peak 1 from the Sephadex G-15 column from both syntheses are presumably higher molecular weight materials; if they contain deletion peptides, the ultimate fate of these species must have been the formation of dimers or oligomers through intermolecular disulfide bonds. The reproducibility of the monitoring data indicates that the factors giving rise to the background are intrinsic to the synthesis.

We have also employed the minitoring method to determine reasonable coupling times for Boc-glutamine and Boc-asparagine in DMF with HOBzt and DCC. Under the conditions we are using, the reactions are about 50% complete in 30 min, and virtually totally complete in 120 min. The same batch of resin was used for all the syntheses of oxytocin, and the reproducibility of the minitoring data demonstrates the applicability of this technique for quality control in such repeated syntheses.

In considering the different yields obtained from syntheses using the three different protecting groups for cysteine, we note that there is no evidence for any variation of the products in synthesis of the protected oxytocin peptide resin as a function of the cysteine protecting group used. The Bzl group with its substantial stability has been used effectively in amino acid and peptide synthesis, and it can be removed completely by exposure to hydrogen fluoride at 20 °C for 30 min in this system. The *p*-MeOBzl group is the most labile[6,9] and provides a point of comparison with the other two, even though

for reasons given earlier it is not ideal for our needs. The yield of oxytocin with Bzl protection under these conditions is about half as great as that obtainable with *p*-MeOBzl protection. The ratios of material in peak 1 (by-product) to that in peak 2 (oxytocin) from the gel filtration are quite similar for both means of protection, as are the TLC, HPLC, and amino acid analysis results for the respective peaks. The *p*-MeBzl group, though not widely used in peptide synthesis, has lived up to the expectations for it mentioned earlier, and the synthetic results with this group are indistinguishable from those with *p*-MeOBzl protection. Further efforts were made to determine whether any more of the desired product could be regenerated from peak 1 of the gel filtration or whether a change in our procedures could increase the yield of oxytocin further. An obvious property of the peak 1 material is a substantial reduction in cysteine content relative to that in oxytocin. The level of cysteine, however, showed no significant variation with protecting group and cleavage conditions, or with sequence. Several other possible causes of this effect were investigated. To check for sulfoxide formation as a source of the problem, acetone treatment in hydrogen bromide–acetic acid was used to reduce any *p*-MeBzl-cysteine sulfoxide to *p*-MeBzl-cysteine.[22] Some of the peak 1 material was treated with acetone after being dissolved in 35% hydrogen bromide–acetic acid. This was followed by treatment with hydrogen fluoride at 0 °C for 60 min, oxidation with performic acid, hydrolysis, and amino acid anaylsis. The results were the same as before. Alternatively, it is possible that deprotection before the coupling of Cys^6 or Cys^1 was incomplete. Employing double deprotections before these couplings, however, did not affect the final results. To test a third alternative we removed the terminal Boc group before hydrogen fluoride cleavage, but also to no avail.

A possible source of some of the peak 1 material is suggested by the amino acid analysis results for the peptide resin and for peak 1, namely that some termination at glutamine occurs during the synthesis. Comparison of tyrosine, isoleucine, and, in the case of AVP, phenylalanine values with that of cysteine indicate that this can only be part of the problem.

In total we are able to account finally for between 85 and 90% of the peptide from the protected peptide resin, with 55– being the desired product, 25% peak 1 by-products, 5% remaining associated with the resin, and possibly 5% lost by termination at glutamine. We have attempted to optimize the synthesis of oxytocin and have succeeded in developing a procedure that is efficient in both time and material. The readily purified product is obtained in a yield which is substantially greater than previously reported (~30%[3]), and the approach appears to be applicable to analogous peptides. Effectively complete couplings can be achieved without resorting to a large excess of reagents or long coupling times. These conditions are particularly important to us because of our interest in preparing labeled peptides.The possibility that these conditions may work well in general is of practical interest to anyone contemplating large scale syntheses. The picrate monitoring method has proved indispensable in assessing the effectiveness of couplings in this work.

The syntheses reported here demonstrate convincingly the value of using *p*-methylbenzyl protection of the cysteine thiol function. The previously suggested[6] value of this protecting group based on amino acid model studies is thus supported by its actual use in peptide synthesis. Since the protected amino acid is easily prepared from readily available materials and has clear advantages over *S*-benzyl- and *S*-*p*-methoxybenzylcysteine, we consider that it is the protecting group of choice in this case.

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Registry No.—*p*-MeBzl-cysteine, 42294-52-0; glycine, 56-40-6; proline, 147-85-3; leucine, 61-90-5; isoleucine, 73-32-5; asparagine, 70-47-3; glutamine, 56-85-9; tyrosine, 60-18-4; oxytocin, 50-56-6; Boc-Cys($CH_2C_6H_4OMe$-H)OH, 18942-46-6; Boc-Cys(CH_2Ph)-OH, 5068-28-0; *tert*-Boc-*S*-*p*-MeBzlCys-Tyr-Ile-Gln-Asn-*S*-*p*-MeBzlCys-Pro-Leu-Gly-NH_2, 63534-39-4; Boc-*N*-tosylarginine, 13836-37-8; Boc-phenylalanine, 13734-34-4; 8-Arginine-vasopressin, 113-79-1.

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δ-Dicarbonyl Sugars. 5. A Novel Synthesis of a Branched-Chain Cyclitol[1]

Charles E. Cantrell,[2] Donald E. Kiely,* Gerald J. Abruscato, and James M. Riordan

Department of Chemistry, University College, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294

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The cyclization of tri-*O*-acetyl-1,7-dideoxy-1,7-bis(diazo)-*xylo*-2,6-heptodiulose (**5**), in acetic acid solution, to DL-3-*C*-acetoxymethyl-2,4,5,6-tetra-*O*-acetyl-2,3,4,6/5-pentahydroxycyclohexanone (**8**) is described. This conversion, considered to take place by way of a carbene, represents a new synthesis of the cyclitol ring system. The reactive diketone (**5**) was prepared by a diazomethane chain extension sequence originating with D-xylose (**1**). Reduction of the keto carbonyl of **8** followed by the acetylation of the resulting products gave DL-2-*C*-acetoxymethyl-1,3,4,5,6-penta-*O*-acetyl-*epi*-inositol (**12**). A minor product from the decomposition of **5** was identified as penta-*O*-acetyl-*xylo*-2,6-heptodiulose (**9**).

The biosynthetic pathways that lead to the carbocyclic ring system as it is found in the cyclitols[3] are thought to involve enzyme-catalyzed aldol condensations of appropriate δ-dicarbonyl monosaccharides. We have recently discovered that some synthetically prepared derivatives of this class of carbohydrates can be chemically induced to undergo these same ring closures.[1,4] This paper describes a new route to the acetylated hydroxymethylcyclitol DL-2-*C*-acetoxymethyl-1,3,4,5,6-penta-*O*-acetyl-*epi*-inositol (**12**) by way of an unusual cyclization of a bisdiazo ketone (**5**) derived from *xylo*-2,6-heptodiulose.

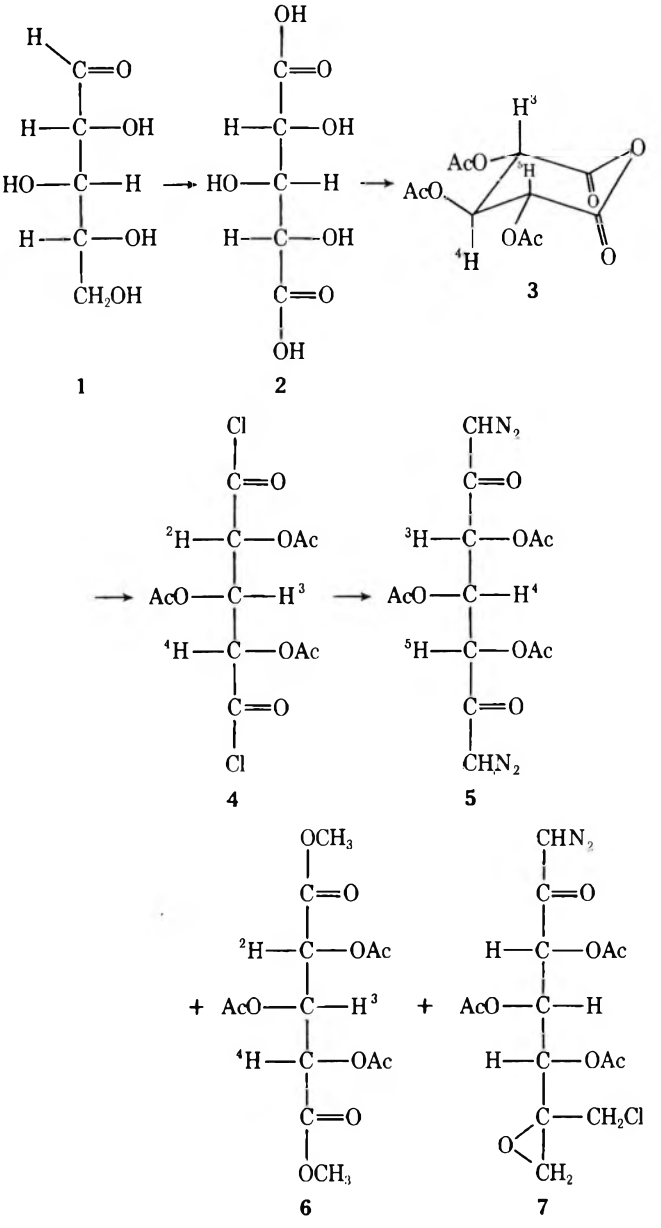
Results and Discussion

The bisdiazo ketone **5** was prepared by a standard diazomethane chain extension sequence beginning with D-xylose (**1**) (Scheme I). In order to obtain satisfactory yields of xylaric acid (**2**) and tri-*O*-acetylxylaric anhydride (**3**), it was necessary to modify the Wolfrom and Usdin procedure for the synthesis of these compounds.[5] When the oxidation of D-xylose with nitric acid was completed, excess oxidizing agent was destroyed with 2-propanol and crystalline xylaric acid was obtained in 44% yield. Deletion of the 2-propanol addition step in the workup procedure resulted in the isolation of a syrup that did not crystallize and eventually decomposed. When the anhydride **3** was prepared by refluxing zinc xylarate in acetyl chloride,[5] the average yield of the product from the reaction was only 30%. Furthermore, the anhydride obtained in this way gradually underwent an irreversible phase change to an oil. However, stable **3** was synthesized in reasonable yield (70–80%) by treating **2** with acetic anhydride that contained a catalytic amount of sulfuric acid.

Syrupy tri-*O*-acetylxylaryl dichloride (**4**),[6] prepared by refluxing the half sodium salt of **2** triacetate with thionyl chloride, was treated with an ether solution of diazomethane and tri-*O*-acetyl-1,7-dideoxy-1,7-bis(diazo)-*xylo*-2,6-heptodiulose (**5**) crystallized as yellow needles directly from the reaction mixture (68%). Thin-layer chromatography of the mother liquors showed a three-component mixture. Silica gel column chromatography of this residue gave first dimethyl tri-*O*-acetylxylarate (**6**). Next off the column was a mixture (ca. 40% of the material from the column) of **7** and an unidentified compound. The characterization of **7** is described in the following paper (ref 18). The third component, **5**, was also isolated (5%).

The bisdiazo ketone **5**, when dissolved in acetic acid that contained cupric acetate, rapidly decomposed (5 min) at 70 °C to give **8** (32%), which crystallized directly from the reaction mixture (Scheme II). The conversion was also accomplished without the presence of copper ion, but required a higher temperature (80–90 °C), and a significantly longer reaction time (10 h).

Scheme I



A first-order analysis of the ^{1}H NMR spectrum of **8** (Figure 1) clearly showed large coupling (J = 10.0 Hz) between H-5, H-6, and H-4, H-5, thus establishing the consecutive anti relationship of these three ring protons. Propanic long-range coupling in the molecule was evidenced by small splitting of the H-4 doublet and broadening of the H-2 singlet. The value

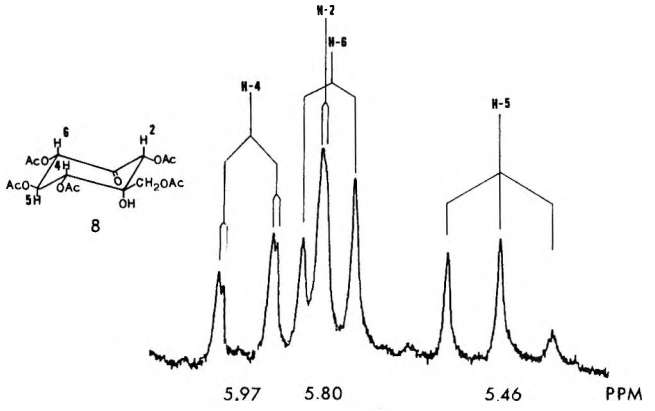


Figure 1. 90-MHz ^1H NMR spectrum of **8** in Me_2SO-d_6 (ring proton region).

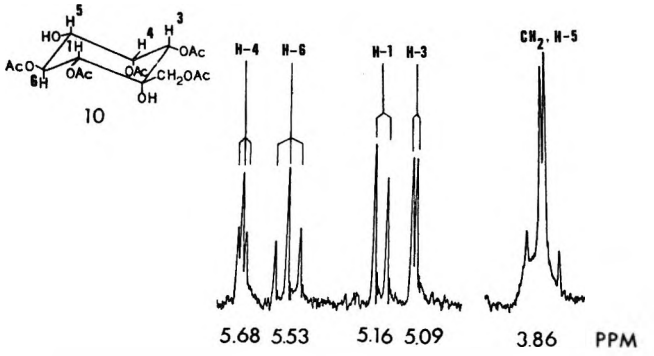
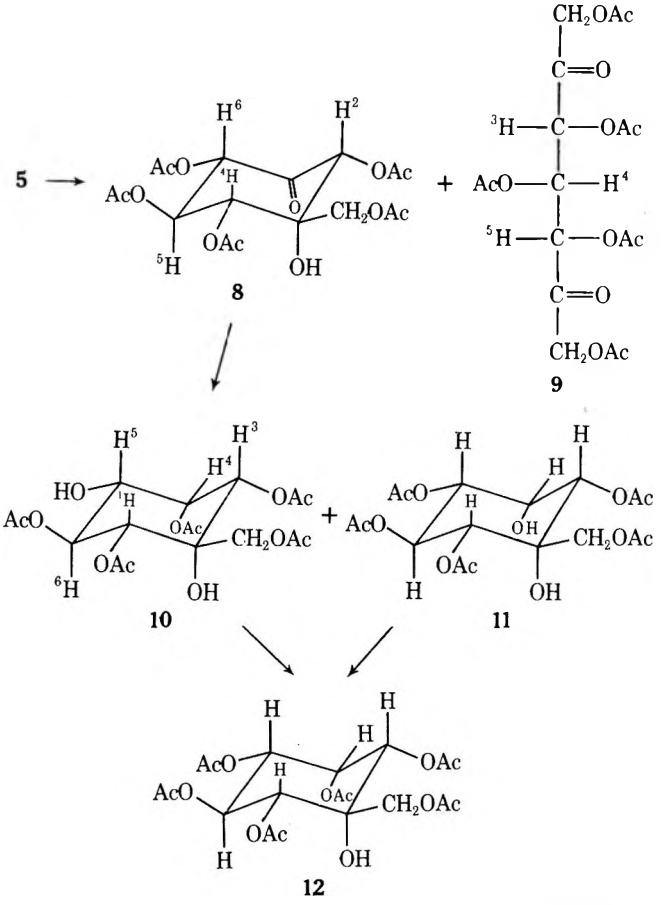


Figure 2. 220-MHz ^1H NMR spectrum of **10** in $CDCl_3$ (ring proton region).

Scheme II



of the coupling (J = 0.8 Hz) falls within the normal range of propanic coupling (−0.3–0.9 Hz) for 1,3-diaxially oriented protons.[7] Excellent agreement between the observed spectrum and the theoretical spectrum served to confirm these assignments.[8]

Two isomeric crystalline cyclitol pentaacetates (**10** and **11**) were obtained after the keto carbonyl of **8** was reduced by catalytic hydrogenation in acetic acid. The minor product (**10**) in the mixture was presumably formed from the major product (**11**) by an acid-catalyzed acetyl migration to the hydroxy group generated in the reduction step. The stereochemistry at four of the ring carbons of **10**, C-1, C-4, C-5, and C-6, was deduced after analysis of the 220-MHz ^1H NMR spectrum of the compound (Figure 2). However, the stereochemistry at C-3 is not discernible from the H-3, H-4 coupling, since the two protons are gauche when H-3 is axial or equatorial. The coupling constants assigned to the ring protons of **10** were unchanged in the ^1H NMR spectrum of **11**, the major product from the reduction of **8** (Table I).

Acetylation of **10** and **11** gave the cyclitol hexaacetate, DL-2-*C*-acetoxymethyl-1,3,4,5,6-penta-*O*-acetyl-*epi*-inositol (**12**). The splitting of the ring proton signals in the ^1H NMR spectrum of **12** was in accord with the assigned stereochemistry for **10** and **11**. The problem of ascertaining the stereochemistry at the remaining two ring carbons common to **8**, **10**, **11**, and **12** was resolved by an x-ray crystallographic structure determination of **10**.[9] The x-ray study revealed that the tertiary hydroxyl group of **10** is axial and both vicinal acetoxy groups equatorial. The ^1H NMR derived stereochemical assignments for the four previously discussed ring protons were found to be correct. The free cyclitol derived from **12**, 2-hydroxymethyl-*epi*-inositol, has been prepared in crystalline form,[10] and most recently by deacetylation of **12**.[11]

The mother liquors from the cyclization of **5**, about 60% of the material in the reaction mixture, were chromatographed on a column of silica gel to give ca. 5% of a single crystalline compound, the acyclic pentaacetate **9**. The poor recovery of material from the column was due largely to extensive decomposition of unidentified compounds in the mixture on the silica gel. However, TLC showed that even at best **9** was a minor component in the original reaction mixture.

Prompted by the successful cyclization of **5**, we sought to gain additional insight into the requirements for this type of ring closure. Two modifications in the structure of the bisdiazo ketone were considered to be the most important for the study: (1) removal of the bulky acetoxy groups from the molecule to see if these groups were responsible for a conformation favorable for cyclic product formation, and (2) changing the type of carbonyl group which was affected in the cyclization. The first modification was realized with 1,7-bis(diazo)heptane-2,6-dione[12] (**15**), while methyl tri-*O*-acetyl-6-deoxy-6-diazo-DL-*xylo*-5-hexulosonate (**14**) satisfied the structural requirement prescribed by the second modification. The preparation of **14** was accomplished in several steps beginning with the anhydride **3**. The first step in the sequence, the methanolysis of **3**, gave the methyl ester **13** and the dimethyl ester **6** in almost equal amounts (Scheme III).

The cupric acetate catalyzed decomposition of **15** in acetic acid at 70 °C gave, as the only identifiable product, the crystalline acyclic diacetate **16** (74%) (Scheme III). The attempted cyclization of **14** in acetic acid yielded a mixture which TLC showed to be composed of a major product and at least two slower moving minor products. The principal product was isolated by silica gel column chromatography (39%) and spectral data and elemental analysis confirmed that the compound was methyl tetra-*O*-acetyl-DL-*xylo*-5-hexulosonate (**17**)[13] (Scheme III). The minor products from the column chromatographic separation were not obtained pure enough or in large enough quantities for identification. The apparent reluctance of either **14** or **15** to cyclize under the conditions

Table I. Proton Magnetic Resonance Chemical Shifts and Coupling Constants for Compounds 2–6 and 8–17

Compd[a-c]	Registry no.	Solvent	H_1, δ	H_2, δ	H_3, δ	H_4, δ	H_5, δ	H_6, δ	Other δ	$J_{2,3}$, Hz	$J_{3,4}$, Hz	$J_{4,5}$, Hz	$J_{5,6}$, Hz	$J_{1,6}$, Hz
2	10158-64-2	Me_2SO-d_6		4.05, d	3.89, t	4.05, d				4.38	4.38			
		D_2O[21]		3.96, d	3.72, t	3.96, d				4.14	4.14			
3	63181-58-8	Me_2SO-d_6			6.20	6.05	6.20			11.0	11.0			
4	63181-59-9	$CDCl_3$		5.60, d	5.85, d	5.60, d				5.0	5.0			
5	38910-01-9	$CDCl_3$	5.51		5.37, d	5.73, t	5.37, d				5.03	5.03		
6	63181-60-2	$CDCl_3$		5.36, d	5.71, t	5.36, d				4.61	4.61			
8	63229-94-7	Me_2SO-d_6		5.82		5.97, dd	5.46, t	5.80, d	3.90 (s, 2, CH_2)			10.0	10.0	
9	38877-05-3	$CDCl_3$			5.46, d	5.74, t	5.46, d				4.33	4.33		
10	43068-08-2	$CDCl_3$	5.16, d		5.09, d	5.68, t	3.86, m	5.53, t			3.5	3.5	10.0	10.0
11	63229-95-8	$CDCl_3$	5.18, d		4.95, d	3.88, m	5.04, dd	5.68, t			3.5	3.5	10.0	10.0
12	52795-30-9	$CDCl_3$	5.23		5.16	5.69	5.15	5.71			3.63	3.12	10.17	10.44
13	63181-61-3	$CDCl_3$		5.44, d	5.73, t	5.44, d				4.57	4.57			
14	63181-63-5	$CDCl_3$		5.34, d	5.80, t	5.44, d		5.58		5.01	6.84			
15	27475-07-6	$CDCl_3$	5.30		2.40, t	2.00, m	2.40, t				7.0	7.0		
16	63181-64-6	$CDCl_3$			2.20, t	2.04, m	2.20, t				7.0	7.0		
17	63229-96-9	$CDCl_3$		5.13	5.47	5.70				4.47	4.55			

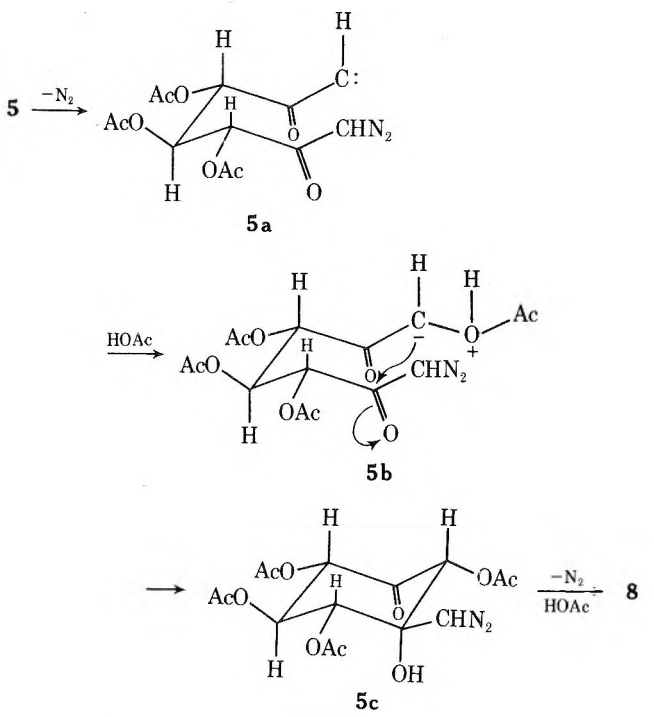
[a] The spectra of compounds 2, 3, 4, 5, 6, 8, 9, 12, 13, 14, and 17 were computer analyzed by LAOCOON III program (see ref 8). All parameters sets have a rms error less than 0.2 Hz. [b] The spectra of compounds 14–16 were recorded at 60 MHz; the spectra of compounds 9–12 at 220 MHz, and the remaining spectra at 90 MHz. [c] The measured values of the coupling constnats of compounds 2, 4, 5, 6, 9, 13, 14 and 17 lie between 4.33 and 5.01 Hz and indicate that the sickle conformer is the major conformer of these acyclic xylo derivatives (see ref 15 and 16).

Scheme III

whereby **5** was converted to the cyclose 8 (Scheme IV) suggests that a proper combination of backbone substitution and carbonyl reactivity is necessary for ring closure to occur.

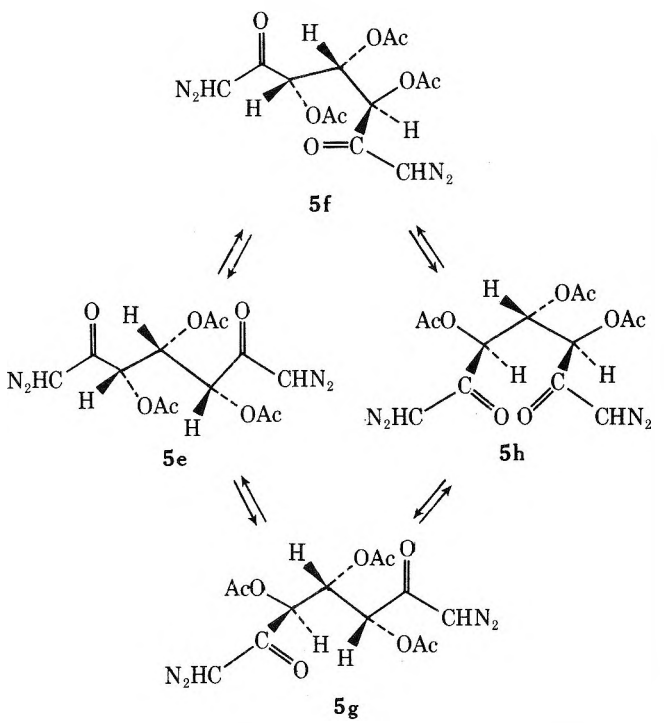
Mechanistic Considerations. The thermal decomposition of a diazo ketone in an aprotic solvent generally gives a carbene, whereas diazonium and carbonium ions are the favored products when the decomposition is carried out in a protic solvent, particularly in the presence of added mineral acid.[14] However, Yamamoto and Moritani reported that decomposition of diethyl diazosuccinate in the protic solvent acetic acid to the corresponding carbene accounted for 66% of the olefinic products, diethyl fumarate and diethyl maleate.[15] In the less acidic solvents ethanol and cyclohexanol, even higher percentages of olefin were produced by the carbene pathway. The mechanism we propose for the formation of the cyclose 8 in acetic acid from the bisdiazo ketone **5** also involes a carbene (**5a**). The reaction between this electrophilic intermediate and the solvent, acetic acid, may then give the ylide **5b,** which can convert to the acyclic pentaacetate **9,** or by a simple intramolecular aldol condensation to **5c,** a precursor of **8.** A similar but less probable scheme would be initiated by the generation of a dicarbene directly from **5.**

Scheme IV



In the ^{1}H NMR spectrum of **5**, the value of the observed coupling constant between H-4 and equivalent H-3 and H-5 ($J_{3,4} = J_{4,5} = 5.0$ Hz) is intermediate between the predicted value for a consecutive gauche arrangement ($J \simeq 3$–4 Hz) and a consecutive anti arrangement ($J \simeq 7$–10 Hz) of the three protons. In considering some idealized conformational possibilities for **5** (Scheme V), the smaller value of the coupling

Scheme V



constant would account for a planar zigzag arrangement of protons and bulky acetoxy groups (**5e**) while a U conformation (**5h**)[16] would fit the larger value of J. The destablizing 1,3 interactions between the eclipsed acetoxy groups in the zigzag conformation can be relieved by rotating either C-3 or C-5 120°. The resulting enantiomeric sickle conformations, **5f** and **5g**, can then be converted directly to the U conformation by rotating previously undisturbed C-5 or C-3 120°.

The low yield conversion of **5** to the acyclic pentaacetate **9** rules against a high percentage of zigzag conformation **5e** being in the reaction mixture at the temperature (70 °C) that **5** decomposed. This conclusion is also based on the assumption that the distribution of the active carbene conformational isomers is essentially the same as that of the precursor bisdiazo ketone conformations. The fact that the substituted bisdiazo ketone **5** produces the cyclic product **8** under the same conditions whereby the unsubstituted bisdiazo ketone **15** gives the acyclic diacetate (**16**) serves to underline the importance of the U conformation (**5h**) for **5** in acetic acid solution. It should be pointed out that in inert solvents the copper-catalyzed decomposition of **15** does give a cyclic product (15–32%), cyclohept-2-ene-1,4-dione,[17] presumably by a dicarbene coupling. However, we found no evidence that either **5** or **15** underwent this kind of ring closure in acetic acid. If such a product was formed from **5** it must have decomposed in the silica gel column chromatographic purification of **9**.

The methyl ester–diazo ketone **14**, since it is structurally akin to **5**, should be conformationally disposed to cyclize. The absence of cyclic products in the decomposition mixture from **14** may simply mean that the methyl ester carbonyl carbon is not electrophilic enough to react with the anionic portion of the ylide, a step that gives the carbocyclic ring. Instead, the ylide is preferentially converted to the final acyclic product **17**.

Experimental Section

General Methods. Melting points were obtained with a Fischer-Johns melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 60, 90, or 220 MHz with tetramethylsilane as the internal standard. The IR spectra were obtained with a Perkin-Elmer Model 337 grating infrared spectrophotometer. Thin-layer chromatography was performed on plates coated with silica gel GF-254 (E. Merck, Darmstadt) and the components were detected by spraying with 20% sulfuric acid. Column chromatography was carried out with columns of silica gel (0.05–0.20 mm; E. Merck). All chromatographic solvent systems employed are given as volume to volume ratios and column dimensions are given as length and outside diameter. Mass spectra were recorded with an LKB-9000 combined gas chromatograph–mass spectrometer or a Hitachi-Perkin Elmer Model RMU-7 double focusing mass spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

Xylaric Acid (2). A solution of D-xylose (**1**, 101 g) in water (78 mL) was charged to a 1-L round-bottom flask equipped with a reflux condenser and magnetic stirrer. Concentrated nitric acid (70%, 203 mL) was added to the flask and the solution was carefully heated until evolution of nitric oxide began (ca. 60 °C). The reaction mixture was immediately transferred to an ice bath until the gas evolution subsided. The flask was then allowed to stand at room temperature for 15 min. The temperature of the solution was maintained at 60 °C for 2 h, and then gradually raised to 90 °C over 30 min. After keeping the reaction mixture at 90 °C for 10 min, the solution was cooled to 60 °C, and 2-propanol (200 mL) was added with stirring in 20-mL portions to destroy excess nitric acid. The solution was diluted with water (100 mL), then with concentrated HCl (10 mL), and warmed at 60–70 °C for 30 min. The yellowish-green solution was concentrated in vacuo at 50 °C until it became a syrup or semicrystalline mass. This material was then taken up in 2-propanol (100 mL), the solution refluxed for 30 min, and then concentrated in vacuo at 50 °C to yield a tacky semicrystalline product. The tacky product was freed of some residual water by freeze drying for 30 min and the resulting crystalline mass was then broken up and washed with cold acetone (50 mL). The suspension was filtered and washed several times with cold acetone to give 53 g (44%) of **2**; mp 145–147 °C (lit.[5] 150–151 °C).

Tri-*O*-acetylxylaric Anhydride (3). A solution of xylaric acid (**2**, 18 g) in acetic anhydride (60 mL) and concentrated sulfuric acid (0.10 mL) was kept at 60 °C for 3 h. The solution was concentrated in vacuo at 70 °C to give a white solid product, which was washed with chloroform (50 mL) and recrystallized from ethyl acetate to give 21 g (73%) of **3**; mp 162–164 °C (lit.[5] 146–147 °C); IR (KBr) 1760 cm^{-1} (broad C=O).

Tri-*O*-acetylxylaryl Dichloride (4). Sodium bicarbonate (3 g, 0.035 mol) was slowly added to a solution of tri-*O*-acetyl xylaric an-

hydride (**3**, 10 g, 0.035 mol) in water (30 mL). The aqueous solution was decolorized with carbon, the suspension filtered, and the filtrate concentrated in vacuo at 50 °C to give a colorless oil that crystallized overnight. The crystalline mass was washed with acetone and the mixture filtered to yield sodium hydrogen tri-*O*-acetylxylarate (11.0 g, 97%). After the salt was dried at ca. 0.10 mmHg for 2 h at 80 °C, it was added to thionyl chloride (40 mL) and the suspension refluxed for 2 h. Excess thionyl chloride was removed in vacuo to give a syrup which was stirred in benzene (50 mL) or ether (15 mL) and then filtered. The filtrate was decolorized with charcoal and concentrated in vacuo to yield crude tri-*O*-acetylxylaryl dichloride (**4**, 11.0 g): IR (neat) no O–H stretching vibrations, 1760 cm^{-1} (C=O). The acid dichloride was used in the preparation of **5** without further purification.

Tri-*O*-acetyl-1,7-dideoxy-1,7-bisdiazo-*xylo*-2,6-heptodiulose (5). A solution of the acid chloride **4** (10.0 g, 0.03 mol) in anhydrous ether (30 mL) was slowly added to a cold (dry ice–acetone bath) stirred solution of diazomethane (0.30 mol) in ether (275 mL). The ether solution was allowed to warm to 0 °C and after 30 min was cooled again (dry ice–acetone bath) with stirring for 1 h. The product was isolated by carefully filtering the mixture under the hood. A solution of the yellow compound in acetone (2 mL) was slowly added to boiling ether (200 mL), the ether solution was concentrated to half volume and upon standing yielded 7.0 g (68%) of the bisdiazo ketone **5**: mp 118–120 °C; IR(KBr) 2100 (C=N=N), 1740 (ester C=O), and 1640 cm^{-1} (N=N).

Anal. Calcd for $C_{13}H_{14}N_4O_8$ (354.28): C, 44.08; H, 3.98; N, 15.81. Found: C, 44.02; H, 4.05; N, 15.89.

The mother liquors were cooled to between −50 and −20 °C in a dry ice–acetone bath and glacial acetic acid was added until no more nitrogen evolved. The solution was freed of acetic acid by azeotropic distillation with benzene in vacuo. The residual syrup was dried in vacuo (ca. 1 mmHg) for 5 h. A TLC analysis (dichloromethane–ether, 4:1) showed that the oil was composed of three products having R_f values of 0.90, 0.75, and 0.60, respectively. The syrup (3.8 g) was dissolved in a minimum amount of dichloromethane–ether (8.5:1.5) and chromatographed on silica gel (250 g in a 30 × 460 mm column) with the same solvent. The fastest moving component of the mixture was identified as dimethyl tri-*O*-acetylxylarate (**6**, 0.15 g): mp 60–62 °C; IR(KBr) 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{18}O_{10}$ (334.29): C, 46.71; H, 5.43. Found: C, 46.93; H, 5.33.

The second component (1.30 g), R_f 0.75, was isolated as an oil. From the oil, 0.55 g of 3,4,5,-tri-*O*-acetyl-6,7-anhydro-6-chloromethyl-1-deoxy-1-diazo-DL-*ido*-2-heptulose (**7**) was obtained.[18] The slowest moving component was the bisdiazo ketone **5**. The 0.62 g of this material was combined with the first crop of crystalline **5**, making its overall yield 73%.

Decomposition of 5 with Acetic Acid. A solution of **5** (3 g) in acetic acid (15 mL) containing cupric acetate (10 mg) was slowly heated until the evolution of nitrogen began (bath temperature 70 °C). The temperature was maintained at 70 °C for 5 min and the reaction mixture afforded 1.15 g (32%) of DL-3-*C*-acetoxymethyl-2,4,5,6-tetra-*O*-acetyl-2,3,4,6/5-pentahydroxycyclohexanone (**8**). The white solid, which gave a positive Scherer's test for a cyclitol,[19] was recrystallized from acetic acid as colorless plates: mp 240–242 °C; IR (KBr) 3320 (O–H) and 1725 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 376 (16), 358 (27), 345 (49), 316 (16), 196 (34), 154 (36).

Anal. Calcd for $C_{17}H_{22}O_{12}$ (418.36): C, 48.81; H, 5.30. Found: C, 48.76; H, 5.47.

Isolation of Penta-*O*-acetyl-*xylo*-2,6-heptodiulose (9) by Column Chromatography. The mother liquor from the reaction of **5** with acetic acid was freeze-dried to give a reddish-brown oil (1.8 g). Thin-layer chromatography (ether) of the oil showed considerable streaking with an intensified spot at R_f 0.60. The mixture was chromatographed on silica gel (90 g in a 25 × 370 mm column) by eluting with ether. The fractions composed mostly of the material of R_f 0.60 were combined and concentrated to give a light yellow oil (0.83 g). A solution of the oil in ether (10 mL), after standing overnight, yielded 0.20 g (5%) of penta-*O*-acetyl-*xylo*-2,6-heptodiulose (**9**): mp 90–92 °C; IR (KBr) no O-H stretching vibrations, 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{22}O_{12}$ (418.36): C, 48.81; H, 5.30. Found: C, 48.83; H, 5.44.

Catalytic Hydrogenation of 8. A solution of **8** (0.40 g) in acetic acid (15 mL) was stirred at 50 °C for 25 h with hydrogen at atmospheric pressure and freshly prepared platinum generated from platinum oxide (0.40 g). The suspension was filtered and the filtrate concentrated in vacuo to give a colorless syrup which, by TLC (acetone–hexane, 1:1), was shown to consist of a major product, R_f 0.66, and a minor product, R_f 0.52. The syrup was dissolved in hot ethanol (5 mL) and ether (15 mL) was then added. The first crop of crystals (0.030 g, 7%) obtained from the mixture was the minor product, DL-2-*C*-acetoxymethyl-1,3,4,6-tetra-*O*-acetyl-*epi*-inositol (**10**): mp 209–211 °C; IR (KBr) 3460 (O–H) and 1725 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 402 (53), 347 (100), 300 (56), 288 (100), 269 (93), 245 (100), 241 (100).

Anal. Calcd for $C_{17}H_{24}O_{12}$ (420.38): C, 48.57; H, 5.75. Found: C, 48.38; H, 5.77.

A second crop of crystals (0.24 g, 60%) proved to be the major product DL-2-*C*-acetoxymethyl-1,3,5,6-tetra-*O*-acetyl-*epi*-inositol (**11**): mp 160–162 °C; IR (KBr) 3400 (O–H) and 1740 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 361 (21), 329 (32), 287 (87), 227 (98), 185 (100), 167 (62), 143 (66), 125 (100).

Anal. Calcd for $C_{17}H_{24}O_{12}$ (420.38): C, 48.57; H, 5.75. Found: C, 48.20; H, 6.03.

Acetylation of the Reduction Mixture Obtained from 8. A solution of the solid mixture (0.10 g) obtained from the hydrogenation of **8** in acetic anhydride (4 mL) and pyridine (1 mL) was kept at room temperature for 8 h and then concentrated in vacuo to give a single crystalline compound. The product, DL-2-*C*-acetoxymethyl-1,3,4,5,6-penta-*O*-acetyl-*epi*-inositol (**12**), was recrystallized from ethanol and 0.08 g (73%) was obtained: mp 189–191 °C; IR (KBr) 3480 (O–H) and 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{26}O_{13}$ (462.42): C, 49.36; H, 5.67. Found: C, 49.11; H, 5.90.

By the same procedure, **10** and **11** were each separately converted to the same hexaacetate **12**.

Methyl Hydrogen Tri-*O*-acetylxylarate (13). A solution of **3** (14 g) in dry methanol (100 mL) was refluxed 40 h and the reaction mixture concentrated to give a colorless oil. The oil was dissolved in water (50 mL) and a white solid formed when the aqueous solution was neutralized with sodium bicarbonate. The solid was removed by filtration and recrystallized from ether to give dimethyl tri-*O*-acetylxylarate (**6**, 3 g, 24%). The aqueous filtrate from the original reaction mixture was extracted with three 50-mL portions of chloroform. The water layer was made acidic by treating it with an acid form cation-exchange resin (8 mL, amberlite IR-120 H^+, 20–50 mesh), the resin was removed by filtration, and the filtrate was extracted with three 50-mL portions of chloroform. The combined chloroform extracts were concentrated to give a white solid, which, when recrystallized from ether, gave **13** (4.0 g, 26%): mp 125–127 °C; IR (KBr) 3000 (broad O–H), and 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{16}O_{10}$ (320.26): C, 45.01; H, 5.04. Found: C, 44.78; H, 5.10.

Methyl Tri-*O*-acetyl-6-deoxy-6-diazo-DL-*xylo*-5-hexulosonate (14). Sodium bicarbonate (0.40 g, 0.0054 mol) was slowly added to an aqueous solution (10 mL) of methyl hydrogen tri-*O*-acetylxylarate (**13**, 1.75 g, 0.0054 mol). The solution was concentrated in vacuo to a syrup, which was dried at room temperature and 0.10 mmHg for 2 h. The glassy solid was added to thionyl chloride (10 mL) and the mixture refluxed for 3 h. Additional thionyl chloride (15 mL in three 5-mL portions) was added during the refluxing period. The excess thionyl chloride was removed in vacuo, and the bulk of the gelatinous mass was dissolved in dry ether (50 mL). Residual inorganic salts were removed by filtration and the filtrate was concentrated in vacuo to give the crude syrupy acid chloride (1.5 g, 0.0044 mol, 82%). A solution of the acid chloride in dry ether (10 mL) was slowly added to a cold (dry ice–acetone bath) solution of diazomethane (1 g, 0.022 mol) in dry ether (50 mL). The reaction mixture was kept cold for 1 h and then concentrated under the hood to give a greenish-yellow oil. Thin layer chromatography (dichoromethane–ether, 4:1) of the mixture showed two products with R_f values 0.90 and 0.75, respectively. The oil (1.5 g) was chromatographed on silica gel (75 g in a 25 × 370 mm column) with dichoromethane–ether, 4:1, as the eluent. The major component, R_f 0.75, was isolated in chromatographically pure form as a light yellow oil (0.80 g, 53%) and identified as methyl tri-*O*-acetyl-6-deoxy-6-diazo-DL-*xylo*-5-hexulosonate (**14**): IR (neat) 2110 (C=N=N), 1740 (C=O), and 1640 cm^{-1} (N=N).

Anal. Calcd for $C_{13}H_{16}N_2O_9$ (344.28): C, 45.35; H, 4.68; N, 8.14. Found: C, 45.21; H, 4.68; N, 7.99.

1,7-Bisdiazoheptane-2,6-dione (15). Glutaryl dichloride was prepared by the method of Marvel and Casey.[20] A solution of dichloride (5.1 g, 0.03 mol) in anhydrous ether (30 mL) was slowly added to a cold solution (dry ice–acetone bath) of diazomethane (0.30 mol). After standing 1 h in the cold, the yellow precipitate was removed by filtration and recrystallized from ether to give 1,7-bis(diazo)heptane-2,6-dione (**15**) as yellow needles (4 g, 74%): mp 62–64 °C (lit.[17] 63–65 °C).

Decomposition of 14 in Acetic Acid. A solution of methyl tri-*O*-acetyl-6-deoxy-6-diazo-DL-*xylo*-5-hexulosonate (**14**, 0.75 g) and

cupric acetate (10 mg) in acetic acid (5 mL) was slowly heated until the evolution of nitrogen began (ca. 65 °C). The temperature was maintained at 65 °C for an additional 5 min and then the solvent was removed by freeze-drying. Thin layer chromatography (dichloromethane–ether, 4:1) of the oily product revealed a distinct spot at R_f 0.75, but with considerable streaking below it. The mixture (0.80 g) was chromatographed on silica gel (40 g in a 20 × 370 mm column) using dichloromethane–ether, 4:1, as the eluent. The major product, isolated in chromatographically pure form, was the one of R_f 0.75 (**17**, 0.32 g, 39%), which on standing for a month crystallized: mp 87–89 °C (lit.[13] 59–61 °C); IR (KBr) 1780 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{20}O_{11}$ (376.32): C, 47.87; H, 5.35. Found: C, 48.05; H, 5.50.

Decomposition of 15 in Acetic Acid. A solution of **15** (1.0 g) and cupric acetate (10 mg) in acetic acid (5 mL) was slowly heated until the evolution of nitrogen began (bath temperature 70 °C). The temperature was maintained at 70 °C for 5 min and the solution was concentrated in vacuo to give a white solid. The solid was recrystallized from ether to give the acyclic diketone **16** (1.0 g, 74%): mp 85–87 °C.

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Registry No.—**1**, 58-86-6; **13** acid chloride, 63181-62-4; sodium hydrogen tri-*O*-acetylxylarate, 63181-65-7; diazomethane, 334-88-3; glutaryl dichloride, 2873-74-7.

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δ-Dicarbonyl Sugars. 6. Preparation of an Unusual Trihaloheptulose from Xylaric Acid

Gerald J. Abruscato,[1a] Donald E. Kiely,*[1a] William J. Cook,[1b] and Charles E. Bugg[1b]

Department of Chemistry and Institute of Dental Research and Department of Biochemistry, University of Alabama in Birmingham, University Station, Birmingham, Alabama 35294

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The formation of 3,4,5-tri-*O*-acetyl-6,7-anhydro-6-chloromethyl-1-deoxy-1-diazo-DL-*ido*-2-heptulose (**3**) as a by-product of the reaction of tri-*O*-acetylxylaryl dichloride (**1**) with diazomethane is described. Treatment of **3** with hydrogen bromide yielded 3,4,5-tri-*O*-acetyl-1,7-dibromo-6-chloromethyl-1,7-dideoxy-α-DL-*ido*-heptopyranos-2-ulose (**5**), which reacted with sodium azide to give a mixture of 3,4,5-tri-*O*-acetyl-2,7-anhydro-1-bromo-6-chloromethyl-1-deoxy-α-DL-*ido*-heptopyranos-2-ulose (**6**) and the 1-azido derivative **7**. The structure of **5** was determined by an x-ray crystallographic analysis.

In an earlier publication from this laboratory,[3] the acetate-induced cyclization of tri-*O*-acetyl-1,7-dibromo-1,7-dideoxy-*xylo*-2,6,-heptodiulose (**4**) was described.[4] This dibromide was prepared by treating crystalline tri-*O*-acetyl-1,7-bisdiazo-1,7-dideoxy-*xylo*-2,6-heptodiulose (**2**) with hydrogen bromide (Scheme I). On the basis of TLC it was deemed that the mother liquors of the reaction mixture that gave **2** were rich in this compound and when treated with hydrogen bromide would give additional **4**. When the crude product from this reaction failed to crystallize, the reaction mixture was treated with sodium azide to see if any bromide displacement might occur. This reaction yielded a crystalline compound whose IR spectrum had a moderately sized absorption due to an azido group, a strong carbonyl absorption, but no hydroxyl peak. Deacetylation gave a crystalline solid whose IR spectrum had the azide peak, a strong hydroxyl peak, but no carbonyl absorption. Reacetylation gave back the precursor acetate.

In order to discover the origin of the acetylated azido compound, a reexamination of the diazomethylation mother liquors was necessary. Column chromatographic purification of a sample of the mother liquors after crystallization of **2** af-

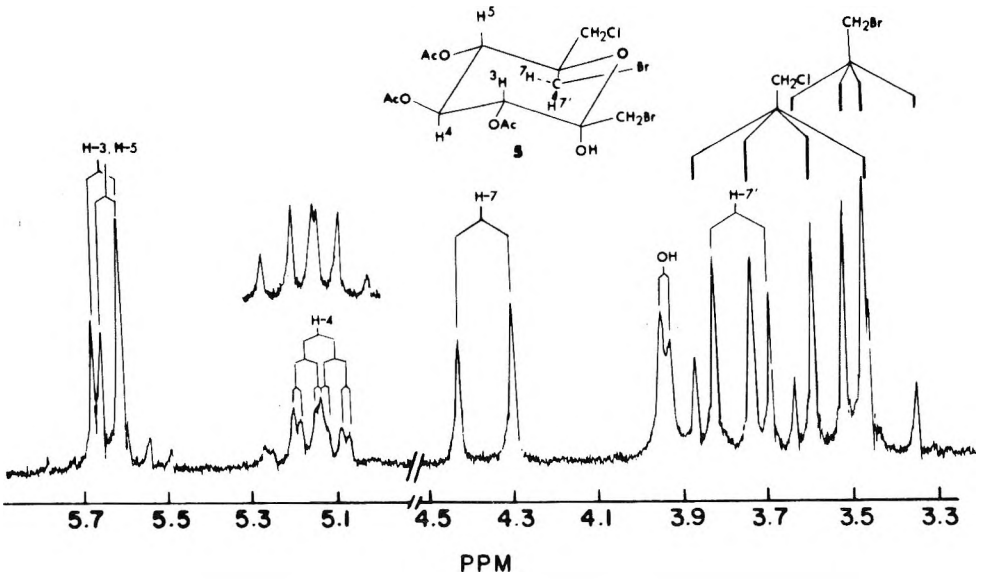
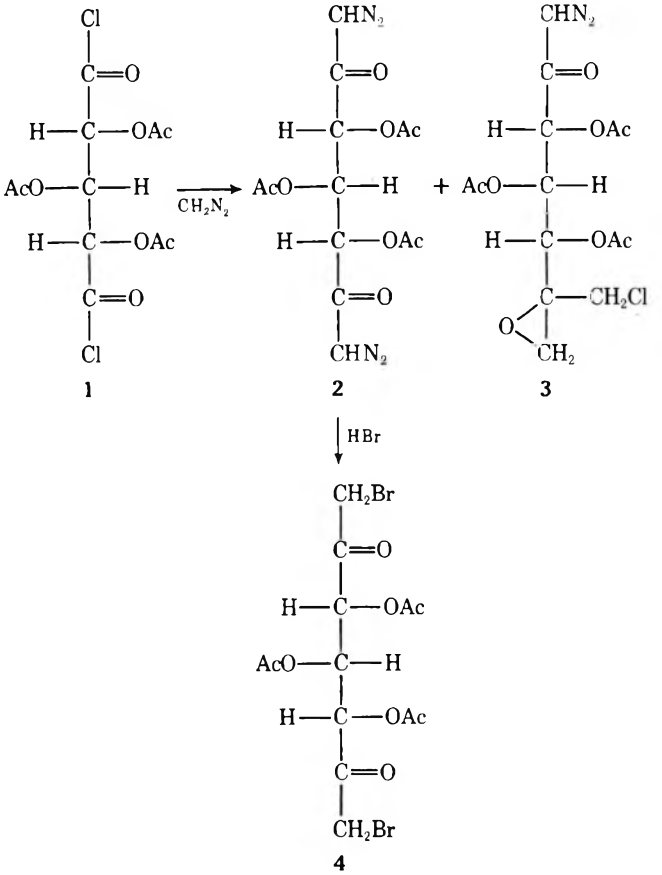
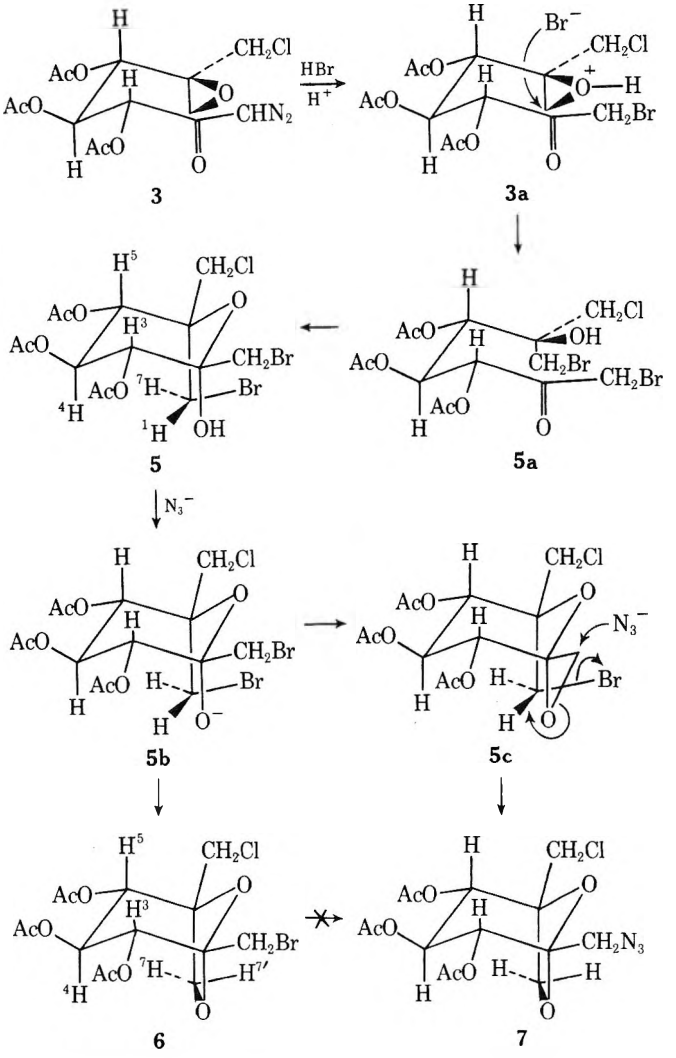


Figure 1. 90-MHz ^1H NMR spectrum of **5** (excluding acetoxy proton signals) with decoupled signals at δ 5.16.

Scheme I



Scheme II



forded additional **2**, dimethyl tri-*O*-acetylxylarate, and a new compound, 3,4,5-tri-*O*-acetyl-6,7-anhydro-6-chloromethyl-1-deoxy-1-diazo-DL-*ido*-2-heptulose (**3**).[2] Treatment of **3** with hydrogen bromide gave crystalline **5**, which was then converted to the product with the azide group (Scheme II).

The ^1H NMR spectrum of **5** (Figure 1) was in good agreement with the structure eventually obtained by x-ray crystallographic analysis (Figure 2). The x-ray structure shows that the molecule in the crystalline state is in a regular chair conformation with the C-1 bromomethyl, chloromethyl, and three acetoxy groups all in equatorial positions. Although crystalline **5** is in a regular chair conformation with the H-3, H-4 and H-4, H-5 dihedral angles calculated to be approximately 175 and 170°, respectively, the conformation of the molecule in $CDCl_3$ solution appears to be somewhat skewed with these same dihedral angles considerably less than what they are in the crystalline state. The couplings between H-4 and its vicinal neighbors are 4.43 and 5.98 Hz, values which are lower than the normal 7–10 Hz associated with two vicinal anti-periplanar protons. H-4 also shows unusual long-range

coupling through five σ bonds with the C-2 hydroxyl proton ($J_{OH,H-4}$ = 1.8 Hz).[5] The fine splitting of the H-4 signal disappears with irradiation of the hydroxyl resonance (Figure 1) or deuterium exchange of the hydroxyl proton.

Although elemental analysis, TLC, and melting point range all indicate that **5** is a homogeneous substance, the ^{1}H NMR spectrum shows some impurities as reflected in the extraneous peaks accompanying the signals from the ring protons, particularly H-4. These impurities might include the β anomer of **5** and/or small amounts of the anomers resulting from bromide attack at the tertiary epoxide carbon of **3.** Excellent correlation between the observed coupled and decoupled spectra of **5** with their theoretical counterparts was obtained when these minor peaks were considered to be from impurities in the sample.

The product obtained from treating **5** with sodium azide was determined to be the bicyclo compound 3,4,5-tri-*O*-acetyl-2,7-anhydro-1-bromo-6-chloromethyl-1-deoxy-α-DL-*ido*-heptopyranos-2-ulose (**6**) contaminated with about 30% of the 1-azido derivative **7** (Scheme II). The mixture of **6** and **7** was separated by preparative TLC, but only with difficulty. However, pure **6** was easily obtained by preparative TLC after the mixture was catalytically hydrogenolyzed, presumably converting **7** to a more polar amine derivative.

The conversion of **5** to **6** was likely the result of a simple intramolecular nucleophilic displacement of the C-7 bromine with the azide-generated C-2 alkoxide ion **5b.** The structural assignment for **7,** and in particular the point of attachment of the azido group, is partially based on a comparison of the ^{1}H NMR spectra of **6** and **7.** The spectrum of **7** shows an upfield shift (0.1 ppm) of the C-1 methylene singlet, a result in keeping with displacement of the C-1 bromide with azide. In all other respects the two spectra are nearly identical.

In considering the formation of **7** direct backside displacement of the C-1 bromide of either **5** or **6** is unlikely due to the steric shielding of this carbon by the C-2 oxygen. In fact, a mixture of **6** and **7** (**6**/**7** ca. 7:3) remains unchanged when treated with azide under those conditions that produced **7** from **5.** We have concluded that the anionic oxygen of **5b** in addition to forming the dioxolane system of **6** can also displace the C-1 bromide giving a transient epoxide **5c,** which is then opened with azide to give **7.**

The evidence for the stereochemistry of the epoxide in **5** is found in the proposed mechanism for the conversion of **3** to **5** with hydrogen bromide. Protonation of the epoxide oxygen to give **3a** is followed by ring opening with bromide at the sterically favored primary carbon, this step leading to **5** by way of its acyclic isomer **5a.**

Experimental Section

General Methods. All melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrophotometer and proton magnetic resonance spectra were obtained on either a Varian Model EM-390 or HA-60IL spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded using a Hitachi-Perkin-Elmer Model RMU-7 double focusing mass spectrometer. All solvent evaporations were done using a flash evaporator at 20–40 mmHg and at a bath temperature of 35–40 °C. Analytical TLC was carried out on microscope slides coated with silica gel GF-254 (E. Merck, Darmstadt, W. Germany) and visualized by spraying with sulfuric acid and then charring. Preparative TLC was carried out on 20 × 20 cm plates precoated with a 1000-μm thickness of silica gel GF (Analtech, Inc., Newark, Del). Column chromatography was carried out using silica gel 60 (70–230 mesh, E. Merck, Darmstadt, W. Germany). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

3,4,5-Tri-*O*-acetyl-6,7-anhydro-6-chloromethyl-1-deoxy-1-diazo-DL-*ido*-2-heptulose (3). The diazomethylation of 2,3,4-tri-*O*-acetylxylaryl dichloride (**1**) was carried out as described in ref 2 to yield crystalline 3,4,5-tri-*O*-acetyl-1,7-bisdiazo-1,7-dideoxy-*xylo*-2,6-heptodiulose (**2**). The mother liquors from **2** were chromatographed affording syrupy **3** (2.1 g), which was homogeneous by TLC but possessed an ambiguous ^{1}H NMR spectrum. Upon dissolving this syrup in methylene chloride, diluting the solution with an equal volume of ether, seeding with crystals of **2,** presumably contaminated with **3,** and storing at −10 °C, crystalline **3** was obtained (300 mg, 1.7% based on **1**). An additional crop of **3** (255 mg, 1.5%) was obtained by concentrating the mother liquor to a syrup, dissolving it in ethanol, diluting with water to a very slight tubidity, and storing at −10 °C. Compound **3** had a mp of 90–92 °C [IR (KBr) 2115 (C=N=N), 1750 (C=O), and 1630 cm^{-1} (N=N); ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 6, two CH_3CO_2), 2.23 (s, 3, CH_3CO_2), 2.85 and 2.96 (both d, each 1, J_{gem} = 5 Hz, epoxide CH_2), 3.63 and 3.85 (both d, each 1, J_{gem} = 12 Hz, CH_2Cl), 5.38 (complex m, 3, three CHOAc), and 5.50 (s, 1, CHN_2); mass spectrum (70 eV) *m/e* 377 (M + 1) and 379 (M + 3) relative intensity ca. 3:1, monochlorine isotopic cluster].

Anal. Calcd for $C_{14}H_{17}O_8N_2Cl$ (376.76): C, 44.36; H, 4.55; Cl, 9.41; N, 7.44. Found: C, 44.56; H, 4.56; C l, 9.61; N, 7.33.

3,4,5-Tri-*O*-acetyl-1,7-dibromo-6-chloromethyl-1,7-dideoxy-α-DL-*ido*-heptopyranos-2-ulose (5). Gaseous HBr was bubbled into a suspension of **3** (100 mg) in 5 mL of anhydrous ether while stirring. After about 2 min the solid went into solution and the effervescence stopped. More HBr was bubbled in for another 2 min and the reaction was allowed to stand for 10 min. The solution was then treated with a molecular sieve until it was no longer acid to litmus. The sieve was removed by filtration and the filtrate concentrated to a syrup and dried in vacuo (ca. 1 mmHg) for 3 h. The resulting froth was crystallized from ether and the solid formed was recrystallized from hot ethanol to yield **5** (100 mg, 74%) [mp 142–145 °C with softening at 140 °C; IR (KBr) 3500 (sharp, free OH), 3450 (broad, hydrogen-bonded OH), and 1750 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, Figure 1) δ 2.01, 2.05, 2.12 (each s, each 3, CH_3CO), 3.53 and 3.77 (both d, each 1, J_{gem} = 12.0 Hz, CH_2Cl), 3.42 and 3.54 (both d, each 1, J_{gem} = 10.5 Hz, equatorial CH_2Br), 3.75 (d, 1, $J_{H-7,H-7'}$ = 11.7 Hz, H-7'), 4.35 (d, 1, $J_{H-7,H-7'}$ = 11.7 Hz, H-7), 3.94 (d, 1, $J_{OH,H-4}$ = 1.8 Hz, OH confirmed by deuterium exchange), 5.16 (m, 1, H-4 coupled to H-3, H-5, and OH), and 5.65 and 5.66 (overlapping doublets, couplings with H-4 of 4.43 and 5.98 Hz, resonances attributed to, but not specifically assigned to, H-3 and H-5); mass spectrum (70 eV) *m/e* 509 (M + 1)]. The mass spectrum of **5** also exhibited the following isotopic clusters: weak, dibromine (M − CH_2Cl) at *m/e* 459, 461, and 463, relative intensity ca. 1:2:1; strong, monochlorine–monobromine (M − CH_2Br) at *m/e* 415, 417, and 419, relative intensity ca. 3:4:1; strong, dibromine (M − CH_2Cl, HOAc) at *m/e* 399, 401, and 403; and strong, monobromine (M − HCl, Br) at *m/e* 393 and 395, relative intensity ca. 1:1.

Anal. Calcd for $C_{14}H_{19}O_8Br_2Cl$ (510.58): C, 32.93; H, 3.75; Br, 31.30; Cl, 6.95. Found: C, 33.19; H, 3.88; Br, 30.94; Cl, 6.77.

For x-ray crystallographic analysis clear, rectangular, platelike crystals of **5** were obtained by room temperature crystallization from ethanol. Weissenberg and oscillation photographs showed that the crystals are monoclinic; the space group is $P2_1/c$, as indicated by the systematic absence of reflections $h0l$ with l odd and $0k0$ with k odd. A crystal with approximate dimensions of 0.4 × 0.3 × 0.2 mm was mounted along its a axis on a Picker FACS-1 diffractometer. Cell

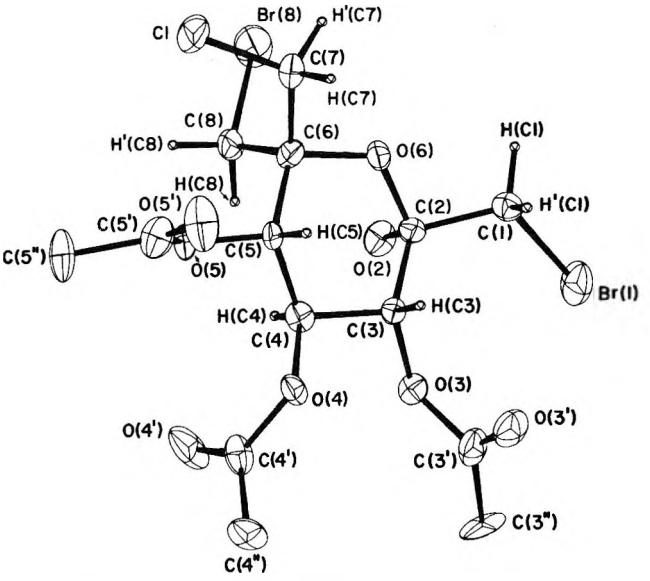


Figure 2. Stereoview of compound **5.**

dimensions, which were determined by a least-squares analysis of the 2θ values for 14 medium-angle reflections (Cu Kα, λ 1.5418 Å), are a = 6.060 (2), b = 13.193 (5), c = 24.688 (4) Å, and β = 102.21 (2)°.

Intensity data were collected with the diffractometer, by use of nickel-filtered copper radiation, a scintillation counter, and a θ–2θ scanning technique. Measurements were made for the 3199 reflections with $2\theta \leq 128°$. The scanning speed was 1°/min for the $h \geq 0, \geq 0, l \geq 0$ sector of reciprocal space. However, the crystal began to show signs of decomposition, and the scanning speed was increased to 2°/min for the remainder of the data collection. The intensities of three reference reflections (200, 020, and 001) that were monitored periodically during the data collection decreased continuously to about 75% of their original values. The intensity values were scaled by a least-squares procedure in which the intensities of the standard reflections were used to calculate scale factors as a function of crystal exposure time. Intensities were assigned variances, $\sigma^2(I)$, according to the statistics of the scan and background counts plus a correctional term $(0.03S)^2$, S being the scan count. The intensities and their variances were corrected for Lorentz and polarization factors, absorption corrections were applied by using the computer program ORABS,[8] and the data were scaled by means of a Wilson[7] plot.

A trial structure was obtained by the heavy-atom method as follows: coordinates for one bromine atom were determined from a sharpened Patterson map; coordinates for the second bromine atom were determined from a sum-function superposition of sharpened Patterson maps translated to the first bromine atom position; and the remaining nonhydrogen atoms were located in a Fourier map that was calculated by using phase angles derived from the two atoms. The trial structure was refined by using a modified version of the full-matrix least-squares program ORFLS.[9,10] The quantity minimized was $\Sigma w[(F_o^2 - F_c^2)/k^2]^2$, where k is a scale factor and weight w is equal to $1/\sigma^2(F_o^2)$. Scattering factors for the nonhydrogen atoms were from the "International Tables for X-Ray Crystallography",[11] anomalous dispersion correction factors for these atoms were from Cromer and Liberman,[12] and hydrogen atom scattering factors were from Stewart, Davidson, and Simpson.[13] Coordinates for those hydrogen atoms bonded to carbon atoms (excluding methyl groups) were calculated by assuming tetrahedral coordination around the carbon atoms and C–H bond distances of 0.95 Å. The hydrogen atoms were assigned the isotropic temperature factors of the carbon atoms to which they are bonded, and were included in the calculation of structure factors, but not in the least-squares refinement. The nonhydrogen atom positional parameters, the anisotropic temperature parameters, and Zachariasen's[14] isotropic extinction parameter g (as formulated by Coppens and Hamilton[15]) were included in the refinement.

The final R index $(\Sigma\|F_o| - |F_c\|/|F_o|)$ is 0.130, and the goodness-of-fit $\{[\Sigma w[(F_o^2 - F_c^2)/k^2]/(m - s)]^{1/2}$, where m is the number of reflections used and s is the number of parameters refined$\}$ is 1.38. During the last cycle of refinement, no parameter shifted more than one-fourth of its estimated standard deviation. A final difference Fourier map showed several peaks and troughs of magnitudes ranging from 0.6 to 1.1 e/Å in the vicinities of the bromine atoms; there were no other peaks or troughs in excess of 0.6 e/Å^3.

3,4,5-Tri-*O*-acetyl-2,7-anhydro-1-bromo-6-chloromethyl-1-deoxy-α-DL-*ido*-heptopyranos-2-ulose (6) and 3,4,5-Tri-*O*-acetyl-2,7-anhydro-1-azido-6-chloromethyl-1-deoxy-β-DL-*ido*-heptopyranos-2-ulose (7). A solution of **5** (200 mg, 0.39 mmol) in 5 mL of anhydrous acetone was stirred at room temperature with NaN_3 (500 mg, 1.3 mmol) overnight. Analysis of this reaction mixture by TLC (6:1, benzene–ether) showed the absence of starting material and only one spot of greater R_f value than the starting material. The mixture was diluted with 100 mL of chloroform and concentrated to a paste. This paste was triturated with chloroform and the resulting solid and liquid mixture was washed twice with water. The chloroform layer was dried and decolorized over a mixture of $CaCl_2$ and decolorizing carbon and after filtration of the mixtures and concentration of the filtrate the product was crystallized from ether. The solid was filtered and washed with ether to yield 100 mg of a slightly yellow-tinted material (mp 122–125 °C) subsequently determined to be a mixture of **6** contaminated with ca. 30% of **7**. No change in the ratio of these compounds, as evidenced by ^{1}H NMR spectroscopy, was observed when the mixture was treated overnight with azide as described. A mass spectrum of this mixture exhibited a parent ion (m/e 428) for **6** and a parent ion (m/e 391) for **7** along with several isotopic clusters: strong, monobromine (from **6**, M − Cl) at m/e 393 and 395, relative intensity ca. 1:1; strong, monochlorine–monobromine (from **6**, M − OAc) at m/e 369, 371, and 373, relative intensity ca. 3:4:1, and strong, monochlorine (from **7**, M − OAc) at m/e 332 and 334, relative intensity ca. 3:1.

The mixture (100 mg) of **6** and **7** dissolved in 10 mL of ethanol containing 0.2 mL of 6 N HCl was hydrogenated over Pt (from 100 mg of PtO_2) for 2 h at atmospheric pressure. A TLC (1:1, benzene–ether) of this reaction mixture showed one spot of identical R_f value with that of the starting mixture and another spot at the origin. After customary workup, the major component, the one not at the origin, was recovered by preparative TLC (9:1, benzene–ether). The crystalline product was recrystallized from hot ethanol to yield pure **6** (55 mg, 33% from **5**) [mp 136–138 °C; IR (KBr) 1755 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.98, 2.03, 2.15 (each s, each 3, CH_3CO_2), 3.47 (s, 2, CH_2Br), 3.68 (s, 2, CH_2Cl), 3.83 (d, 1, J_{gem} = 8.0 Hz, H-7′), 4.34 (d, 1, J_{gem} = 8.0 Hz, H-7), and 5.28 (unresolved m, 3, H-2, H-3, and H-4)].

Anal. Calcd for $C_{14}H_{18}BrClO_8$ (429.66): C, 39.13; H, 4.22; Br, 18.60; Cl, 8.25. Found: C, 39.29; H, 4.24; Br, 18.70; Cl, 8.49.

Another sample of the mixture of **6** and **7** (100 mg) was separated by preparative TLC (developing with 9:1 benzene–ether and visualizing with iodine vapor) into three fractions: the head, middle, and tail of a broad band. The head fraction was found to still contain a small amount of azide **7** (IR band at 2100 cm^{-1}), so it was chromatographed again on a preparative TLC plate. Again, the head fraction of this band was scraped off and extracted with acetone to give 15 mg of pure **6**. The tail fraction of the first chromatogram was also chromatographed again and the tail of this band yielded 5 mg of **7** [mp 125–128 °C; IR (KBr) 2110 (N_3) and 1750 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3, CH_3CO_2), 2.04 (s, 6, two CH_3CO_2), 3.37 (s, 2, CH_2N_3), 3.68 (s, 2, CH_2Cl), 3.84 (d, 1, J_{gem} = 8.0 Hz, H-7′), 4.33 (d, 1, J_{gem} = 8.0 Hz, H-7), and 5.27 (unresolved m, 3, H-2, H-3, and H-4)].

Deacetylation of the Mixture of 6 and 7. A 200-mg sample of the mixture of **6** and **7** was suspended in 5 mL of absolute methanol and sodium methoxide was added in small amounts while stirring until the solid dissolved. The reaction was stirred for an additional 5 min and a TLC (6:1, benzene–ether) at this point showed the absence of starting material and only one spot at the origin. The reaction mixture was treated with acid ion-exchange resin until neutral and then allowed to stand over decolorizing carbon for 10 min. The resin and charcoal were removed by filtration and the filtrate was concentrated to a syrup. This syrup crystallized upon standing overnight. The solid was recrystallized by dissolving it in several drops of absolute methanol, diluting with 25 mL of $CHCl_3$, and then concentrating just until crystallization began to occur. This yielded 50 mg of a solid of mp 135–139 °C. An IR of this solid showed a strong, broad hydroxyl absorption at 3340 cm^{-1}, a small sharp azide peak at 2100 cm^{-1}, but no carbonyl absorption. Its ^{1}H NMR spectrum, taken in both acetone-d_6 and D_2O, showed the absence of any acetate groups, a complex multiplet centered at about δ 3.8, and a broad peak for the hydroxyl protons at about δ 4.5.

This solid and its mother liquor were combined and concentrated to a syrup. The syrup was dissolved in 2 mL of pyridine and 1.5 mL of acetic anhydride and allowed to stand for 3 h. TLC (6:1, benzene–ether) showed the complete disappearance of starting material and only one spot of identical R_f value as that of the original mixture of **6** and **7**. Standard workup of the reaction mixture yielded 35 mg of a solid (mp 123–125 °C), identified as the mixture of **6** and **7** by its IR and NMR spectra.

Acknowledgment is made to the National Institutes of Health, Grants No. GM-19252, CA-12159, DE-02670, and CA-13148, for support of this research. We thank Drs. C. L. Watkins and J. M. Riordan of the Chemistry Department for running some of the ^{1}H NMR spectra and Drs. T. P. Pitner and J. D. Glickson of the University of Alabama in Birmingham Comprehensive Cancer Center as well as J. M. Riordan for their help in obtaining the theoretical ^{1}H NMR spectra.

Registry no.—**2**, 38910-01-9; **3**, 63181-43-1; **5**, 63181-44-2; **6**, 63181-45-3; **7**, 63215-73-6.

Supplementary Material Available: Tables of hydrogen and nonhydrogen atomic parameters with estimated standard deviations and a table of selected bond angles (4 pages). Ordering information is given on any current masthead page.

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Synthesis of Cholest-5-ene-3β,11α,15β-triol-7-one. A Model for the Steroid Nucleus of Oogoniol, a Sex Hormone of the Water Mold *Achlya*

Evelyn J. Taylor[1] and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

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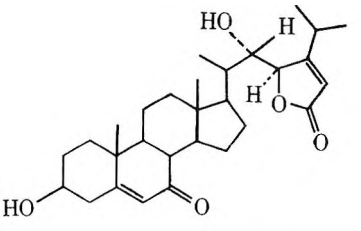
The synthesis of cholest-5-ene-3β,11α,15β-triol-7-one (**4**), a compound containing the nuclear functionalities of oogoniol, is described. Starting from a relatively unfunctionalized steroid, 7-dehydrocholesterol benzoate, oxygen functions were introduced into rings B, C, and D. The first stage of the synthesis was the oxygenation of C-15 through the hydroboration of cholesta-7,14-dien-3β-ol (**7b**) to give cholest-7-ene-3β,15α-diol (**8**). Then the 11α-alcohol and C-7 ketone functions were introduced via the Δ^7 double bond by a series of reactions first developed in the early 1950s to oxygenate C-11 of ring C unsubstituted steroids for corticosteroid syntheses. The resulting cholestane-3β,11α,15α-triol-7-one (**12a**) was selectively acetylated at C-3 and C-11 and the Δ^5 double bond was introduced through a bromination–dehydrobromination sequence. The final stage of the synthesis was the inversion of the C-15 alcohol to generate the desired β configuration. The 15α-alcohol was oxidized to the ketone and subsequent hydride reduction yielded predominantly the 15β-alcohol. This reduction also reduced the unsaturated C-7 ketone which was then oxidized with manganese dioxide. Saponification of the 3β- and 11α-acetates produced the desired cholest-5-ene-3β,11α,15β-triol-7-one (**4**), which proved to be biologically inactive.

Sexual reproduction in the water mold *Achlya* has been thoroughly studied and the involvement of sex hormones regulating this process has been conclusively demonstrated.[2] Sexual reproduction in *Achlya bisexualis* is initiated by the secretion of antheridiol (**1**) by the female strain which induces the formation of antheridial branches in the male strain. Antheridiol, isolated as a crystalline compound[3] and shown to have structure **1**,[4] was the first steroidal sex hormone to be identified in the plant kingdom and several syntheses have been reported.[5] After stimulation by anteridiol, the sexually activated male strain releases a second hormone, hormone B, which causes the female strain to develop oogonial branches. From a hermaphroditic strain of *Achlya heterosexualis* which produces hormone B without prior stimulation by anteridiol, McMorris and co-workers have recently isolated and characterized two crystalline compounds having hormone B activity.[6] They have named these compounds oogoniol-1 and -2 and have proposed structures **2a, 2b,** and **2c,** respectively, for these two compounds plus a third closely related compound, oogoniol-3, which was obtained as part of a noncrystalline mixture.



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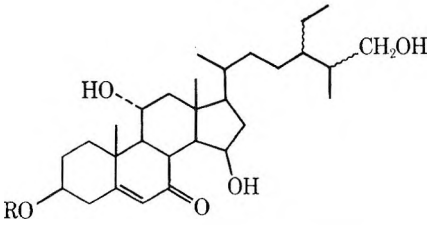
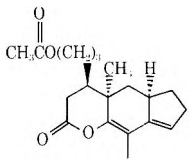


2a, R = $(CH_3)_2CHC{=}O$
2b, R = $CH_3CH_2C{=}O$
2c, R = Ac
2d, R = H

The oogoniols are therefore the second example of steroidal plant sex hormones to be identified, and confirmation of the structure assignment by synthesis is desirable. Even more importantly, structural modification would permit an evaluation of the structural specificity of the biological activity associated with the different functionalities of structure **2.** Oogoniol-1, -2, and -3 (**2a, 2b,** and **2c**) differ only in the kind of ester group present at C-3. The parent tetraol **2d,** which will be referred to here simply as oogoniol, has been shown to be even slightly more biologically active than **2a** and **2b.**[6] It was therefore decided to devise a synthesis of oogoniol (**2d**) rather than any of the C-3 esterified compounds **2a, 2b,** and **2c.**

Any synthesis of oogoniol utilizing a steroidal starting material can be logically divided into two parts. One part is the construction of the side chain, which ideally should be stereospecific so that the stereochemistry and absolute configuration at C-24 and C-25 can be determined. The other part



iii

identical with the lactone prepared from **8** by hydrolysis and acetylation. This confirms the trans relationship between the methyl and side chain in **12**.

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Robert K. Boeckman, Jr.,*[23,24] James P. Bershas
Department of Chemistry, Wayne State University
Detroit, Michigan 48202

Jon Clardy,*[25] Barbara Solheim
Ames Laboratory USERDA and Department of Chemistry
Iowa State University
Ames, Iowa 50011

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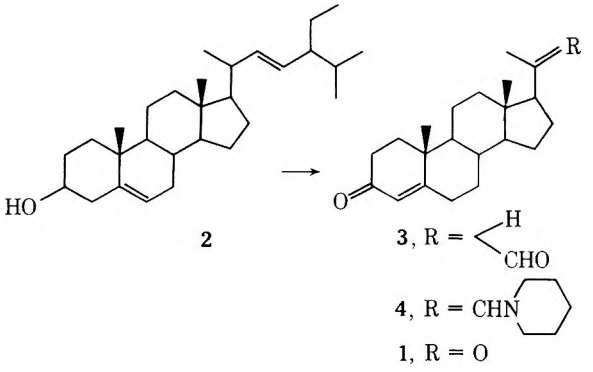
A Convenient Synthesis of Progesterone from Stigmasterol

Summary: A convenient synthesis of progesterone from stigmasterol is described involving as the key step the high yield photooxygenation of the 20-aldehyde **5** to the 20-ketone **10.**

Sir: One of the most important manufacturing processes[1] of the female sex hormone progesterone (**1**), which is also a key intermediate in the synthesis of corticosteroids, starts with stigmasterol (**2**). The final steps involve selective conversion of the aldehyde **3** to the 22-enamine **4**, followed by oxidation



2

3, R =

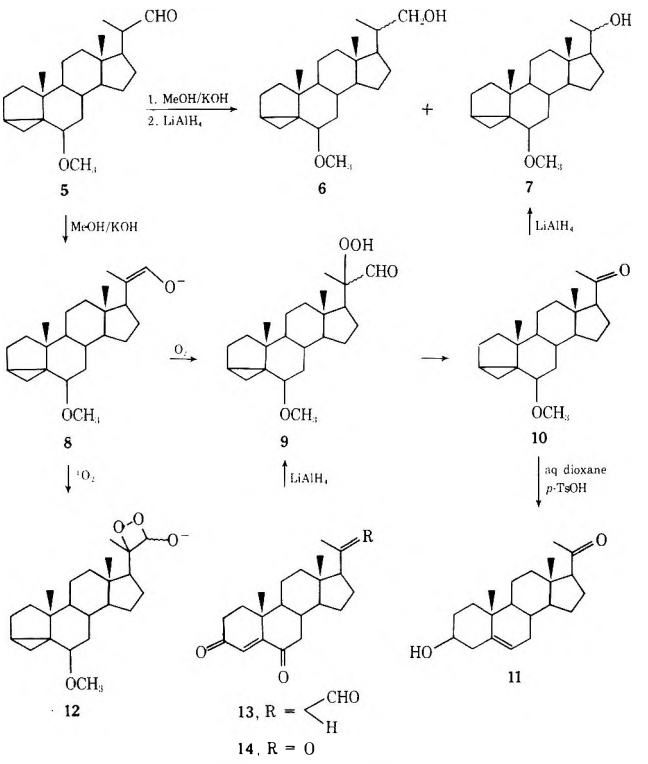
4, R =

1, R = O

under a variety of conditions (ozonization, photooxidation) to progesterone.

During a recent synthesis[2] of novel marine sterols, we encountered an unexpected oxidation reaction: epimerization of aldehyde **5** with methanolic potassium hydroxide for 60 h, followed by reduction with lithium aluminum hydride yielded, in addition to the expected mixture of alcohols **6**, the epimeric 20-hydroxy pregnane derivatives **7** in 35% yield (Scheme I). This side reaction, which probably proceeds via the intermediate hydroperoxide[3] **9**, prompted a more detailed study which has now resulted in a simple one-step conversion of the aldehyde **5** into the corresponding 20-ketone **10** and thence to progesterone (**1**).

Scheme I



12

13, R =

14, R = O

Stigmasterol (**1**) can be converted in excellent overall yield[4] to the 22-aldehyde **5**, 1.0 g of which was dissolved in 50 mL of 10% methanolic potassium hydroxide solution and cooled to 0 °C. After the addition of 15 mg of rose bengal sensitizer, oxygen was bubbled through the solution for 10 min with continuous irradiation from a 1000 W tungsten lamp. The reaction mixture was poured into water, extracted with ether, and washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water. Evaporation of the dried ether extract gave the 20-ketone **10**, which was directly hydrolyzed by heating for 15 min under reflux in 20% aqueous dioxane containing 100 mg of *p*-toluenesulfonic acid, to afford the standard progesterone precursor pregn-5-en-3β-ol-20-one (**11**) in 94% overall yield (based on **5**). The Oppenauer oxidation of **11** to progesterone (**1**) is a standard commercially utilized operation.[5]

When the reaction was carried out in the absence of light or of the sensitizer no detectable amount of the ketone **10** was formed. Under identical conditions, but in the presence of Dabco,[6] a singlet oxygen quencher, only a 35% conversion (GC analysis) to **10** was realized. These reactions confirm that the 20-ketopregnane **10** is formed by a photooxidation process probably via the dioxetane intermediate **12** formed from the enol **8** by a (2 + 2) cycloaddition process[7] with singlet oxygen.

The reaction sequence outlined in this communication, coupled with the facile high-yield conversion[4] of stigmasterol (**2**) to the 22-aldehyde **5**, provides a very efficient and relatively inexpensive method for the synthesis of pregnenolone (**11**) and hence of progesterone.

An attempt was also made to eliminate the need for the *i*-methyl ether protecting group of **5** by carrying out the sensitized photooxygenation directly on the unprotected keto aldehyde **3**. While progesterone (**1**) was formed in 60% yield, it was invariably contaminated by ~10% each of the 6-keto aldehyde **13**[8] and the trione **14**,[9] thus making this alternative and much shorter synthesis of progesterone (**1**) a less efficient one.

Acknowledgment. We are grateful to the National Institutes of Health for financial assistance (Grant No. GM-06840)

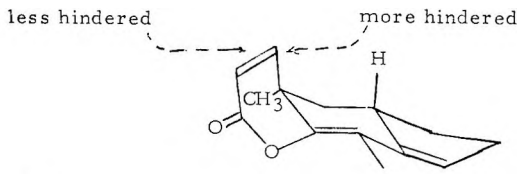
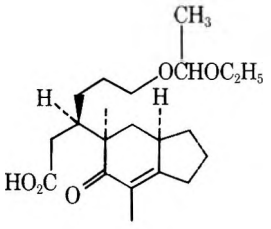


Figure 2.

difficult. Examination of a model (Figure 2) suggests that the required mode of addition, while favored stereoelectronically, is rather more hindered than addition from the outside of the concave ring system. Precedent exists that steric hindrance to approach of the reagent can markedly influence the stereochemical outcome.[20]

Treatment of **4b** under comparable conditions with the mixed cuprate described above (1.7 equiv, −40 → 0 °C, 18 h) provided adduct **12** as the major product (50%).[21] In this case, stereoelectronic control still dominates in spite of the steric hindrance. Lactone **12** was then elaborated to ketone **15** by a comparable series of steps as those described for **8** to **11** (Scheme I).

We have examined two methods for introduction of the final asymmetric center in the ceroplastol series. Treatment of lactone **8** with KOH in ethanol (1.8 equiv, 25 °C, 18 h) afforded **16.** Reduction of **16** with Li/NH_3 (excess) and reoxidation (CrO_3/acetone, 0 °C) gave **17** in ~60% overall yield.[22] As can



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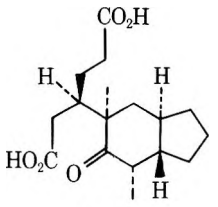

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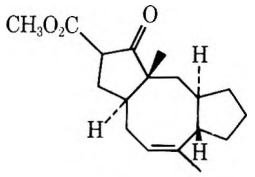

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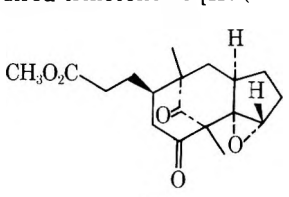
be seen, transformation of acid **17** via the lactone rearrangement–fragmentation sequence would be expected to lead to ester **18** possessing the correct relative asymmetry for the ceroplastols.[10,13] Alternatively, diketo ester **9** undergoes stereoselective epoxidation (MCPBA/CH_2Cl_2, 25 °C), affording ester **19** in ~70% yield. Rearrangement of **19** with boron trifluoride etherate (1.05 equiv, CH_2Cl_2, −78 °C) gave the desired triketone **20** [IR (cm^{-1}) 1740, 1735, 1715] in which the



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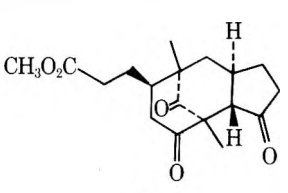

20

final asymmetric center is introduced stereospecifically by migration of the adjacent β hydrogen. Again, triketone **20** possesses all the asymmetry required for the ceroplastol system.[10,13]

We are currently exploiting this methodology in our approaches to the natural substances **1** and **2.**

Acknowledgment. This research was generously supported by a grant (AI-11662) from the Allergy and Infectious Diseases Institute of the National Institutes of Health, to whom we are grateful.

Supplementary Material Available: Fractional coordinates and temperature factors (Table I), bond distances (Table II), and bond angles (Table III) for compound **10** (4 pages). Ordering information is given on any current masthead page.

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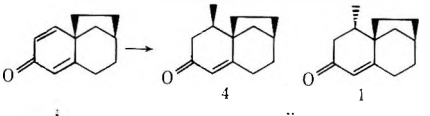
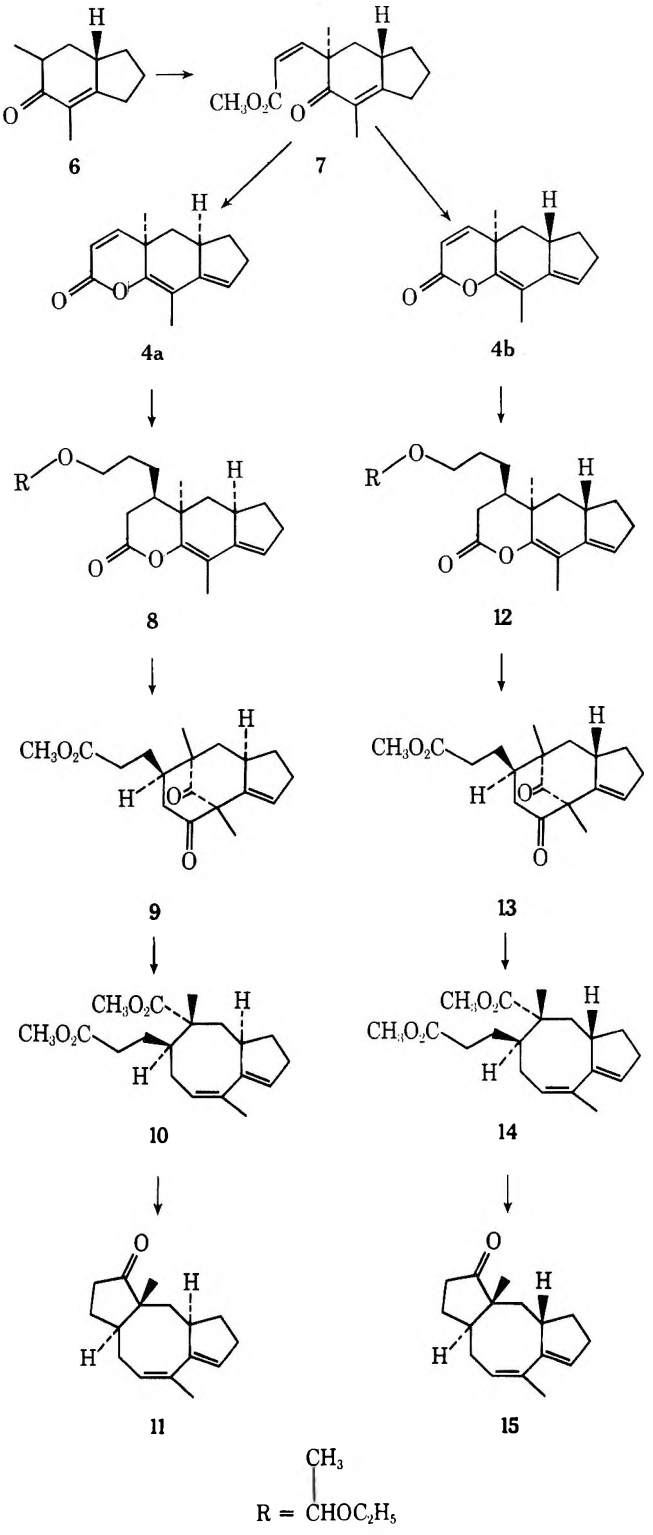
(13) Note that the apparent epimerization which occurs upon transformation of **8** → **10** is the result of the change in the stereochemical plane of reference from the six-membered ring in **8** to the eight-membered ring in **10.** No actual change of configuration occurs.
(14) R. A. Raphael, J. Martin, and W. Parker, *J. Chem. Soc.*, 289 (1964).
(15) Compound **10** crystallized in the triclinic crystal class with unit cell dimensions $a = 8.334$ (2), $b = 9.753$ (3), $c = 11.466$ (3) Å, $\alpha = 78.10$ (2), $\beta = 92.47$ (2), and $\gamma = 78.04$ (2)°. An approximate density of 1.20 g/cm^3 indicated two molecules of $C_{19}C_{19}H_{28}O_4$ per unit cell of either *P*1 or *P*$\bar{1}$. All unique reflection data with $2\theta \leq 114°$ were collected using graphite monochromated Cu Kα (1.54178 Å) x rays. A total of 2690 diffraction maxima were surveyed and after correction for Lorentz, polarization, and background effects 2371 (91%) were judged observed ($F_o^2 \leq 3\sigma(F_o^2)$).
Intensity statistics[16] suggested the centric space group *P*$\bar{1}$, and solution of the crystal structure was undertaken in this space group. Signs were determined for the 200 largest normalized structure factors using a multisolution, weighted sign determining procedure.[17] All nonhydrogen atoms were located in three-dimensional *E* synthesis from the most consistent set. Full-matrix least-squares refinement followed by a difference synthesis revealed all of the hydrogen atoms.[18] Further refinement with anisotropic thermal parameters for the nonhydrogen atoms and isotropic thermal parameters for the hydrogens have currently reached a minimum of 0.047 for the observed reflections. Bond distances and angles generally agree well with accepted values. Additional crystallographic details may be found in the supplementary material.
Figure 1 is a computer-generated drawing of the final x-ray model without hydrogens. Both enantiomers are present in the unit cell. The important point is the relative configurations at the three asymmetric centers C(2), C(1), and C(10). With reference to the eight-membered ring the hydrogens at C(2) and C(10) and the carbomethoxy group at C(11) are all on the same side.
(16) A. J. C. Wilson, *Acta Crystallogr.*, 2, 318 (1949); H. Hamptmann and J. Karle, ACA Monograph No. 3, Polycrystal Book Service, Pittsburgh, Pa., 1953.
(17) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(18) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT, and FRIEDEL", USAEC Report IS-2625, Iowa State University, Institute for Atomic Research, Ames, Iowa 1971; W. R. Busing, K. O, Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP", A Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(19) G. H. Posner, *Org. React.*, **19**, 1 (1972).
(20) Marshall observed primarily equatorial introduction of methyl (**4**:1) to cyclohexadienone i to give ii; presumably axial approach is prohibited, cf. J. A. Marshall and S. F. Brady, *J. Org. Chem.*, **35**, 4068 (1970).



i ii

(21) Adduct **12** was compared to **8** by saponification and relactonization under equilibrating conditions. This procedure provided a lactone iii which was

Scheme I



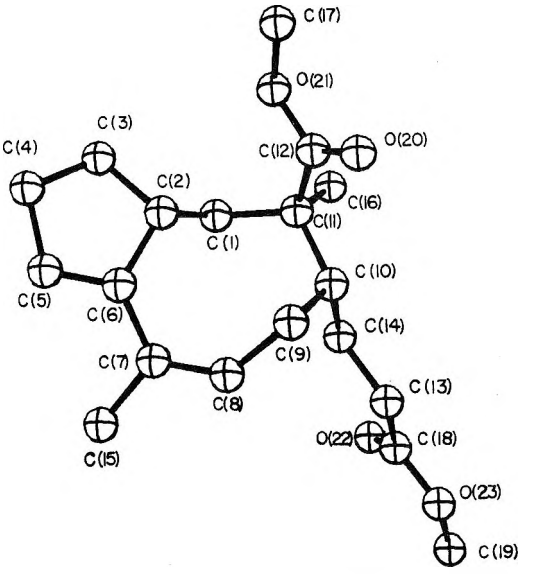


Figure 1. A computer-generated perspective drawing of **10**. Hydrogens are omitted for clarity.

the required functionalized cyclooctenes by fragmentation. We have demonstrated the successful application of this strategy as described below.

Treatment of the pyrrolidine enamine of cyclopentanone with isopropenyl ethyl ketone under modified conditions provided bicyclic ketone **6** [bp 84–88 °C (1.5 mm)] in 59% yield (Scheme I).[5,6] To produce the required *cis*-acrylate side chain, we employed the cross-conjugated enolate of **6** (LiICA, −28 °C) to control regiochemistry.[7] Quenching with *cis*-3-chloroacrylate (1.1 equiv, −78 °C, 5 h) afforded, by addition–elimination, the required *cis*-acrylate ester **7** [bp 125 °C (0.4 mm)], NMR δ 5.90 (s, 2 H), 3.65 (s, 3 H), in 74% yield. This is the first example of addition–elimination to a cross-conjugated enolate, and it proceeds with clean retention (for the trans isomer also). It appears that use of the *cis*- and *trans*-chloroacrylates will be a valuable method for stereospecific introduction of an acrylate side chain in some cases. After saponification of **7** (1.1 equiv of KOH, 25 °C 48 h) which provided **3**,[8] the crystalline (mp 72.5–75 °C) enol lactone **4a** [NMR δ 6.7 (d, J = 10 Hz, 1 H)] was obtained as the major product (3:1) under acidic lactonization conditions [$HClO_4$-(cat), 10 equiv of Ac_2O, 0 °C, 2 m] in ~80% yield.[9] Epimerization occurs during lactone formation, leading to **4a** in the ceroplastol series.[10] Isolation of the intermediate mixed anhydride and completion of lactonization under basic conditions, shown not to equilibrate the epimers, led to the same major product, suggesting equilibration prior to cyclization. Alternatively, **4b** [NMR δ 6.6 (d, J = 10 Hz, 1 H)] is produced as the major isomer (7:1) upon lactonization under basic conditions ($NaOAc/Ac_2O$, 150 °C).[11]

Control of stereochemistry during introduction of the three-carbon side chain must be assured as this operation sets the geometry of the key trans BC ring junction required for *both* series. Treatment of **4a** with the mixed cuprate derived from *tert*-butylacetyene and the ethyl vinyl ether protected 1-bromo-3-propanol (1.7 equiv, −40 → 0 °C, 18 h) provided the diene lactone **8** (56%).[12] Lactone **8** was reductively rearranged (1.5 equiv of DIBAL, 0 °C, 2 h) to a mixture of ketols, which upon Jones oxidation and esterification (CH_2N_2) afforded the crystalline (mp 114.5–115 °C) diketo ester **9** (~35% from **7**).[12,13] Reduction of **9** with $Li(O\text{-}t\text{-}Bu)_3H$ (1.5 equiv), tosylation (0 °C, py), and fragmentation (4.0 equiv of $NaOCH_3$, 65 °C) provided the crystalline diester **10** (mp 111–112.5 °C) in approximately 33% overall yield.[14] The structure of **10** was confirmed by single-crystal x-ray analysis to have the stereochemistry shown[15] (Figure 1). The ring system was completed by Dieckmann cyclization (3.0 equiv of LiHMDS, 115 °C, 4 h) of **10** to **11** (~40%) [NMR δ 5.3–5.9 (m, 2 H); M^+ calcd for $C_{16}H_{22}O$ 230.1670, found 230.1660].

The stereochemical outcome of the conjugate addition is in accord with the expected stereoelectronic control usually observed in organocuprate chemistry.[19] We have found in this case, as well as a number of related systems, that enol lactones serve as excellent acceptors, although the corresponding open-chain esters are sluggish and few examples of additions to lactones have been recorded. The addition to lactone **4b** required for the ophiobolin series is, however, somewhat more

to nitrogen.[5] Therefore, in order to prove this hypotesis we monitored the course of the reaction of *O,O*-diisopropylphosphoroselenoic acid (**1f**) with DCC (Figure 1)[11] by the low-temperature ^{31}P NMR. Thus, a solution of DCC in ether was treated with an equimolar amount of **1f** at −80 °C and the resulting mixture was examined at 24.3 MHz using ^{31}P Fourier transform NMR with proton noise decoupling.[6] Two signals of high intensity were observed at $\delta_{^{31}P}$ −48.5 and −10.3 ppm. The first of them was attributed to the salt of seleno acid **1f** with DCC. It is interesting to point out that the coupling between phosphorus and selenium, $^1J_{^{31}P-^{77}Se}$ = 789 Hz, was observed, providing additional support of this assignment.[7] The δ −10.3 signal with the characteristic coupling constant $^1J_{^{31}P-^{77}Se}$ = 410 Hz corresponds undoubtedly to the expected *Se*-diisopropylphosphoryl-*N,N'*-dicyclohexylisoselenourea (**2f**).[8] The spectrum showed also the low intensity signal at +2.2 ppm corresponding to the already characterized *N*-diisopropylphosphoryl-*N,N'*-dicyclohexylselenoura (**3f**) and two doublets centered at −52 and +16.5 ppm due to tetraisopropyl monoselenopyrophosphate. Then we raised the temperature to −50 °C and observed the spectrum every 10 min. It showed gradual decrease of the signals at δ −48.5 and −10.3 ppm and at the same time fast increase of the signal due to **3f**. The signals due to **3f** and selenopyrophosphate in a ratio 4:1 were the only signals in the spectrum at room temperature.

The unstable adducts **2** and **4** were observed similarly using other acids **1** as the reaction components.[9] Their spectral characteristics are given in Table II.[10,11]

The mechanism of the phosphorylation by means of *N*-phosphorylthio(seleno)ureas **3** is under current investigation.

Supplementary Material Available. Tables I and II, including physical and spectral properties of the adducts **2, 3, 4,** and **5,** and Figure 1, showing the low-temperature FT ^{31}P NMR study of the reaction between DCC and **1f** (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) H. G. Khorana and A. R. Todd, *J. Chem. Soc.*, 2257 (1953).
(2) M. Mikołajczyk, *Chem. Ber.*, **99,** 2083 (1966).
(3) The only remark concerning the reaction between DCC and dialkyl phosphorothioic acid was found in the paper by McIvor, McCarthy, and Grant, who stated that no reaction took place at room temperature and a mixture of products was obtainec on heating: R. A. McIvor, G. D. McCarthy, and G. A. Grant, *Can. J. Chem.*, **34,** 1819 (1956).
(4) The natural abundance of ^{77}Se is 7.58%. For the application of $^{31}P-^{77}Se$ coupling in structural and stereochemical studies see: I. A. Nuretdinov and E. I. Loginova, *J. Gen. Chem. USSR*, 2380 (1971); Perkin-Elmer NMR Quarterly, 1 (November), 6; W. McFarlane and J. A. Nash, *Chem. Commun.*, 913 (1969); W. J. Stec, A. Okruszek, B. Uznański, and J. Michalski, *Phosphorus*, **2,** 97 (1972); W. J. Stec, *Z. Naturforsch. B*, **31,** 393 (1976).
(5) Similar rearrangement has been observed by Chupp and Leschinsky in the reaction between isocyanides and phosphorus thio acids: J. P. Chupp and K. L. Leschinsky, *J. Org. Chem.*, **40,** 66 (1975).
(6) ^{31}P NMR spectra were obtained with a Jeol-JNM-FX60 Fourier transform NMR spectrometer. Chemical shifts are given in parts per million downfield from external 85% H_3PO_4.
(7) Triethylammonium salt of seleno acid **1f** has $\delta_{^{31}P}$ −50.4 ppm and $^1J_{^{31}P-^{77}Se}$ = 808 Hz, whereas the free acid **1f** absorbs at $\delta_{^{31}P}$ −60.8 ppm with $^1J_{^{31}P-^{77}Se}$ = 910 Hz.
(8) The proton-undecoupled ^{31}P NMR spectrum revealed that the signals at −48.5 and −10.3 ppm are triplets ($^3J_{POCH}$ = 7.3 Hz), whereas the resonance signal at +2.2 ppm is a double triplet due to an additional coupling $^3J_{PNCH}$ = 23 Hz, discussed earlier.
(9) We were not able to detect under similar conditions the 1:1 adducts of type **2** or **3** from *O*-isopropylmethylphosphonothioic acid and diethylphosphinothioic acid with DCC. The low-temperature FT ^{31}P NMR spectra of the mixtures of *O,O*-diethylphosphoric acid, *O,O*-dineopentylphoric acid, and *O,O*-diphenylphosphoric acid with DCC revealed the formation of corresponding *O*-phosphorylisoureas having $\delta_{^{31}P}$ +10.1 (10.9), +10.2, and +20.7 (21.6) ppm, respectively. However, in contrast to *S*-phosphorylisothioureas they did not undergo rearrangement to *N*-phosphorylureas, but reacted further to form pyrophosphates. These results and mechanistic differences will be discussed in a full paper.
(10) It is interesting to note that in some instances small, minor peaks (given in Table II in parantheses) are seen in the region characteristic of the adducts **2** and **4** which may be interpreted as evidence of syn–anti isomerism.
(11) See paragraph at the end of paper about supplementary material.

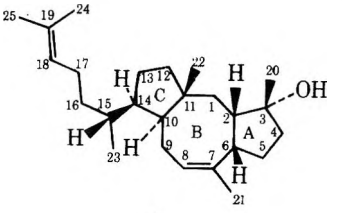
Marian Mikołajczyk,* Piotr Kiełbasiński
Zofia Goszczyńska
Centre of Molecular and Macromolecular Studies
Polish Academy of Sciences
Department of Organic Sulfur Compounds
90-362 Łódź, Boczna 5, Poland

Received July 22, 1977

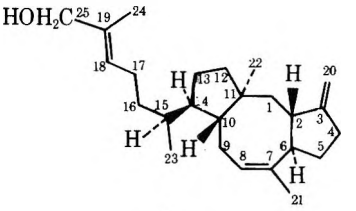
Sesterterpenes. 1. Stereospecific Construction of the Ceroplastol and Ophiobolin Ring Systems via a Common Bicyclic Intermediate

Summary: The ring systems present in the two major classes of ophiobolane sesterterpenes have been obtained via a common bicyclic intermediate. In each case, the eight-membered ring was constructed by fragmentation of an appropriately functionalized bicyclo[3.3.1]nonane ring system.

Sir: We have been investigating, for some time, the development of protocols for the synthesis of various classes of sesterterpenes. Among those under study are the two major stereochemical subclasses of the ophiobolane system exemplified by ophiobolin F (**1**)[1] and ceroplastol I (**2**).[2] Recent reports from other laboratories have prompted us to report our studies in this area.[3,4]

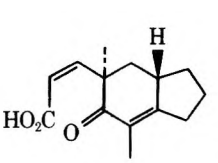


1

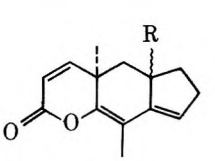


2

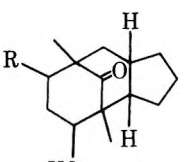
The structures of **1** and **2** present considerable synthetic challenges, since they possess four asymmetric centers about the central eight-membered ring. We were intrigued, however, by the fact that the systems differ in relative stereochemistry at only one center (C-2) about the eight-membered ring, although they possess different absolute stereochemistry. To exploit this observation, we undertook the construction of a bicyclic intermediate, ketone **3,** which we felt might be readily elaborated to intermediates of either stereochemical series. It was hoped that the trienol lactones **4,** which were plausibly derived from **3,** would serve as efficient precursors of bicyclo[3.3.1]nonanones of general structure **5,** and ultimately of



3



4a, R = α-H
b, R = β-H



5

Direct Observation, Isolation, and Structure of 1:1 Adducts from Carbodiimides and Dialkylphosphorothio(seleno)ic Acids

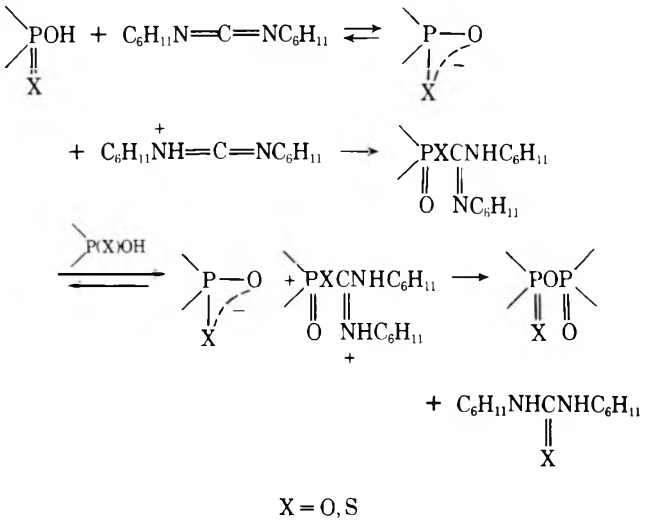
Summary: The reaction between *O,O*-dialkylphosphorothio(seleno)ic acids **1** and carbodiimides (dicyclohexylcarbodiimide, dibenzylcarbodiimide) has been shown to give *N*-phosphorylthio(seleno)ureas **3** and **5**; the low-temperature FT ^{31}P NMR study revealed that they result from the initially formed, unstable *S(Se)*-phosphorylisothio(seleno)ureas **2** and **4** via migration of the phosphoryl group from sulfur or selenium to nitrogen.

Sir: The reaction of *O,O*-dialkylphosphoric acids with dicyclohexylcarbodiimide (DCC) has been shown by Khorana and Todd[1] to give pyrophosphates and dicyclohexylurea. Khorana and Todd explained the formation of products by assuming the two-step mechanism involving *O*-phosphorylisourea as an intermediate (see Scheme I). Similar reaction between DCC and monothiophosphonic and monothiophosphinic acids results in the formation of the corresponding monothiopyrophosphate systems and dicyclohexylthiourea.[2] In this case the addition of thio acid to DCC has been assumed to take place by means of the sulfur atom leading to *S*-phosphorylisothiourea, which reacts further with the second molecule of thio acid to give directly the unsymmetrical form of monothio anhydride.

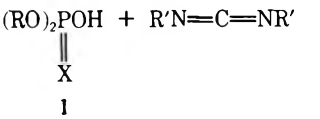
Although this sequence of events is commonly accepted, the postulated 1:1 adducts formed in the first reaction stage have neither been isolated nor observed by means of spectroscopic methods. We now wish to report the first, direct detection by ^{31}P NMR spectroscopy of *S(Se)*-phosphorylisothio(seleno)ureas **2** and **4** formed from monothio(seleno)phosphoric acids **1** and carbodiimides (Scheme II), as well as their facile rearrangement to *N*-phosphorylthio(seleno)ureas **3** and **5**, which are new, stable, and isolable intermediates of the reaction under consideration.[3]

We found that treatment of DCC in ether with an equimolar amount of *O,O*-dialkylphosphorothio(seleno)ic acids (**1**) affords the 1:1 adducts, as evidenced by elemental analysis and mass spectra. Spectroscopic study of the adducts isolated in nearly quantitative yields revealed, however, that they are not

Scheme I

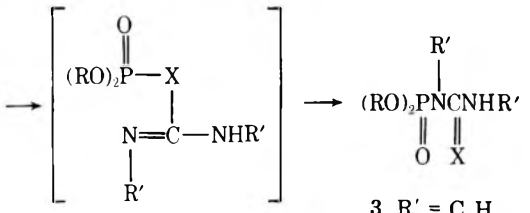


Scheme II



1

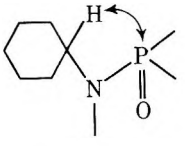
a, R = CH_3; X = S
b, R = CH_3CH_2; X = S
c, R = $(CH_3)_2CH$; X = S
d, R = $(CH_3)_3CCH_2$; X = S
e, R = C_4H_7; X = S
f, R = $(CH_3)_2CH$; X = Se
g, R = $(CH_3)_3CCH_2$; X = Se
h, R = $(CH_3)_3C$; X = S



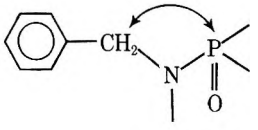
2, R' = C_6H_{11}
4, R' = $PhCH_2$

3, R' = C_6H_{11}
5, R' = $PhCH_2$

the expected *S*-phosphoryldicyclohexylisothioureas (**2**). For instance, the lack of the absorption band at ~1650 cm^{-1} in the infrared spectrum excludes the presence of the >C=N– grouping. Moreover, in the case of the adduct of *O,O*-dineopentyl phosphoroselenoic acid (**1g**) to DCC the ^{31}P–^{77}Se coupling[4] (~400 Hz) characteristic of the direct P–Se bond was not observed in the proton-decoupled ^{31}P NMR spectrum, which rules out the structure **2**. On the other hand, all the spectral data of the adducts are consistent with the isomeric structure of *N*-phosphoryldicyclohexylthio(seleno)urea (**3**).



$^3J_{PH} \simeq 23$ Hz



$^3J_{PH} \simeq 9.5$ Hz

The most important evidence supporting this view is the observation in the ^{31}P NMR spectra of a coupling constant about 23 Hz which can be attributed only to the interaction between phosphorus and the proton at C(1) of the cyclohexyl moiety in **3**.

Since it was not possible to observe the same coupling constant in the ^1H NMR spectra of the adducts from DCC due to the complex splitting pattern of the cyclohexyl ring protons, we prepared in a similar manner the adducts from dibenzylcarbodiimide (DBC) and acids **1**. ^{31}P NMR spectra of these adducts showed that the resonance signal of phosphorus is split into a triplet by the methylene protons, whereas the signal of the methylene group in the ^1H NMR spectra is split by phosphorus into a doublet with the same coupling constant equal to ~9.5 Hz.

Physical and spectral properties of the adducts **3** and **5** are collected in Table I.[11]

The most reasonable assumption is that thio(seleno)ureas **3** and **5** result from the initially formed, unstable **2** and **4** by the migration of the phosphoryl group from sulfur or selenium

In conclusion, the photocyclization preparation of alkyl-substituted benzo[c]phenanthrenes and chrysenes offers a convenient, general synthetic route, with distinct advantages over previously published procedures.

Experimental Section

Melting points were obtained on a Thomas Hoover Uni Melt and are corrected. Microanalyses were performed by Micro-Tek Associates, Skokie, Ill. The IR, ^1H NMR, UV, and MS data were consistent with the assigned structures. The IR data were recorded on a Beckman IR-9, ^1H NMR data on Varian Associates Model HA-100 or CFT-20, UV data on a Cary 14 or Beckman Acta CIII, MS data on an AEI MS-9 equipped with a DS-30 data system. MS samples were introduced either via a variable temperature direct probe (Variset Co., Madison, Wis.) or a GC inlet.

1-Methyl-7-naphthaldehyde. To a stirred solution of 5.0 g (22 mmol) of 7-bromo-1-methylnaphthalene in 125 mL of dry ether was added 50 mmol of *N*-butyllithium in hexane (Alpha Chemical Co., Danvers, Mass.). After stirring for 30 min at room temperature, 7.8 mL (100 mmol) of dry DMF was added in one portion. Following 2 h of additional stirring, the solution was treated with 50 mL of 6 N HCl. The organic phase was washed with 50 mL of H_2O, dried (Na_2SO_4), and concentrated in vacuo. Recrystallization of the yellow solid from hexane gave 2.76 g (86%) of the aldehyde as white needles (mp 55.5–56.5 °C): IR ($\nu_{c=O}$) 1680 cm^{-1}; NMR ($CDCl_3$) s, δ 10.12 (1 H, CHO), m, 8.40–7.20 (6 H, aromatic), s, 2.72 (3 H, CH_3).

Anal. Calcd for $C_{12}H_{10}O$: C, 84.68, H, 5.92. Found: C, 84.71, H, 5.89.

2-Bromomethyl-6-methylnaphthalene. A solution of 20.25 g (0.13 mol) of 2,6-dimethylnaphthalene and 20.76 g (0.12 mol) of *N*-bromosuccinimide in 250 mL of carbon tetrachloride was refluxed under UV irradiation for 2 h in the presence of a catalytic amount of benzoyl peroxide. The reaction mixture was cooled and the succinimide removed by filtration. The solution was washed with sodium bisulfite, dried (Na_2SO_4), concentrated, and chromatographed on alumina, eluting with benzene/hexane to give 13.29 g (44%). Recrystallization from ethanol gave crystals: mp 160–161 °C (dec) (lit 92–93 °C);[12] NMR ($CDCl_3$) m, δ 7.78–7.12 (6 H, aromatic), s, 4.66 (2 H, CH_2Br), s, 2.45 (3 H, CH_3). Exact mass (M^+) calcd for $C_{12}H_{11}Br$: 234.0044. Found: 234.0056. Anal. Calcd for $C_{12}H_{11}Br$: C, 61.30; H, 4.72. Found: C, 61.23; H, 4.82.

General Synthetic Procedure for Preparation of the Naphthylstyrene via the Wittig Reaction. A solution of 125 mL of anhydrous DMF, 0.10 mol of the benzyl halide, and 0.10 mol of triphenylphosphine was stirred magnetically at reflux for 1.5 h in a 250-mL round-bottom flask fitted with a reflux condenser. The mixture was cooled to room temperature and the white precipitate was filtered, washed with ether, and dried overnight at 50 °C in vacuo (yields 82–97%).

A solution of 380 mL of freshly prepared 0.2 M sodium ethoxide (0.077 mol) in ethanol was added over 20 min to a stirred solution of 0.07 mol of a benzyltriphenylphosphonium bromide in 75 mL of dry ethanol at room temperature. The resultant ylide was stirred for 10 min and a solution was added consisting of 0.07 mol of the acetylnaphthalene in 25 mL of dry ethanol. After refluxing for 8 h, the milky white solution had turned bright yellow. The solvent was removed in vacuo, taken up in ether, washed with H_2O, concentrated, and chromatographed on alumina eluting with hexane. A mixture of the cis and trans isomers was usually obtained.

General Synthetic Procedure for the Preparation of Alkylbenzo[c]phenanthrenes and Chrysenes via Photocyclization. A solution of 0.01 mol of the appropriate naphthylstyrene and 127 mg of iodine in 500 mL of freshly distilled cyclohexane was placed in a 500-mL quartz tube equipped with a gas-dispersion tube at the bottom. Irradiation for 12 h (Rayonet Preparative Photochemical Reactor RPR-208, New South England Ultraviolet Co., Middleton, Conn.) with 3000-Å lamps and a brisk air flow through the dispersion tube resulted, in most instances, in precipitation of solid material. The solid was dissolved in chloroform, combined with the cyclohexane supernatant, and concentrated in vacuo. The residue was absorbed into 1.5 g of neutral alumina, placed on a 2× 150-mm column of the same, and eluted with cyclohexane to yield the desired alkylpolycyclic aromatic hydrocarbon.

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Registry No. —Triphenylphosphine, 603-35-0; 7-bromo-1-methylnaphthalene, 33295-35-1; 2,16-dimethylnaphthalene, 581-42-0.

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Table I. Benzo[*c*]phenanthrenes and Chrysenes Prepared by Photocyclization[a]

Compd	Registry no.	% yield[b]	Mp, °C	Lit. mp, °C
2a	4076-39-5	89	140–141.5	136.8–141[2c]
2b	2606-85-1	52	80–81	80.6–81.4[2c]
2c	2381-19-3	66	53–54.5	54.4–55.4[2c]
2d	4076-40-8	68	65–66	64.6–65.6[2c]
2e	652-04-0	72	69–70	70.6–71.6[2c]
2f	2381-34-2	72	76–77	76.8–77.6[2c]
2g	4176-45-8	94	91.5–92	90–91[2b]
4a	3697-24-3	65	116–117	116.8–117.6[13]
4b	54986-62-8	80	91–92	91.4–92.4[14]
6	202-98-2	8	171–173	172.4–172.9[15]

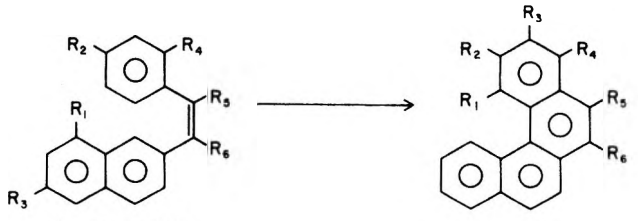
[a] See Experimental Section for general photocyclization procedure. [b] Isolated yields following column chromatography.

Table II. Preparation of Naphthylstyrenes Via the Wittig Reaction[a]

Napthyl-styrene[b]	Registry no.	Alkyl bromide[c]	Registry no.	Carbonyl Compd[c]	Registry no.	% yield[d]	Mp, °C	Lit. mp, °C
1a	63216-64-8	Benzyl bromide	100-39-0	1-Methyl-7-naphthaldehyde[a]	63216-67-1	94	80–81	
b	35160-96-4	4-Methylbenzyl bromide	104-81-4	2-Naphthaldehyde	66-99-9	88	189–190.5	(188–189)[16]
c	63216-65-9	2-Bromomethyl-6-methylnaphthalene[12]	52988-15-5	Benzaldehyde	100-52-7	73	173–174	
d	63216-66-0	2-Methylbenzyl bromide	89-92-9	2-Naphthaldehyde		87	86–87	
e	20883-24-3	2-Bromomethylnaphthalene	939-26-4	Acetophenone	98-86-2	59	146–147	(147.5–148)[17]
f	17181-02-1	Benzyl bromide		2′-Acetonaphthone	98-08-3	81	137–138	(139)[6b]
g	23833-60-5	2-Bromomethylnaphthalene		4-Methoxybenzaldehyde	123-11-5	96	135–136	(134–135)[18]
3a	63269-87-4	Benzyl bromide		1′-Acetonaphthone	941-98-0	81	oil	
b	63269-88-5	Benzyl bromide		1′-Propionaphthone	2876-63-3	84	oil	
5	21844-25-7	Benzyl bromide		Acenaphthone	2235-15-6	14	98–99	(99–100)[11]

[a] See Experimental Section for preparation. [b] Accurate mass measurements were obtained on all molecular ions. Experimental values were in agreement (±0.001 amu) with calculated values. [c] All compounds were obtained from Aldrich Chemical Co., Milwaukee, Wis., unless otherwise noted. [d] Isolated yields following column chromatography.

Scheme I



1a, $R_1 = CH_3$
b, $R_2 = CH_3$
c, $R_3 = CH_3$
d, $R_4 = CH_3$
e, $R_5 = CH_3$
f, $R_6 = CH_3$
g, $R_2 = OCH_3$

2

Note: R_n = H unless otherwise indicated.

rations of these isomers. The preparations of the naphthylstyrene precursors are documented in Table II.

The photocyclization of α-naphth-2-ylstyrenes, on the other hand, can yield only chrysenes (Scheme II). The yields are comparable to cyclizations involving the benzo[*c*]phenanthrenes (Table I). Again spectral properties (^{1}H NMR, UV) correlate well with previously published data.[1b,9,10]

Since the photocyclization procedure has been utilized in the preparation of phenanthrenes with fluoro, chloro, bromo, methoxyl, trifluoromethyl, carboxyl, phenyl, hydroxy and

Scheme II

3a, $R = CH_3$
b, $R = C_2H_5$

4

cyano substituents,[6b] the synthesis by this route of similarly substituted benzo[*c*]phenanthrenes and chrysenes seemed feasible. Hence, 2-methoxybenzo[*c*]phenanthrene was prepared in good yield. However, 4,5-methylene chrysene (**6**), a reported carcinogen, was prepared in low yield, possibly due to the increased distance between the potential reactive centers in (**5**). Attempted synthesis of **5** from 1,8-dibromomethylnaphthalene by the method of Bestman et al.[11] produced only acenaphthene.

Scheme III

6 5

C_2Cl_4)[19] 1756 (s), 1729 (s), 1407, 1281 (m), 1199 (s), 1177, 1136 (s), 1123 (sh), 1092 (s), 995 (sh), 956, 865; MS *m/e* 342 (<1, M^+), 341 (1), 131 (100, $M - C_{15}H_{31}$), 103 (10, $M - C_{15}H_{31}CO$), 43 (49). Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18; O, 18.69. Found: C, 69.97; H, 11.37; O, 18.51.

***trans*-3a:** yield 1.39 g (46%, based on **2a**); mp 30–30.5 °C; IR (CS_2, C_2Cl_4)[19] 1748 (s), 1726 (s), 1410, 1335, 1279 (m), 1199 (s), 1135 (s), 1120 (sh), 1094 (s), 1045 (m), 990, 947, 860; MS *m/e* 342 (<1), 341 (1), 131 (100), 103 (6), 43 (12). Anal. Found: C, 70.16; H, 11.17; O, 18.67.

***cis*-3b:** yield, 1.04 g (31%, based on **2b**); liquid at 0 °C; IR (liquid film)[19] 2940 (m), 1748 (s), 1723 (s), 1640, 1403 (m), 1340 (m), 1284 (m), 1202 (s), 1180 (sh), 1135 (s), 1092 (s), 1058 (m), 1028 (m), 960, 933 (m), 865; MS *m/e* 368 (1, M^+), 367 (1), 131 (100, $M - C_{17}H_{33}$), 103 (20, $M - C_{17}H_{33}CO$), 43 (56). Anal. Calcd for $C_{22}H_{40}O_4$: C, 71.70; H, 10.94; O, 17.36. Found: C, 71.74; H, 10.93; O, 17.21.

***trans*-3b:** yield 1.38 g (42%, based on **2b**); liquid at 0 °C; IR (liquid film)[19] 2958 (m), 1752 (s), 1730 (s), 1645, 1412 (m), 1342 (m), 1285 (m), 1205 (s), 1136 (s), 1095 (s), 1045 (m), 1023 (sh), 957 (sh), 938 (m), 867; MS *m/e* 368 (1), 367 (1), 131 (100), 103 (19), 43 (49). Anal. Found: C, 71.66; H, 10.95; O, 17.14.

2-Alkyl-4-hydroxymethyl-1,3-dioxolanes (4) were prepared from the four respective 4-methoxycarbonyl acetals (*cis*- and *trans*-**3a**, and *cis*- and *trans*-**3b**) by reduction in a saturated solution of $LiAlH_4$[5,10] in dry Et_2O (dropwise addition of **3**, reflux for 2 h, decomposition of excess $LiAlH_4$ with moist Et_2O) and extraction from the basic medium followed by TLC[7] purification (R_f 0.56; developing solvent, hexane–Et_2O, 40:60, v/v) produced the stereomeric five-ring glycerol acetals (**4a, 4b**) in essentially quantitative yields.

2-Pentadecyl-4-hydroxymethyl-1,3-dioxolanes (4a). *cis*-4a: mp 41.5–42.5 °C. Anal. Calcd for $C_{19}H_{38}O_3$: C, 72.56; H, 12.18; O, 15.26. Found: C, 72.71; H, 12.25; O, 15.47.

***trans*-4a:** mp 44.5–45.5 °C. Anal. Found: C, 72.44; H, 12.31; O, 15.32.

2-(*cis*-8′-Heptadecenyl)-4-hydroxymethyl-1,3-dioxolanes (4b). *cis*-4b: liquid at 0 °C. Anal. Calcd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84; O, 14.09. Found: C, 73.87; H, 11.73; O, 14.28.

***trans*-4b:** liquid at 0 °C. Anal. Found: C, 73.87; H, 11.69; O, 14.44.

2-Alkyl-4-acetoxymethyl-1,3-dioxolanes (5) were prepared from the individual hydroxymethyl acetals 4 by acetylation with 100 parts (v/w) of acetic anhydride in the presence of 10 parts (v/w) of dry pyridine for 2 h at 80 °C.[5] After extraction from the basic medium, the acetates were purified by TLC[7] (R_f 0.46; developing solvent, hexane–Et_2O, 70:30, v/v). All physical characteristics of the pentadecyl derivatives *cis*- and *trans*-**5a** were identical to those reported previously for the respective five-ring glycerol acetal acetates prepared by an alternate route.[5]

2-(*cis*-8′-Heptadecenyl)-4-acetoxymethyl-1,3-dioxolanes (5b). *cis*-5b: liquid at 0 °C; MS *m/e* 382 (1 M^+), 381 (1), 145 (100, $M - C_{17}H_{33}$), 117 (95, $M - C_{17}H_{33}CO$), 43 (74). Anal. Calcd for $C_{23}H_{42}O_4$: C, 72.21; H, 11.06; O, 16.73. Found: C, 71.99; H, 10.86; O, 17.15.

***trans*-5b:** liquid at 0 °C; MS, *m/e* 382 (1, M^+), 381 (2), 145 (100, $M - C_{17}H_{33}$), 117 (82, $M - C_{17}H_{33}CO$), 43 (84). Anal. Found: C, 71.99; H, 11.00; O, 17.00.

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Registry No.—**1**, 615-34-9; **2a**, 629-80-1; **2b**, 2423-10-1; glyceric acid calcium salt hydrate, 6057-35-8; ethanediol, 107-21-1.

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Synthesis of Alkyl-Substituted Benzo[*c*]phenanthrenes and Chrysenes by Photocyclization

Donald L. Nagel,* Robert Kupper, Kenneth Antonson and Lawrence Wallcave

Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, Nebraska 68105

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The synthesis of alkyl-substituted polycyclic aromatic hydrocarbons is often necessary to provide samples to aid trace analyses of these compounds in environmental samples. The reported syntheses of monomethylchrysenes and monomethylbenzo[c]phenanthrenes, many of which are reported to be carcinogenic,[1] are generally multistep.[2,3]

We report herein on the syntheses of alkyl-substituted benzo[c]phenanthrenes and chrysenes by photocyclization[4] of the requisite naphthylstyrenes.[5,6] Since naphthylstyrenes can be readily prepared via the Wittig or Grignard reactions, this procedure appeared to offer a convenient general synthetic route to alkylchrysenes and alkylbenzo[*c*]phenanthrenes.

The six isomeric monomethylbenzo[c]phenanthrenes **2a–f** were prepared as outlined in Scheme I, in yields ranging from 66 to 89% (Table I). The spectral properties of these compounds (^1H NMR, UV) correlate well with published data.[7,8]

In addition, ^1H NMR and GLC data indicated the photocyclization products were free of benzo[c]phenanthrene and other isomeric methylbenzo[c]phenanthrenes. In all preparations, however, we found small amounts (1%) of isomeric methylbenz[*a*]anthracenes produced through cyclization involving the β position of the naphthalene moiety. However, the chromatographic properties of the benzo[c]phenanthrenes and the benz[*a*]anthracenes on alumina permit facile sepa-

Table I. H-2 NMR Signals in the Spectra of Isomeric 4-Substituted 2-Alkyl-1,3-dioxolanes[a]

	δ, ppm (J, Hz)					
Isomer	3a	Registry no.	4a	Registry no.	5a	Registry no.
cis	4.98 (4.7)	63340-16-9	4.90 (4.5)	30889-28-2	4.90 (4.5)[b]	63340-18-1
trans	5.08 (4.5)	63340-17-0	5.00 (4.5)	30889-31-7	4.98 (4.5)[b]	63340-19-2

[a] Chemical shifts (δ) of the H-2 triplets (1 H) in 2-pentadecyl-1,3-dioxolanes **3a–5a**. The shifts for H-2 in the 2-*cis*-8′-heptadecenyl derivatives **3b–5b** are identical to those of **3a–5a**, respectively. [b] See also ref 5.

Table II. ^{13}C Chemical Shifts in the Spectra of Isomeric 2-Alkyl-1,3-dioxolanes[a]

	δ (ppm)						
Carbon No.	4-Methoxycarbonyl		4-Hydroxymethyl		4-Acetoxymethyl		2-Pentadecyl-1,3-dioxolane[b,j]
	cis-3b[g]	*trans*-3b[g]	*cis*-4b[h]	*trans*-4b[h]	*cis*-5b[i]	*trans*-5b[i]	
2	106.8	106.3	105.3	105.1	105.6	105.0	104.9
4	73.7	73.7	76.4	76.3	73.7	73.5	64.8
5	68.5	68.0	66.5	66.8	67.1	67.2	64.8
C=O[c]	171.3	171.8			170.6	170.6	
CH_3[d]	52.2	52.2			20.7	20.7	
CH_2[e]			63.5	62.9	64.8	64.3	
1′[f]	33.8	33.5	34.0	34.4	34.0	34.0	34.1
2′[f]	24.0	23.8	24.0	24.0	23.9	23.9	24.1

[a] Proton-decoupled spectra of 2-*cis*-8′-heptadecenyl 4-substituted 1,3-dioxolanes **3b–5b** and of 2-pentadecyl-1,3-dioxolane at 20 MHz; the respective data for the pentadecyl acetals **3a–5a** were identical; chemical shifts (δ) in parts per million downfield from Me_4Si; solvent $CDCl_3$. [b] Prepared from ethanediol and hexadecanal essentially as described for **3a**. [c] Methyl ester C=O in **3b**, acetyl C=O in **5b**. [d] Methyl ester CH_3 in **3b**, acetyl CH_3 in **5b**. [e] Hydroxymethyl CH_2 in **4b**, acetoxymethyl CH_2 in **5b**. [f] 1′ and 2′ refer to the first and second methylene groups of the long side chain. Additional aliphatic signals occur at δ 29.4–29.7 (methylene envelope), 14.1 (ω CH_3), 22.7 (ω-1 CH_2), and 32.0 (ω-2 CH_2), with olefinic signals at 129.9 (C-8′, C-9′), 27.3 (C-7′, C-10′) and at 29.8 (C-6′, C-11′).[14] [g] Registry no.: *cis*-**3b**, 63340-20-5; *trans*-**3b**, 63392-99-4. [h] Registry no.: *cis*-**4b**, 63340-21-6; *trans*-**4b**, 63393-00-0. [i] Registry no.: *cis*-**5b**, 63340-22-7; *trans*-**5b**, 63393-01-1. [j] Registry no.: 4360-57-0.

ents on the adjacent C-5 methylene ^{13}C shifts. While all 4-substituents in both isomers caused deshielding, the methoxycarbonyl function showed the strongest effect (3.2–3.7 ppm). Deshielding of the CH_2 carbon in the 4-hydroxymethyl group (**4b**) upon acetylation (**5b**) resulted in a downfield shift by 1.3–1.4 ppm as expected for primary acetates.[15]

We had hoped that the significant polarity differences observed in chromatography between *cis*- and *trans*-4-methoxycarbonyl-1,3-dioxolanes **3** would be reflected in the carbonyl chemical shifts due to a different degree of C=O polarization in cis and trans isomers. However, such polarization would mostly affect the electron density at the carbonyl oxygen, while the simultaneous net electron-density change at the carbonyl carbon could well be compensated by resonance participation of methoxy electrons. In fact, such phenomena have previously been measured in other carbonyl-substituted ring systems where a change in ^{17}O chemical shifts by 20 ppm was accompanied by a ^{13}C shift of a mere 0.4 ppm in the same carbonyl group.[16]

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian CFT-20 pulse Fourier transform instrument equipped for ^{13}C (20 MHz) and proton (79.54 MHz) observation. Spectra were measured with 4K data points at a spectral width of 1000 (^1H) or 4000 Hz (^{13}C) at ambient probe temperatures of 35 ± 1 and 39 ± 1 °C, respectively. $CDCl_3$ served as solvent and for locking purposes, unless noted otherwise. Chemical shifts (δ) are given in parts per million (ppm) downfield from Me_4Si (δ 0.0); coupling constants (*J*) are expressed in Hz. Mass spectra (MS) were recorded on a Hitachi Perkin-Elmer single-focusing instrument, RMU-6D, at a 70-eV ionization potential (source temperature, 230 °C; inlet temperature, 190 °C; direct inlet), or on an LKB-9000 spectrometer under comparable conditions. Relative ion intensities are given in parentheses. Infrared spectra were taken with a Perkin-Elmer Model 21 spectrophotometer on CS_2 and C_2Cl_4 solutions, or on liquid films. Melting points were determined on a Kofler hot stage and are corrected. Elemental analyses were carried out by M-H-W Laboratories, Garden City, Mich.

Methyl Glycerate (1). Calcium salt of glyceric acid (hydrate, Aldrich), 14.3 g (0.1 mol), 100 mL of dry MeOH, and 50 mL of 14% (w/v) methanolic BF_3 were stirred under N_2 at reflux temperature for 45 min. After cooling to room temperature, 450 mL of dry Et_2O and 6.0 g of NaF were added, and the mixture was stirred for 30 min. The precipitate was filtered on a sintered glass funnel and washed with 200 mL of Et_2O–MeOH, 3:1 (v/v), and the solvent was removed under reduced pressure. Distillation (bp 67–69 °C, 0.1 mm; lit.[17] 123–125 °C, 10 mm) yielded 7.6 g of methyl glycerate (**1**) (63%): R_f in TLC (developing solvent, $CHCl_3$–MeOH, 60:40, v/v) 0.76; ^1H NMR (MeOH-d_4) δ 3.75 (s, 3 H, CH_3), 3.76 (d, J = 4.5 Hz, CH_2), 4.23 (t, J = 4.3 Hz, 1 H, CH); ^{13}C NMR (MeOH-d_4) δ 52.4 (CH_3), 65.0 (CH_2), 73.3 (CH), 174.5 (C=O); assignments were verified by off-resonance proton decoupling.

2-Alkyl-4-methoxycarbonyl-1,3-dioxolanes (3) were synthesized by condensation of **1** with long-chain aldehyde **2**.[6] A representative procedure is given for the preparation of **3a**.

2-Pentadecyl-4-methoxycarbonyl-1,3-dioxolanes (3a). Hexadecanal (**2a**)[6] (2.40 g, 10 mmol), 1.44 g (12 mmol) of methyl glycerate (**1**), 0.5 g of *p*-toluenesulfonic acid, and 200 mL of benzene were placed in a three-necked flask equipped with water separation head, reflux condenser, inlet and outlet for dry nitrogen, and magnetic stirrer. The reaction mixture was kept at reflux temperature for 2 h, while the water formed was continuously removed by azeotropic distillation; then most of the benzene was distilled off. After cooling, ice-cold 2% aqueous K_2CO_3 was added, and the products were extracted with three 150-mL portions of Et_2O. The organic phase was washed with two 50-mL portions of water, dried (Na_2SO_4), and concentrated in vacuo, yielding 3.05 g (89%) of **3a**, consisting of 41.3% of *cis*-**3a** and 58.7% of *trans*-**3a**, as determined by densitometry[18] of a thin-layer chromatogram.[7] Although stabile, the isomers were not separable by gas chromatography on EGSS-X, OV-1, DEGS or SILAR 10-C.

2-(*cis*-8′-Heptadecenyl)-4-methoxycarbonyl-1,3-dioxolanes (3b). Condensation of 2.66 g (10 mmol) of *cis*-9-octadecenal (**2b**)[6] and 1.44 g (12 mmol) of **1**, as described for **3a**, produced 3.34 g (91%) of **3b**.

The geometrical isomers of **3a** and of **3b** were separated by preparative TLC[7] (developing solvent, hexane–Et_2O, 75:25, v/v) to yield pure *cis*- and *trans*-**3a**, and *cis*- and *trans*-**3b** (R_f of *cis*-**3a** and *cis*-**3b** 0.54; R_f of *trans*-**3a** and *trans*-**3b** 0.64).

***cis*-3a:** yield 0.61 g (20%, based on **2a**); mp 34–34.5 °C; IR (CS_2,

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(15) Rearrangement of 10 in 0.1 M $HClO_4$ (heterogeneous) for 2.5 h at 25 °C gave a 90% yield of isomers 11α–δ in the ratio 37(δ):11(α):26(γ):26(β). Subsequent equilibration (see ref 5) with $SnCl_4$ gave the same ratios reported in the Experimental Section.

Long-Chain Stereomeric 2-Alkyl-4-methoxycarbonyl-1,3-dioxolanes in Glycerol Acetal Synthesis[1]

Yuri Wedmid and Wolfgang J. Baumann*

Division of Organic Chemistry, The Hormel Institute, University of Minnesota, Austin, Minnesota 55912

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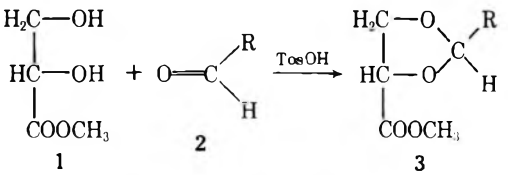
The prostaglandin-like, smooth muscle contracting effect of lipophilic glycerol acetal phosphates, the physiologically active principle of "Darmstoff" described by Vogt[2] and others,[3] has stimulated interest in an efficient synthesis of isomeric long-chain cyclic glycerol acetals. Current procedures of glycerol acetal synthesis are based on the condensation of glycerol and aldehyde[4,5] and favor formation of the isomeric 1,3-dioxanes;[5] the lesser amounts of *cis*- and *trans*-1,3-dioxolanes formed are separable, as acetates only, by tedious multiple gas chromatographic (GC) fractionation.[5]

In the present note we describe a convenient preparative method for the specific synthesis of pure *cis*- and pure *trans*-2-alkyl-4-hydroxymethyl-1,3-dioxolanes. 1,3-Dioxane formation is avoided through use of methyl glycerate as the three-carbon backbone. More important, the stereomeric glycerate acetals are separable by adsorption chromatography due to their significantly different polarities dependent upon the orientation of the methoxycarbonyl function relative to the long-chain substituted ring system. Subsequent conversion of the individual glycerate acetals to glycerol acetals by $LiAlH_4$ hydrogenolysis is quantitative.

Results and Discussion

Acid-catalyzed condensation of methyl glycerate (**1**) with hexadecanal (**2a**),[6] or *cis*-9-octadecenal (**2b**),[6] afforded a mixture of geometrical isomers of methyl glycerate cyclic acetals **3** (Scheme I) which were readily separated by thin-layer

Scheme I



1 2 3

a, R = pentadecyl ($C_{15}H_{31}$)
b, R = *cis*-8-heptadecenyl ($C_{17}H_{33}$)

chromatography (TLC)[7] (developing solvent, hexane–diethyl ether, 75:25, v/v). Both the smaller (~40%), more polar (R_f 0.54) fraction, and the larger (~60%), less polar (R_f 0.64) fraction of **3a** (or **3b**) showed mass spectral fragmentation profiles consistent with the long-chain acetal structure **3** with characteristic ions M^+, $[M - H]^+$, $[M - alkyl]^+$, and $[M - alkyl\ CO]^+$ (ref 8). Their infrared spectra showed characteristic carbonyl splittings ($\Delta\nu$ ~22 cm^{-1}) probably due to coupling between the carbonyl stretching mode and ring vibrations.[9]

When the glycerate acetal fractions of **3a** were reduced with $LiAlH_4$,[10] the more polar isomer (R_f 0.54) gave *cis*-2-pentadecyl-4-hydroxymethyl-1,3-dioxolane (*cis*-**4a**), the less polar isomer (R_f 0.64) yielded *trans*-2-pentadecyl-4-hydroxymethyl-1,3-dioxolane (*trans*-**4a**). *cis*- and *trans*-4a were identified, after acetylation with Ac_2O/pyridine,[5] by comparison with authentic 2-pentadecyl-4-acetoxymethyl-1,3-dioxolanes *cis*- and *trans*-**5a** of known configuration prepared via an alternate route (Scheme II)[5]

Scheme II

cis *trans*

3, X = MeO–CO–
4, X = HO–CH_2–
5, X = MeCO–O–CH_2–

Configurational assignments for the isomers of glycerate acetal **3** were substantiated by ^1H NMR on the basis of the chemical shifts observed for the H-2 signals in the spectra of **3a–5a** (Table I).[11] The H-2 triplet at δ 4.98 ppm for the *cis*-methoxycarbonyl-1,3-dioxolane **3a** was shifted to 5.08 ppm for the trans-isomer **3a**. Such deshielding by 0.1 ppm was also observed for the *trans*-hydroxymethyl and *trans*-acetoxymethyl isomers **4a** and **5a**.[5,12] These NMR data also demonstrated that configurations were maintained in the process of converting **3a** to **5a**.

The ^1H NMR spectra of the 4-hydroxymethyl and 4-acetoxymethyl-1,3-dioxolanes (**4** and **5**) showed poorly resolved signals near 3.5–4.3 ppm due to H-4,5 and the 4-substituent protons. In contrast, the methoxycarbonyl isomers **3a** (or **3b**) gave characteristic and better resolved H-4,5 signals. The pairs of doublets centered at 4.55 ppm ($J_{4,5}$ = 7.5 Hz, *cis*-**3a**) and 4.58 ppm ($J_{4,5}$ = 7.1 Hz, *trans*-**3a**) were readily assigned to the proton (1 H) at carbon-4 with J values as expected for such 1,3-dioxolane systems.[13] The spectrum of the trans isomer also exhibited well-resolved signals at 4.28 ppm (pair of doublets, 1 H) and 3.86 ppm (pair of doublets, 1 H) for the H-5 protons in positions syn and anti, respectively, relative to the vicinal methoxycarbonyl function. Interference between 2-alkyl and 4-methoxycarbonyl substituents in the cis isomer of **3a** resulted in a less methoxycarbonyl-deshielded syn H-5 and in overlapping multiplets in the 4.29–3.92 ppm region for syn and anti H-5 in *cis*-**3a**.

Proton-decoupled ^{13}C NMR spectra of the glycerate and glycerol cyclic acetals **3–5** revealed distinct spectral differences between cis/trans isomeric pairs, and as a result of different substituents in position 4 (Table II). Assignments of ring and 4-substituent carbons were based on off-resonance proton decoupling and on specific deuteration in position 2 and in the methylene group in position 4 (**4b, 5b**).

Comparison of the carbon chemical shifts in 2-pentadecyl-1,3-dioxolane with those of the unsubstituted 1,3-dioxolane (C-2, 94.3; C-4, 63.8)[15] made it possible to estimate the deshielding increments due to the 2-alkyl group. 2-Alkyl substitution produced a downfield shift of 10.6 ppm for C-2, while the effect of the 4-substituents on C-2 in **3b–5b** was in the order of 0.1–1.9 ppm downfield, with cis substitution leading to larger deshielding than trans. In contrast, introduction of a 2-alkyl substituent into 1,3-dioxolane affected C-4,5 by a small (1.0 ppm) downfield shift only, but methoxycarbonyl (**3**) or acetoxymethyl (**5**) substitution at the 4 position produced a deshielding effect of ~8.9 ppm on C-4, and hydroxymethyl substitution (**4**) an even larger effect of ~11.6 ppm. The C-4 chemical shifts were minimally affected by the dioxolane configuration.

More surprising was the overall effect of the C-4 substitu-

200 mL of saturated NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo to a dark red oil.

Without further purification, the crude xanthate **2** was transferred to a 250-mL 3-neck flask fitted with a magnetic stirrer, thermometer, and short path distillation apparatus leading to an ice-cooled receiver. By means of a heating mantle, the internal temperature was gradually raised to 220–240 °C (Hood!) at which time the crude diene **3** was collected as a yellow oil (bp 120–160 °C). The product was extracted with 4 × 20 mL of 20% KOH, dried over $MgSO_4$, and short path distilled to give 20 g (46%) of the diene **3** as a pale yellow oil: bp 63–63.5 °C (20 mm); IR (CCl_4) 3080, 1670, 1640, 990, 910 cm^{-1}; NMR (CCl_4) δ 5.8–4.8 (m, 3H), 4.7 (m, 1H), 2.1 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 1.1–1.5 (m, 4H), 0.93 (d, 3H).

Minor sulfur-containing contaminants could be removed by distillation of **3** from Na. These contaminants were more effectively removed, however, in the subsequent peracid oxidation (vide infra). A neat sample of **3** gave an $[\alpha]^{25}_D$ −4.50° indicating an optical purity of 46%.

(3*R*,6*R*,*S*)-3,7-Dimethyloct-1-ene-6,7-diol (5). To a magnetically stirred solution of 22.0 g (0.159 mol) of diene **3** in 250 mL of CH_2Cl_2 was added 35.4 g (0.175 mol) of 85% *m*-chloroperbenzoic acid at a rate sufficient to maintain the temperature below 10 °C. After addition was complete, the mixture was allowed to stir at ice bath temperature for an additional 30 min whereupon the *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed with 50 mL of 10% $NaHSO_3$ and 2 × 25 mL of saturated $NaHCO_3$. TLC analysis using hexane–ether (1:1) as eluent showed a single major product. A sample was purified by Kugelrohr distillation: bp 100 °C (bath) (20 mm); IR (CCl_4) 3080, 1640, 920, 900 and 880 cm^{-1}; NMR (CCl_4) δ 5.6 (m, 1H), 4.9 (m, 2H), 2.5 (m, 1H), 2.1 (m, 1H), 1.7 –1.1 (m, 4H), 1.22 (s, 3H), 1.18 (s, 3H), 0.9 (overlapping d, 3H).[13]

The crude epoxide **4** was added dropwise at 0 °C to a magnetically stirred solution of 100 mL of 0.1 M $HClO_4$ in 380 mL of THF. After 10 h at ambient temperature, TLC analysis (1:1 hexane–ether; R_f = 0.1) revealed a single major component. The mixture was concentrated in vacuo to ⅓ volume and the product extracted into 100 mL of ether. After washing with 40 mL of 2 N NaOH, followed by 10 mL of brine, the mixture was dried over $MgSO_4$, concentrated in vacuo and short path distilled to give 17.1 g (63% from **3**) of the diol **5** as a viscous, colorless oil: bp 79–80 °C (0.1 mm); IR (CCl_4) 3400, 3080, 1640, 920 cm^{-1}; NMR (CCl_4) δ 5.6 (m, 1H), 4.9 (m. 2H), 4.7 (br s, 2H, D_2O exchange), 3.2 (m, 1H), 2.1 (m, 1H), 1.1–1.8 (br m, 4H), 1.12 (s, 3H), 1.07 (s, 3H), 1.0 (d, 3H).

(4*R*)-Methylhex-5-enal (6). To a magnetically stirred solution of 15.0 g (87 mmol) of diol **5** in 125 mL of ether was added portionwise 48.1 g (96 mmol) of $Pb(OAc)_4$ (containing 10% HOAc) at a rate sufficient to maintain the temperature <20 °C (ice bath). After addition was complete the mixture was stirred at ambient temperature for 45 min whereupon the lead salts were removed by suction filtration. After adding 200 mL of saturated $NaHCO_3$, the mixture was continuously extracted for 20 h with ether. The product was isolated from the ether solution by drying over $MgSO_4$, concentration at ambient pressure, and short path distillation of the residue into an ice-cooled receiver. The aldehyde **6** (7.49 g, 77%) was isolated as a colorless, pungent oil: bp 39–40 °C (20 mm); IR (CCl_4) 3080, 2820, 2720, 1720, 1630, 990, 910 cm^{-1}; NMR (CCl_4) δ 9.6 (t, 1H), 5.8–5.2 (m, 1H), 5.0–4.5 (m, 2H), 2.4–1.8 (m, 3H), 1.6–1.2 (m, 2H), 0.9 (d, 3H); MS *m/e* 112 (M^{+}, 10), 68 (100); VPC (column A, 100 °C) retention time 3.5 min (>95% pure).

***N*-((4*R*)-Methylhex-5-en-1-ylidene)-*tert*-butylamine (7).** A mixture of 5.03 g (69 mmol) of *t*-$BuNH_2$, 7.00 g (63 mmol) of aldehyde **6** and 11.7 g of anhydrous Na_2CO_3 in 30 mL of ether was magnetically stirred under N_2 at ambient temperature for 12 h. The mixture was filtered, concentrated in vacuo, and short path distilled to give 9.02 g (86%) of Schiff base **7** as a colorless oil: bp 69–70 °C (20 mm); IR (CCl_4) 1670, 1640, 990, 930 cm^{-1}; NMR (CCl_4) δ 7.5 (t, 1H, *J* = 4 Hz), 5.8–5.4 (m, 1H), 5.0–4.8 (m, 2H), 2.2 (m, 3H), 1.5 (m, 2H), 1.10 (s, 9H), 1.02 (d, 3H).

(2*R*,*S*,4*R*)-2,4-Dimethylhex-5-enal (8). A flame-dried 250-mL 3-neck flask fitted with a condenser, magnetic stirrer, addition funnel, and nitrogen inlet was charged with 37 mL (56 mmol) of 1.5 M *n*-BuLi in hexane and 40 mL of ether. After cooling to 0 °C under nitrogen, 5.67 g (56 mmol) of $(i\text{-Pr})_2NH$ (freshly distilled from CaH_2) in 10 mL of ether was added, followed after 15 min by dropwise addition of 8.5 g (51 mmol) of Schiff base **7**[14] in 15 mL of ether. Stirring was continued at 0 °C for 1 h whereupon 14.4 g (102 mmol) of MeI was added dropwise. The mixture was then refluxed for 30 min, stirred at ambient temperature for 63 h, and finally treated, with rapid magnetic stirring, with 112 mL of 1.0 M oxalic acid. The ether layer was washed with 5 mL of saturated $NaHCO_3$. The aqueous layer was neutralized with solid $NaHCO_3$ (until CO_2 evolution ceased) and continuously extracted with ether for 20 h. The combined ether extracts were dried over $MgSO_4$ and concentrated at ambient pressure. The residue was short path distilled to give 4.04 g (62%) of the aldehyde **8** as a colorless oil: bp 47–48 °C (20 mm); IR (CCl_4) 3080, 2817, 2710, 1720, 1630, 988, 810 cm^{-1}; NMR (CCl_4) δ 9.5 (t, 1H, *J* = 2 Hz), 5.8–5.3 (m, 1H), 5.1–4.8 (m, 2H), 2.3 (br m, 1H), 1.7 (m, 1H), 1.3 (m, 2H), 1.2–1.0 (set of 3 overlapping doublets, 6H); VPC (column A, 110 °C) one major component (>95%) retention time 3.8 min.

(4*R*,*S*,6*R*)-4,6-Dimethyloct-7-en-3-one (9). To the Grignard reagent prepared from 2.00 g (82 mg-atom) of Mg and 5.97 g (55 mmol) of EtBr in 45 mL of ether was added dropwise at ambient temperature 3.48 g (27.4 mmol) of aldehyde **8** in 10 mL of ether. After stirring for 1 h the mixture was cooled to 0 °C and quenched with 50 mL of saturated NH_4Cl. The ether layer was washed with 25 mL of water, dried over $MgSO_4$, and concentrated in vacuo to a colorless oil which was used in the next step without further purification.

To a magnetically stirred solution of the crude carbinol (vide supra) in 40 mL of acetone cooled to 0 °C was added dropwise 10.1 mL of 2.67 M H_2CrO_4. After addition was complete the mixture was stirred an additional minute, concentrated in vacuo to ~5 mL, diluted with 30 mL of H_2O and extracted with 4 × 10 mL of ether. The combined ether layers were washed with 2 × 15 mL of 0.15 M NaOH followed by one wash with 10 mL of H_2O. After drying over $MgSO_4$, the solvent was removed in vacuo and the residue short path distilled to give 3.31 g (79% from **8**) of enone **9** identical by NMR, IR, and MS with an authentic sample kindly provided by Professor Silverstein. VPC analysis (column A, 120 °C) showed a single major component (>95%), retention time 5.4 (>95%), retention time 5.4 min.

(4*R*,*S*,6*R*,7*R*,*S*)-4,6-Dimethyl-7,8-epoxyoctan-3-one (10). The epoxyketone **10** was prepared in 77% yield as described by Silverstein and co-workers.[5]

(−)-α-Multistriatin (11α). The epoxyketone **10** rearranged in benzene solution in the presence of $SnCl_4$[15] to give an 80% isolated yield of the four isomers **11α–δ** as previously described.[5] Using column B (170 °C) the four isomers eluted from the gas chromatograph in the following order (% composition, retention time in min): **11δ** (53, 23.4), **11α** (35, 23.9), **11γ** (8, 25.6), and **11β** (4, 27.9). The retention times and ratios of isomers were virtually identical with a sample provided by Professor Silverstein.

A pure sample of **11α** was collected by preparative VPC (column B, 170 °C) and was identical by IR and NMR with the data reported[5] for **11α**. An $[\alpha]_D$ −18.7° was observed for an 0.074 M solution **11α** in hexane.

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Registry No.—**1**, 1117-61-9; **2**, 63215-84-9; **3**, 10281-56-8; **4**, 15103-27-2; **5**, 57714-93-9; **6**, 63215-85-0; **7**, 63215-86-1; **8**, 63215-87-2; **8** (carbinol deriv.), 63466-90-0; **9**, 63323-26-2; **10**, 63324-22-1; 59014-03-8;,**11α**, 59014-03-8; **11β**, 59014-05-0; **11γ**, 59014-07-2; **11δ**, 59014-09-4; EtBr, 74-96-4.

References and Notes

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A Synthesis of (−)-α-Multistriatin[1]

G. J. Cernigliaro and P. J. Kocienski*[2]

Department of Chemistry, State University of New York at Binghamton, Binghamton, New York 13901

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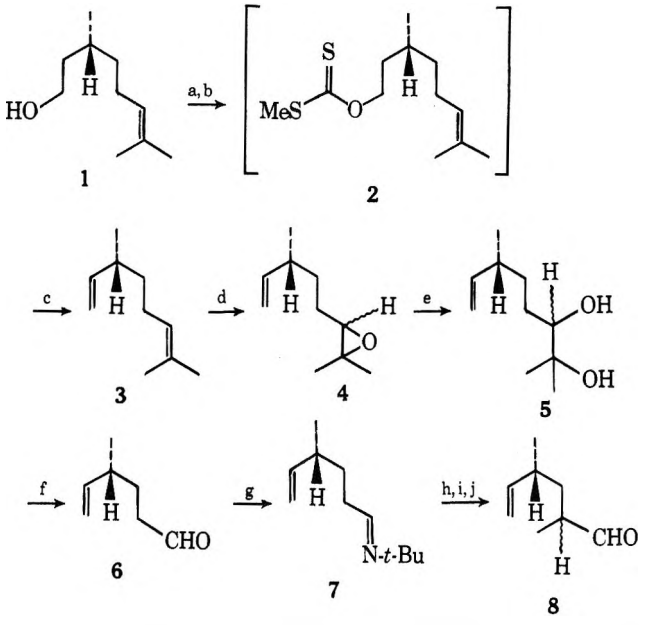
α-Multistriatin is the principal attractant of the smaller European elm bark beetle *Scolytus multistriatus* (Marsham), a vector of the Dutch elm disease pathogen *Cerocystis ulmi*. The severe devastation of elm populations in the northeastern United States has motivated the structure elucidation of the aggregation pheromone by Silverstein and co-workers[3] in the hope that mortality traps baited with the pheromone might be used for the bioassay and control of *S. multistriatus*.

The gross structure of α-multistriatin (**11α**) was deduced spectrometrically and by efficient confirmative total synthesis.[3,4] Subsequently, the relative configuration was established by a stereorational synthesis[4] and recently, the absolute configuration of (−)-**11α** was deduced by comparison of the ^{13}C NMR spectra of natural (−)-**11α** with synthetic material, prepared from chiral precursors, in the presence of a chiral shift reagent.[5,6] We report below an approach to the synthesis of natural (−)-α-multistriatin[7] from (+)-3R-citronellol (**1**).

As shown in Scheme I, (+)-(3*R*)-citronellol $[\alpha]_D$ +1.98[8] was

Scheme I

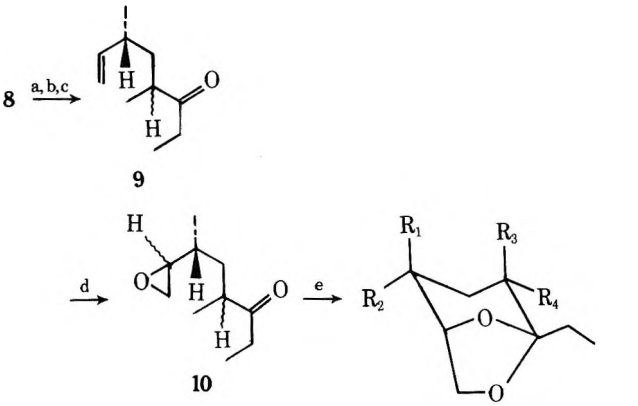


(a) NaH, CS_2; (b) MeI; (c) 240 °C; (d) *m*-$ClC_6H_4CO_3H$; (e) H_3O^+; (f) $Pb(OAc)_4$; (g) *t*-$BuNH_2$, Na_2CO_3; (h) $(i\text{-}Pr)_2NLi$; (i) MeI; (j) H_3O^+.

converted to the known diene[9] **3** (46% yield from **1**) by pyrolysis of the corresponding xanthate **2**. Chemospecific epoxidation of the trisubstituted olefin of **3** afforded the epoxide **4** which was solvolyzed to the diol **5**. Subsequent $Pb(OAc)_4$ oxidation of **5** gave the aldehyde **6** in 49% overall yield from **3**. The aldehyde **6** was methylated in a three-step sequence via the Schiff base **7**[10] to give the aldehyde **8** in 53% overall yield from **6**.

To complete the synthesis, the aldehyde **8** was converted by a two-step sequence to the known[5] (4*R*,*S*,6*R*)-dimethyl-7-octen-3-one (**9**). At this point our synthesis strategically intersects the procedure originally developed by Silverstein and co-workers[5] (Scheme II). The epoxide **10** reacted with $SnCl_4$ in benzene at room temperature to afford a mixture of the isomers **11α–δ** from which the desired α-isomer was isolated by preparative VPC and identified by comparison with an authentic sample kindly provided by Professor Silverstein. The observed $[\alpha]_D$ −18.7° for synthetic (−)-**11α** indicates an optical purity of 40%.[5]

Scheme II



	R_1	R_2	R_3	R_4
11α	H	Me	H	Me
11β	Me	H	Me	H
11γ	H	Me	Me	H
11δ	Me	H	H	Me

(a) EtMgBr; (b) H_3O^+; (c) H_2CrO_4; (d) *m*-$ClC_6H_4CO_3H$; (e) $SnCl_4$.

Our synthetic plan was founded upon the possibility of preparing both antipodes of **11α** from readily available, chiral precursors in order to avoid a potentially tedious resolution of racemic starting materials. Unfortunately, the advantage accrued from this approach was to some extent nullified by the insufficient enantiomeric purity of commercial (−)-(3*S*)- and (+)-(3*R*)-citronellol.[11] Although natural citronellol would have sufficed for the determination of the absolute configuration of **11α** as reported by Silverstein and co-workers,[5] further purification[12] will be essential for the bioassay of the pure **11α** antipodes prepared by the synthesis reported herein.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on a Varian HA-100 spectrometer using Me_4Si as an internal standard. Infrared spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer using ca. 5% solutions in CCl_4. Mass spectra were obtained at 70 eV ionization potential using a DuPont 29-491B mass spectrometer utilizing the batch inlet. Vapor phase chromatographic (VPC) analysis was achieved with a Perkin-Elmer Model 3920 gas chromatograph equipped with a thermal conductivity detector. Unless otherwise stated, all VPC analyses were performed with a 4 ft × ¼ in. 10% SE-30/Chromosorb P (60–80 mesh) column (column A) or a 25 ft × ¼ in. 5% Carbowax 20M/Chromosorb G (60–80 mesh) column (column B). Helium served as the carrier gas. Optical rotatory dispersion curves were recorded with a JASCO ORD/CD-5 instrument. All thin layer chromatographic (TLC) analyses were performed with 2.5 × 7.5 cm Baker-flex pre-coated silica gel plates using phosphomolybdic acid for development.

The (+)-citronellol was obtained from ICN-K and K Laboratories. The $Pb(OAc)_4$ (containing 10% HOAc), obtained from Alfa Inorganics, Inc., and the *m*-chloroperbenzoic acid (unassayed, ca. 85%), obtained from Aldrich Chemical Co., were used without further purification. The *n*-BuLi was purchased from Aldrich Chemical Co.

(3*R*)-3,7-dimethylocta-1,6-diene (3). A flame-dried, 500-mL 3-neck flask fitted with a condenser, addition funnel, and magnetic stirrer was charged with 16.9 g (0.35 mol) of 50% NaH (dispersed in mineral oil) and 150 mL of dry THF. Over the course of 1 h, 50 g (0.32 mol) of (+)-(3*R*)-citronellol in 25 mL of CS_2 was added with occasional water bath moderation. After addition was complete, the mixture was refluxed for ½ h and then cooled to room temperature. After the dropwise addition of 43 g (0.40 mol) of MeI was complete, the reaction mixture was refluxed for ½ h, poured onto 300 g of ice, and the product extracted into 200 mL of ether. The organic layer was washed with

(20*R*)- and (20*S*)-Cholest-5-ene-3β,21-diol 3-Tetrahydropyranyl Ether, (9a) and (10a). To 470 mg of olefin **8a** in 5 mL of anhydrous THF was added 1.1 mL of 1 M diborane in THF under a nitrogen atmosphere at 0 °C and the solution was stirred for 30 min at 0 °C. Then 2 mL of 10% sodium hydroxide solution and 2 mL of 30% hydrogen peroxide solution were added dropwise, and stirring was continued for an additional 1 h. After extraction with ethyl acetate, the extract was washed with water and saturated sodium chloride solution and dried (Na_2SO_4). The HPLC separation of this epimeric mixture was carried out in hexane–acetone (4:1) on 2 × 8 ft Porasil A column to give 230 mg of diols. The 20*S* and 20*R* epimers **10a** and **9a** were completely resolved in three recycles in a ratio of 1:2. The former had the longer retention time.

9a: mp 155–156 °C; NMR δ 0.71 (s, 3, 18-CH_3), 0.87 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.02 (s, 3, 19-CH_3), 3.70 (s, 2, -CH_2OH), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

10a: mp 105–107 °C; NMR δ 0.69 (s, 3, 18-CH_3), 0.87 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.01 (s, 3, 19-CH_3), 3.62 (m, 1, -CH_2OH), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{32}H_{54}O_3$: C, 78.96; H, 11.18. Found: C, 78.92; H, 11.49.

(20*R*)- and (20*S*)-Cholest-5-ene-3β,21-diol (9b) and (10b). (a) To a solution of 24 mg of THP ether **9a** in 3 mL of THF was added one drop of concentrated HCl and the mixture was allowed to stand at 50 °C for 20 min. Then it was poured into a saturated solution of sodium bicarbonate and the product was extracted with ethyl acetate. The extract was washed with water and dried (Na_2SO_4). Purification of this crude diol **9b** was carried out on TLC (30% acetone in hexane) to give 14 mg of **9b:** mp 149–151 °C; NMR δ 0.70 (s, 3, 18-CH_3), 0.86 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 18-CH_3), 3.70 (s, 2, -CH_2OH), 5.34 ppm (m, 1, 6-H).

Anal. calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.31; H, 11.29.

(b) A pure sample (11 mg) of diol **10b** was obtained from 20 mg of THP ether **10a** by the same methods described for the diol **9b.** This compound had: mp 147–149 °C; NMR δ 0.68 (s, 3, 18-CH_3), 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 19-CH_3), 3.62 (m, 2, CH_2OH), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: 80.38; H, 11.58.

Cholesterol 3-Tetrahydropyranyl Ether (9c). This sequence (tosylation followed by hydride reduction) was carried out exactly as described by Bottin and Fetizon.[4] The reduction product was purified on a TLC plate which gave, after recrystallization from methanol, clean **9c:** mp 155–161 °C; NMR δ 0.68 (s, 3, 18-CH_3), 0.88 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.91 (d, 3, J = 6 Hz, 21-CH_3), 1.00 (s, 3, 19-CH_3), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

(20*S*)-Cholest-5-en-3β-ol 3-Tetrahydropyranyl Ether (10c) from 10a. This was carried out exactly as described above for the 20*R* epimer. The material was recrystallized from methanol to give pure **10c:** mp 96–98 °C; NMR δ 0.68 (s, 3, 18-CH_3), 0.84 (d, 3, J = 6 Hz, 21-CH_3), 0.87 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.01 (s, 3, 18-CH_3), 4.72 (m, 1, -OCHO-), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56. Found: C, 81.87; H, 11.88.

3β,21-Dihydroxypregn-5-en-20-one 3,21-Ditetrahydropyranyl Ether (5b). To the stirred solution of 9.0 g of 3β,21-dihydroxypregn-5-en-20-one (**5a**) in 20 mL of dry tetrahydrofuran was added 30 mg of *p*-toluenesulfonic acid and 10 mL of dihydropyran. After 3 h, the solution was extracted with benzene. The benzene layer was washed with a sodium bicarbonate solution and with water and dried over sodium sulfate, and the solvent was evaporated off in vacuo. The syrupy residue was crystallized from hexane to give 6.9 g of pure ether **5b:** mp 126–128 °C; IR ν 1725 (CO), 1030 and 965 cm^{-1} (ether); NMR δ 0.63 (s, 3, 18-CH_3), 0.99 (s, 3, 19-CH_3), 4.18 (s, 2, 21-CH_2-O-), 5.32 ppm (m, 1, 6-H).

Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.28; H, 9.66.

3β,20,21-Trihydroxycholest-5-ene 3,21-Ditetrahydropyranyl Ether (20-Isomeric Mixture) (6b). To a stirred Grignard solution, prepared from 6 g of isohexyl bromide and 1.0 g of magnesium turnings in 100 mL of ether, was added dropwise a solution of 8 g of the ketone **5b** in 200 mL of tetrahydrofuran. The solution was heated under reflux for 3 h and left at 50 °C overnight. The mixture was hydrolyzed with a saturated solution of ammonium chloride. The organic material was extracted with ethyl acetate, the organic layer washed with water and dried over sodium sulfate, and the solvent evaporated in vacuo to give a yellow oil. A recrystallization from hexane gave 7.4 g of ether **6b:** mp 121–124 °C; IR ν 3350 (OH), 1025 and 960 cm^{-1} (ether); NMR δ 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$]; 0.86 (s, 3, 18-CH_3), 0.99 (s, 3, 19-CH_3), 5.35 ppm (m, 1, 6-H).

Anal. Calcd for $C_{37}H_{62}O_5$: C, 75.72; H, 10.65. Found: C, 75.99; H, 10.73.

3β,20,21-Trihydroxycholest-5-ene 21-Tetrahydropyranyloxy Ether (20-Isomeric Mixture) (6c). To 20 mL of dimethyl sulfoxide was added 10.0 mL of water and 4.0 mL of 7% perchloric acid. The resulting solution was cooled to 0 °C and 500 mg of the ether **6b** was added with stirring to the dimethyl sulfoxide solution. If, after 1 h, the steroid had not completely dissolved, 3–4 mL of tetrahydrofuran was added to the solution. The mixture was allowed to stand at room temperature for 3 days, after which time it was poured onto ice and extracted three times with ethyl acetate. These extracts were washed thoroughly with water and once with saturated sodium bicarbonate solution. After drying the organic extracts over sodium sulfate and evaporation, there was obtained a crystalline residue which was purified on TLC. The more mobile fraction gave 198 mg of starting material **6b,** while 225 mg of ether **6c** could be isolated from the more polar fraction. A recrystallization from methanol gave 215 mg of **6c:** mp 168–169 °C; IR ν 3400 (OH), 1020, and 960 cm^{-1} (ether); NMR δ 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.86 (s, 3, 18-CH_3), 1.00 (s, 3, 19-CH_3), 5.35 ppm (m, 1, 6-H).

Anal. Calcd for $C_{32}H_{54}O_4$: C, 76.44; H, 10.83. Found: C, 76.17; H, 10.75.

3β,20,21-Trihydroxycholest-5-ene (20-Isomeric Mixture) (6a). (a) Hydrolysis of Ether 6b. To the solution of 500 mg of the ether **6b** in 50 mL of tetrahydrofuran was added 1 drop of concentrated HCl and the solution was kept at 50 °C for 30 min. Then it was poured into a saturated solution of sodium bicarbonate and the product was extracted with ether. This extract furnished 403 mg of triol **6a,** mp 182–186 °C, after recrystallization from aqueous methanol. This mixture resembled very closely (IR, NMR, mobility on TLC, mixture melting point) the authentic[10] (20*R*) isomer.

(b) Isohexylmagnesium Grignard on 3β,21-Diacetoxypregn-5-en-20-one (5c). This was carried out with **5c** in a very similar fashion to the reaction of identical Grignard reagent with the ether **5b.** This reaction was carried out on a 5-g scale. Purification of the crude triol **6a** was achieved by dissolving the oil in a minimum of benzene, followed by careful addition of hexane to bring about crystallization of 2.9 g of pure product, identical with that obtained from the Grignard reaction on the tetrahydropyranyl ether, and followed by acid hydrolysis.

3β-Hydroxy-21-norcholest-5-en-20-one (7b). To the stirred solution of 3 g of the triol **6a** in 50 mL of dioxan was added dropwise the solution of 3.5 g of lead tetraacetate in 50 mL of benzene. After 18 h, the inorganic material was removed by filtration and washed with benzene. The filtrate was washed with saturated sodium bicarbonate solution and water and dried, and the solvent was evaporated. The syrupy residue was crystallized from methanol to give 2.4 g of pure ketone **7b,** indistinguishable from authentic[8] material.

Registry No.—1, 35961-41-2; **2a,** 63216-14-8; **2b,** 63216-15-9; **3a,** 63216-16-0; **3b,** 63216-17-1; **5a,** 1164-98-3; **5b,** 63216-18-2; **5c,** 1693-63-6; (20*R*)-**6a,** 61505-31-5; (20*S*)-**6a,** 26273-31-4; (20*R*) **6b,** 63216-19-3; (20*S*)-**6b,** 63268-04-2; (20*R*)-**6c,** 63268-05-3; **7a,** 34026-85-2; **7b,** 38673-20-0; **8a,** 34153-88-3; **8b,** 41083-90-3; **9a,** 63268-02-0; **9b,** 63216-21-7; **9c,** 6252-45-5; **10a,** 34026-87-4; **10b,** 63268-03-1; **10c,** 34026-88-5; 3-methylbutanal, 590-86-3; isohexylbromide, 626-88-0.

References and Notes

(1) This work is supported by United States Public Health Service Grant AM-03419 from the Institute of Arthritis, Metabolism, and Digestive Diseases, and National Science Foundation Research Grants GB-38612 and PCM76-20223. P. C. thanks Dr. Jean Choay, Institut Choay, for continued support and encouragement.
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While this study was in progress Danishefsky et al.[11] published a method[12] for the synthesis of the norketone **7b** by the reaction of 3β-hydroxyetiochol-5-enic acid (**4**) with isohexyllithium.

The ketone **7a** was subjected to a Wittig reaction as described[3,4] to give cholesta-5,20-dien-3β-ol 3-tetrahydropyranyl ether (**8a**), identical with authentic material in all respects. A small aliquot of the ether **8a** was hydrolyzed to give cholesta-5,20-dien-3β-ol (**8b**), mp 109–111 °C. Similarly, the ketone **7b** was reacted with methylene triphenylphosphorane to give the olefin **8b** which was then transformed with dihydropyran and *p*-toluenesulfonic acid to its ether **8a**. The hydroboration of the olefin **8a** with diborane at 0 °C gave a mixture of the two 20*R* and 20*S* alcohols **9a** and **10a** in a ratio of 2:1. The two isomers were separated by adsorption chromatography to give **9a** (mp 155 °C, δ 3.70, s, $-CH_2-OH$) and **10a** (mp 105 °C, δ 3.62, m). The IR spectra of the two epimers are very similar.

Proof of Structure for 9a and 10a. Both alcohols **9a** and **10a** were converted to their tosylates and the crude sulfonates were reduced with lithium aluminum hydride. Thus, the reduction product from the major isomer **9a**, mp 155 °C, gave (20*R*)-cholest-5-en-3β-ol 3-tetrahydropyranyl ether (**9c**) (cholesterol tetrahydropyranyl ether), mp 155–161 °C, identical in all respects with authentic[13] material. The reduction of the minor isomer **10a**, mp 105 °C, gave (20*S*)-cholest-5-en-3β-ol 3-tetrahydropyranyl ether (**10c**) (20-isocholesterol 3β-tetrahydropyranyl ether), mp 96–98 °C, identical in all respects with a sample made from (20*S*)-cholest-5-en-3β-ol.[14] 21-Hydroxycholesterol (**9b**), mp 149–151 °C, was obtained by acid hydrolysis of its tetrahydropyranyl ether **9a**, while (20*S*)-cholest-5-ene-3β,21-diol (**10b**) was obtained in the same fashion from the ether **10a**.

These results contradict those of Bottin and Fetizon,[3,4] since (1) we did not observe (hydroboration with disiamylboran gave similar results) any stereoselectivity (on the Δ^{20} bond) in the hydroboration of olefin **8a** and (2) our hydroxylated material, mp 155–156 °C (Bottin and Fetizon give mp 143–145 °C), belongs to the 20*R* (natural) configuration. This has been ascertained by comparison of the NMR spectra[15] of the 20*R* and the 20*S* configurations, as well as by mixture melting point depression(s). Characteristically, the 21-hydroxy sterols of the 20*R* (natural configuration) series exhibit a resonance at δ 3.70 as a singlet ($-CH_2OH$), while those of the 20*S* configuration show a multiplet centered at δ 3.62. The difference in the NMR spectra of the reduced materials (21-CH_3) is also very well documented: cholesterol tetrahydropyranyl ether (**9c**) shows resonances at δ 0.86 (doublet for the 26,27-methyls) and at 0.92 (doublet for the 21-methyl), while (20*S*)-cholest-5-en-3β-ol tetrapyranyl ether (**10c**) gives δ 0.79 (doublet for 21-methyl) and 0.85 (doublet for the 26,27-methyls).

Experimental Section

Melting points were determined on a Kofler melting-point apparatus and are uncorrected. The UV spectra were determined for methanolic solutions on a Cary Model 14 recording spectrophotometer. The NMR spectra were obtained in deuteriochloroform solution on a 60-MHz Varian EM360 and a 100-MHz Varian HA100D-15, with C1024 computer, using tetramethylsilane as an internal reference, and the positions of the proton signals are expressed in parts per million downfield from tetramethylsilane signals.

(23*R*)-3β,23-Dihydroxy-21-norcholest-5-en-20-one 3-Tetrahydropyranyl Ether (2a) and (23*S*)-3β,23-Dihydroxy-21-norcholest-5-en-20-one 3-Tetrahydropyranyl Ether (2b). To the stirred solution of 9.0 g (84 mmol) of lithium diisopropylamide in dry tetrahydrofuran at −78 °C was added at once a solution of 30 g (75 mmol) of 3β-tetrahydropyranyloxypregn-5-en-20-one (**1**)[6] in 100 mL of dry tetrahydrofuran. To this was added, dropwise, the solution 8.6 mL of 3-methylbutanal dissolved in 20 mL of dry tetrahydrofuran. After 15 min of stirring the cooling was removed and the solution neutralized at once with a solution of acetic acid in ether. The solution was then concentrated in vacuo and diluted with benzene. The organic phase was washed with water several times and dried over anhydrous sodium sulfate, and the solvents were evaporated. The residue, upon crystallization from methanol, gave 30 g of condensation product **2** (23-isomeric mixture): mp 129–150 °C; IR ν 3500 (–OH), 1680 (–CO–), 1030 and 970 cm^{-1} (ether); NMR δ 0.63 (s, 3, 18-CH_3), 0.93 [d, 6, *J* = 6 Hz, 26,27-CH(CH_3)$_2$], 1.01 (s, 3, 19-CH_3), 5.34 ppm (m, 1, 6-H).

Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.73; H, 10.41.

A TLC, using as solvents 5–10% acetone in hexane, on 120 mg of the above mixture gave 55 mg of a more polar compound and 46 mg of less polar material. A determination of the configuration at C-23 according to Horeau and Kagan[7] revealed the more polar compound to have the 23*R* configuration, mp 134–136 °C, after two recrystallizations from methanol; IR and NMR are very similar to those of the isomeric mixture.

Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.76; H, 10.46.

The less polar compound has the 23*S* configuration and a mp 151–153 °C after recrystallization from methanol; IR and NMR are virtually indistinguishable from those of the mixture or of the 23*R* isomer.

Anal. Calcd for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.55; H, 10.38.

(*E*)-3β-Hydroxy-21-norcholesta-5,22-dien-20-one (3b) and (*E*)-3β-Tetrahydropyranyloxy-21-norcholesta-5,22-dien-20-one (3a). A solution of 24 g of the ketol **2** in 200 mL of benzene containing 250 mg of *p*-toluenesulfonic acid was heated under reflux for 10 min. After cooling, the solution was washed several times with saturated sodium bicarbonate solution, dried over sodium sulfate, and evaporated to dryness in vacuo. Chromatography of a small aliquot (1.25 g) of the residue (either on alumina or on TLC) yielded first the less polar tetrahydropyranyl ether which was recrystallized from hexane to give 793 mg (70%) of **3a**: mp 153–154 °C; UV_{max} (CH_3OH) 228 nm (ε 12 000); IR ν 1680 and 1610 (conj CO), 1030 and 960 cm^{-1} (ether); NMR δ 0.60 (s, 3, 18-CH_3), 0.90 [d, 6, *J* = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 19-CH_3), 3.51 (m, 1, 3-H), 5.32 (m, 1, 6-H), 6.12 (d, 1, *J* = 16 Hz, 22-H), 6.78 ppm (t of d, 1, *J* = 8 and 16 Hz, 23-H).

Anal. Calcd for $C_{31}H_{48}O_3$: C, 79.43; H, 10.32. Found: C, 79.21; H, 10.45.

The more polar alcohol was recrystallized from hexane to give 205 mg (10%) of **3b**: mp 110–112 °C, IR ν 3300 (OH), 1670, and 1610 cm^{-1} (conj CO); NMR δ 0.60 (s, 3, 18-CH_3), 0.90 [d, 6, *J* = 6 Hz, 26,27-CH(CH_3)$_2$], 1.00 (s, 3, 19-CH_3), 3.52 (m, 1, 3-H), 5.34 (m, 1, 6-H), 6.10 (d, 1, *J* = 16 Hz, 22-H), 6.78 ppm (t of d, 1, *J* = 9 Hz and 16 Hz, 23-H).

Anal. Calcd for $C_{26}H_{40}O_2$: C, 81.20; H, 10.48. Found: C, 81.55; H, 10.84.

3β-Tetrahydropyranyloxy-21-norcholest-5-en-20-one (7a). (a) Catalytic Reduction. A solution of 500 mg of the conjugated ketone **3a** in 100 mL of ethyl acetate was reduced, at 1 atm, with hydrogen and 40 mg of prereduced platinum oxide. The reaction was stopped after absorption of 1.1 equiv of hydrogen and the mixture was then evapoarted to dryness. The product was dissolved in methylene chloride and the catalyst was removed by filtration through Celite. The filtrate was evaporated to dryness and the residue purified on TLC. In this fashion there was obtained, after recrystallization from ethanol, 443 mg of saturated ketone **7a**, mp 112–119 °C, identical in all respects with an authentic standard.[3,4] This material also had IR and NMR spectra indistinguishable from those obtained from authentic material.

(b) Reduction with Lithium and Ammonia. A solution of 500 mg of the enone **3a** in 20 mL of dry tetrahydrofuran was added rapidly to a well-stirred solution of 300 mg of lithium in liquid ammonia. After 15 min (the color was still deep blue), solid ammonium chloride was added and the ammonia allowed to evaporate. Isolation with methylene chloride gave a crude product which was purified on TLC. Recrystallization from ethanol gave 396 mg of saturated ketone **7a**, identical in all respects with an authentic[3,4] sample.

20-Keto-21-norcholesterol (7b). This product was obtained from the ether **7a** by hydrolysis with hydrochloric acid (5.0 g of **7a**/100 mL of THF/three drops of concentrated HCl/50 °C/3h). The mixture was poured into water, the tetrahydrofuran partially evaporated off in vacuo, and the product extracted with ether. The organic layer was washed with a saturated solution of sodium bicarbonate, dried, and concentrated to give 4.1 g of product **7b** indistinguishable from an authentic[8] sample.

3β-Hydroxycholesta-5,20-diene (8b). A Wittig reaction on the ketone **7b**, exactly as described[3,4] for the 3-tetrahydropyranyl ether, gave the desired diene **8b**, mp 109–111 °C.

(20*R*)- and (20*S*)-Cholest-5-ene-3β,21-diol[1]

Chang-yon Byon, Güniz Büyüktür, Patrick Choay, and Marcel Gut*

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

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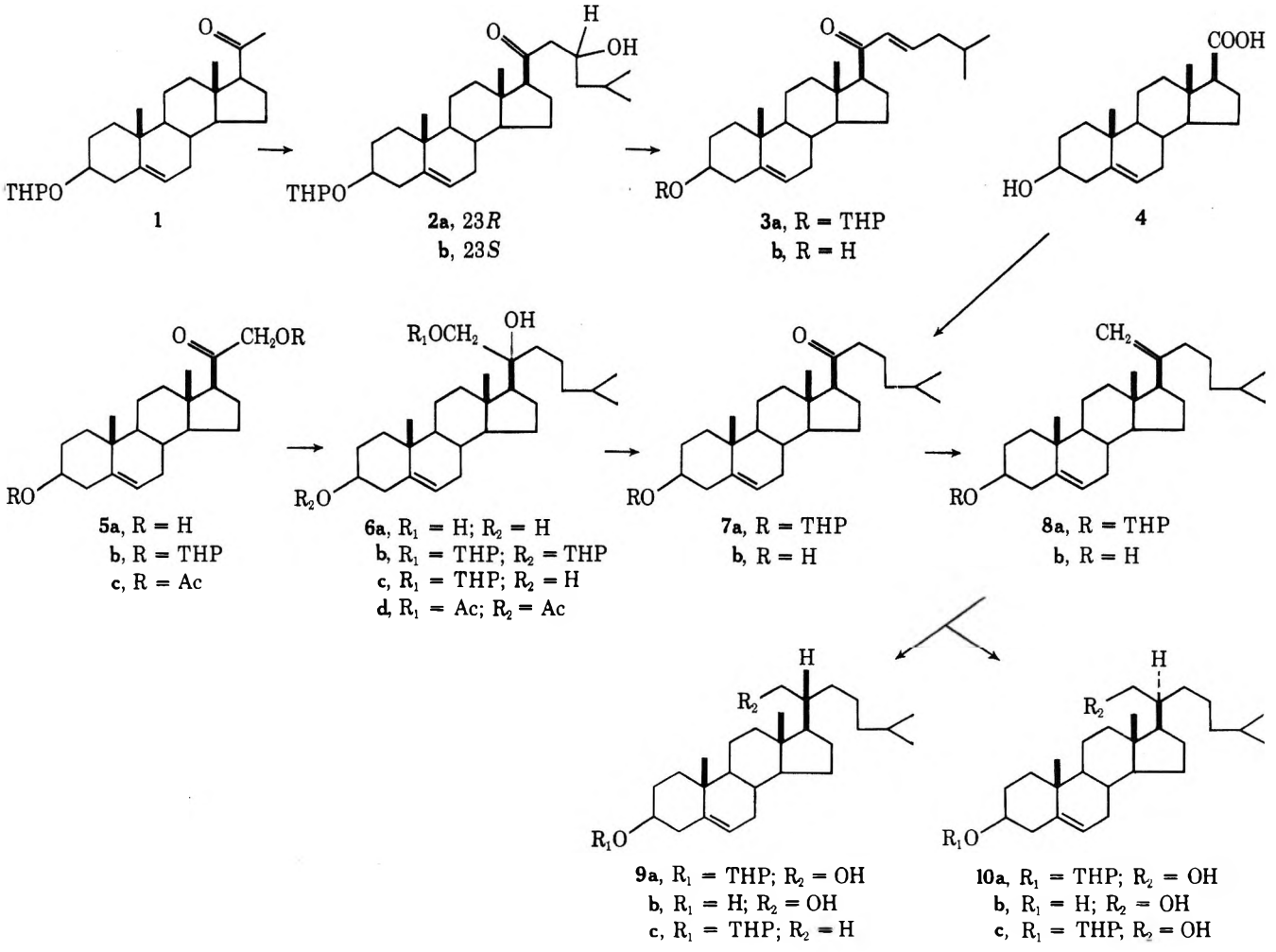
Our interest[2] in inhibitors of the cholesterol side-chain cleavage enzyme system in adrenocortical preparation made it desirable to test (20*R*)- and (20*S*)-cholest-5-ene-3β,21-diol. An approach to these compounds has already been described by Bottin and Fetizon.[3,4]

The starting material, 20-keto-21-norcholesterol can be made in many different ways, as already indicated by Bottin and Fetizon.[3,4] We have explored the regiospecific aldol condensation, as described by Stork et al.,[5] of 3β-hydroxypregn-5-en-20-one tetrahydropyranyl ether (**1**),[6] via its kinetic lithium enolate, with 3-methylbutanal to give 3β,23-dihydroxy-21-norcholest-5-en-20-one 3-tetrahydropyranyl ether (23-isomeric mixture) (**2**). The NMR spectrum indicated the completion of the side chain with a doublet at δ 0.93 for the 26,27-dimethyl group. The two 23 epimers could be separated by preparative TLC and were then analyzed according to the method of Horeau and Kagan.[7] The more polar compound **2a**, mp 134–136 °C, had the 23*R* configuration, while the less polar material was the 23*S* epimer **2b**, mp 151–153 °C. Dehydration of the ketol **2** (23-isomeric mixture) was carried out with *p*-toluenesulfonic acid in boiling benzene. In spite of the short reaction time (10 min), there was a substantial hydrolysis of the 3-tetrahydropyranyl (3-THP) ether (70% **3a** and 10% **3b**, both UV_{max} 228 nm (ε 12 000)). This high extinction (in the UV) together with the coupling constant of 16 Hz for 22-H and 23-H (in the NMR) ascertain the *E* geometry for the 22(23) double bond. In preparative runs the isolated crude product was routinely subjected to a treatment with dihydropyran and a catalytic amount of *p*-toluenesulfonic acid in benzene in order to obtain **3a** as a uniform product. The enone **3a** was then reduced (H_2/PtO_2 or Li/NH_3) to give in good yield the known saturated ketone **7a**.[3,4] Acid hydrolysis of the tetrahydropyranyl ether gave 3β-hydroxy-21-norcholest-5-en-20-one (**7b**),[8] identical in all respects with authentic material.

Another[9] synthesis of the ketone **7** proceeds by reacting 3β,21-dihydroxypregn-5-en-20-one 3,21-ditetrahydropyranyl ether (**5b**) with isohexylmagnesium bromide, followed by acid hydrolysis to give cholest-5-ene-3β,20,21-triol (20-isomeric mixture) (**6a**), which is very similar (NMR and IR) to the known 20*S* isomer.[10] The same product was also obtained from the Grignard reaction on 3β,21-diacetoxypregn-5-en-20-one (**5c**). A lead tetraacetate oxidation of the triol **6a** gave the desired norketone **7b**.

Scheme I



Acetylation of 7 with Ac_2O/Pyr under the usual conditions produced diacetate 8.

$NaBD_4$ Reduction of Peroxyferolide (1). Compound 1 (90 mg) in 12 mL of EtOD was treated with 25 mg of $NaBD_4$ for 30 min. After the usual workup including chromatography, the product was recrystallized several times from Et_2O–$CHCl_3$, mp 165–166 °C. ^1H NMR ($CDCl_3$) showed loss of one proton between 2.3 and 2.8 ppm and the 3-proton doublet at 1.28 of 6 changed to a 2-proton broadened singlet at δ 1.26; MS (CI, isobutane) *m/e* 327 (21%, MH^+, $C_{17}H_{22}D_2O_6$ requires 326), 325 (0), 309 (5, MH − H_2O), 267 (100, MH − AcOH), and 249 (25, MH − H_2O − AcOH).

Acetylation of Dihydrodeoxyperoxyferolide (6). A 50-mg sample of 6 was dissolved in 3 mL each of Ac_2O and Pyr at room temperature. The next day ice was added and the mixture extracted with $CHCl_3$. The extract was washed with dilute H_2SO_4, $NaHCO_3$, H_2O. The oily $CHCl_3$ residue was crystallized from Et_2O–EtOH to give 35 mg of 8: mp 121–122 °C; $[\alpha]^{22}_D$ +35.7° (*c* 0.42, MeOH); IR ($CHCl_3$) 1775 (lactone), 1730 and 1735 (acetate), and 1640 (olefin); MS (EI) no M^+ peak at 366, *m/e* 306 (3%, M − AcOH) and 246 (2, M − 2AcOH).

Anal. Calcd for $C_{19}H_{26}O_7$: C, 62.28; H, 7.15. Found: C, 62.04; H, 7.22.

Ozonolysis of 6 to 9. A stream of 3% O_3 in O_2 was bubbled through 5 mL of AcOH containing 40 mg of 6 at ~10 °C for 5 min. The reaction mixture was diluted with 50 mL of H_2O and distilled. The distillate (15 mL) was passed into 15 mL of cold saturated aqueous dimedone. After storing overnight in the cold, the crystalline precipitate, as needles (24 mg, mp 189–170 °C), was collected and found to give an undepressed mixture melting point with the dimedone derivative of formaldehyde.

The nonvolatile residue from the still was combined with material of a repeat ozonolysis and chromatographed on 5 g of silica gel with Me_2CO–$CHCl_3$ (1:4). The effluent material, TLC R_f 0.43 with Me_2CO–$CHCl_3$ (2:3), weighing 34 mg was crystallized from Et_2O–EtOH to give 22 mg of 9: mp 168–169 °C; $[\alpha]^{25}_D$ −45.8 (*c* 0.48, MeOH); UV λ_{max} 297 nm (ϵ 42) and end absorption ϵ_{210} 230; IR ($CHCl_3$) 3470 (OH), 1775 (lactone), 1740 (acetate), and 1710 (ketone); and positive tests with periodic acid reagent and 2,4-dinitrophenylhydrazine.

Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.88; H, 6.80. Found: C, 58.87; H, 6.90.

Reduction of Peroxyferolide (1) to 10. A 200-mg sample of 1 in 25 mL of MeOH was stirred 1 h with 2 mL of 10% aqueous KI and then at 0 °C treated with 0.1 mL of AcOH for 1 h. The residue after evaporation of solvent was taken up in 25 mL of $CHCl_3$ and extracted successively with 5% $NaHCO_3$, 5% $Na_2S_2O_3$, and H_2O. The $CHCl_3$ residue was purified by preparative TLC on silica gel PF-254 with EtOH–$CHCl_3$ (1:19), R_f 0.74 after triple development. The band was eluted with MeOH–$CHCl_3$ (1:1) and the extract residue crystallized from *i*-Pr_2O–EtOH to give 148 mg of deoxyperoxyferolide (10): mp 169–171 °C; $[\alpha]^{22}_D$ +17° (*c* 0.30, MeOH); IR ($CHCl_3$) 3600 and 3500 (OH), 1770 (lactone), 1750 (acetate), 1670 (conjugated olefin), 1645 cm^{-1} (olefin); MS (EI) *m/e* 322 (33%, M^+, $C_{17}H_{22}O_6$ requires 322), 304 (14, M − H_2O), 280 (11, M − CH_2CO), 262 (28, M − AcOH), 244 (22, M − H_2O − AcOH), 127 (100) and 43 (74, Ac), and CI (isobutane) *m/e* 323 (15, MH^+), 305 (100, MH − H_2O) and 245 (5, MH − H_2O − AcOH).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.14; H, 6.81.

Acetylation of Deoxyperoxyferolide (10) to 11. A 100-mg sample of 10 was dissolved in 0.1 mL of Ac_2O and 0.1 mL of Pyr. After 6 h at room temperature, the reaction residue on reduced pressure evaporation was dissolved in 5 mL of $CHCl_3$ and extracted successively with 0.1 M HCl, 5% $NaHCO_3$, and H_2O. Recrystallization of the $CHCl_3$ residue from Et_2O–EtOH gave 88 mg of 11: mp 112–115 °C; $[\alpha]^{22}_D$ +52° (*c* 0.17, $CHCl_3$); IR ($CHCl_3$) 1780 (lactone) and 1740 cm^{-1} (double intensity, acetate); MS (EI) *m/e* 364 (2, M^+, $C_{19}H_{24}O_7$ requires 364), 322 (3, M − CH_2CO), 304 (30, M − AcOH), 262 (24, M − AcOH − CH_2CO), 244 (36, M − 2AcOH) and 43.

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.24; H, 6.81.

Photooxygenation of Lipiferolide (2) to 1. 2 (102 mg, 0.33 mmol) and Methylene Blue (1.3 mg) were dissolved in 7 mL of absolute EtOH, placed in a U-shaped reaction tube fitted with a sintered glass frit at the bottom, and connected to an oxygen source in a closed system. Oxygen was circulated via the frit by a peristatic pump and measured manometrically. The reaction tube was placed into a 4-L silver-lined Dewar flask and 10 cm from a Sylvania DWY 650 W quartz-halogen lamp. Cooling water passed into the Dewar was maintained at 16 ± 1 °C. After 5 h, O_2 uptake ceased at 0.34 mmol and the crystalline precipitate (40 mg) of peroxyferolide (1) was collected. The filtrate was passed through a short silica gel (5 g) column to remove the dye, and the residue was combined with the crystals and recrystallized from EtOH–$CHCl_3$ to give 86 mg of 1. The product showed the same IR, UV, NMR, mass spectra, melting point characteristic, $[\alpha]_D$, and TLC mobility as peroxyferolide (1) from nature.

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Registry No.—1 pyrazoline derivative, 63528-73-4.

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With the allylic hydroperoxide function of peroxyferolide (1) characterized, formation of the anhydro-derivative 3 under acylating conditions is understood to arise by elimination of acetate from the transient acetyl peroxyferolide, since pyridine alone is inert. Similar facile eliminations have been reported for hydroperoxides α to a ketonic[11] or aromatic group.[12] The stability of methylperoxyferolide (5), in comparison, rests with the poor leaving property of methoxide vs. acetate.

Preparation of peroxyferolide (1) was accomplished in high yield by photooxygenation of lipiferolide (2)[5] by visible light and Methylene Blue as sensitizer. This confirmed the stereochemical assignments for carbons 4 through 8, and requires that the hydroperoxy group be placed β at C-1, since the solution conformation of lipiferolide as in 12 has been related chemically to epitulipinolide (13),[5] which in turn has been related to costunolide (14) by circular dichroism. Costunolide from nuclear Overhauser effect analysis was shown to have the olefins crossed and the methyl groups up.[13] The stereochemistry of singlet-oxygen addition has been established to proceed via a cis cyclic mechanism, with the oxygen approaching perpendicular to the olefinic plane. Thus, for peroxyferolide the oxygen introduction would be to the β position.

Prior to the isolation of peroxyferolide, two hydroperoxides were characterized from nature, 3α,22α-dihydroxy-7α-hydroperoxystigmast-5-ene from horse-chestnut (*Aesculus hippocastanum*),[15] and peroxy-Y base, an elaborated tRNA purine from several plant and animal sources.[9b] A third, verlotorin, from *Artemisia verlotorum*, was reported as 4, but recent work requires it be revised to an allylic hydroperoxide.[16] Peroxyferolide (1) is therefore the first recognized sesquiterpene hydroperoxide from nature. The genesis of these products is unknown, but an artifactual origin seems unlikely as plant material from different parts of the country varied in their content of peroxyferolide (some were totally devoid), yet processing was the same. Lipiferolide (2) was found in all samples. Chlorophyll-mediated oxygenation appears probable, since peroxyferolide (1) was obtained from leaves in which lipiferolide (2) is the most abundant germacranolide, and chlorophyll is known to be an effective sensitizer.[14] A spinach-leaf preparation has already been reported to convert α-terpinene to ascaridole, an endoperoxide.[17]

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. The UV spectra were determined in MeOH on a Cary Model 15 instrument, and IR spectra were obtained on a Beckman 4230 or Perkin Elmer 257 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian A-60A or Bruker HX-90E instrument; the latter equipped for Fourier transform analysis was also used for ^{13}C NMR determinations. Mass spectra were measured on AEI MS-902 and MS-9, Finnigan 1015, or DuPont 21-491 spectrometers. CD spectra were taken in MeOH on a Durrum-Jasco ORD/UV-5 spectropolarimeter with Sproul Scientific SS-20 modification, and specific rotations on a Perkin-Elmer 241 photoelectric polarimeter. Elemental analyses were by the Scandinavian Microanalytical Laboratory, Herley, Denmark. Silica gel G (E. Merck) was used for TLC with H_2SO_4–Et_2O (1:4) as a spray reagent followed by heating, or by 0.3% aqueous $KMnO_4$.

Isolation of Peroxyferolide (1). The dried powdered leaves of *Liriodendron tulipifera* L. were percolated with EtOH. The residue remaining after removal of the solvent at reduced pressure was partitioned and the 10% aqueous MeOH fraction was chromatographed on silicic acid as already described.[5] The column fraction (285 mg) preceding lipiferolide (2) was rechromatographed on a column of 17 g of silica gel G (E. Merck) prepared from TLC grade adsorbent by powdering the dried cake as prepared for plate pouring and sieved through a 50 mesh screen. Elution with 8% EtOH in $CHCl_3$ and collection of 5-mL fractions gave in fractions 16–23 one-spot material, R_f 0.17 on TLC with the same system as used in the column. The residue (101 mg) was crystallized from EtOH–$CHCl_3$ to give colorless needles (45 mg, 0.02% from dried leaves) of peroxyferolide (1): mp 190 °C softens and then decomposes gradually on further heating up to 300 °C without melting; $[\alpha]^{22}_D$ +30° (c 0.30, MeOH); CD curve $[\theta]_{257}$ −2000 and $[\theta]_{214}$ −31 300; UV end absorption (ϵ_{215} 9000); IR ($CHCl_3$) bands at 3515 and 3370 (OH), 1770 (lactone C=O), 1740 (acetate C=O), 1665 and 1640 (C=C), and 1210–1250 (C–O) cm^{-1}; chemical ionization mass spectrum (isobutane) *m/e* 339 (32%. MH$^+$, $C_{17}H_{22}O_7$ requires 338), 323 (9, MH − O), 321 (24, MH − H_2O), 305 (6, MH − H_2O_2), 279 (43, MH − AcOH), 263 (72, MH − O − AcOH), 261 (100, MH − H_2O − AcOH), and 245 (72, MH − H_2O_2 − AcOH).

Anal. Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.26; H, 6.60.

Pyrazoline of Peroxyferolide (1). A 40-mg sample of 1 in 5 mL of $CHCl_3$ was treated overnight with 24 mL of Et_2O containing ~0.1 g of diazomethane at 5 °C. Removal of the solvent and crystallization of the residue several times from Me_2CO–Et_2O gave colorless cubes, mp 177–178 °C (d, with effervescence), which decomposed rapidly on handling and storage. The NMR spectrum (Pyr-d_5, 60 MHz) contained changes expected for a pyrazoline derivative, e.g., loss of the H-13 doublets, simplification of the H-7 pattern to a pair of doublets (3.85 ppm, J = 2, 10 Hz), and a large downfield shift of the H-6 triplet from 4.51 to 5.45 ppm (J = 10 Hz), which requires the diazene group to be placed α.[18]

Attempted Acetylation of Peroxyferolide (1). (A) By Ac_2O/Pyr. A 50-mg sample of 1 was dissolved in 20 mL of Ac_2O and 1 mL of Pyr at room temperature. The following day ice and 10 mL of 1% $NaHCO_3$ were added. The mixture was extracted with $CHCl_3$ and the extract washed with dilute HCl, $NaHCO_3$, and H_2O. The $CHCl_3$ residue was crystallized from $CHCl_3$–i-Pr_2O and Et_2O–EtOH to yield fine needles of anhydroperoxyferolide (3): mp 157–158 °C; R_f 0.58 on TLC with Me_2CO–$CHCl_3$ (1:3); $[\alpha]^{22}_D$ −24° (c 0.50, MeOH); UV λ_{max} 323 nm (ϵ 30) and 212 (17 000); IR ($CHCl_3$) no OH bands but peaks at 1770 (lactone), 1740 (acetate), 1685 and 1670 cm^{-1} (unsaturated C=O); MS (EI) *m/e* 320 (0.2%, M$^+$, $C_{17}H_{20}O_6$ requires 320), 278 (0.4, M − CH_2CO), 277 (0.9, M − Ac), 260 (0.9, M − AcOH), and 43 (100, Ac).

Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.74; H, 6.42.

(B) By Acetylimidazole. Peroxyferolide (1, 10 mg) and 5 mg of acetylimidazole in 2 mL of $CHCl_3$ were refluxed for 2 h and then diluted with 18 mL of $CHCl_3$ and washed with H_2O. Chromatography of the reaction residue on 5 g of silica gel with 5% EtOH in $CHCl_3$ removed the imidazole, and the 6 mg of effluent residue was crystallized from i-Pr_2O–EtOH to give 3 identical with the product obtained with Ac_2O/Pyr.

Methylation of Peroxyferolide (1) to 5. A 50-mg sample of 1 in $CHCl_3$ was stirred with 270 mg of MeI and 250 mg of Ag_2O for 16 h at room temperature. The mixture was filtered and the colorless filtrate on evaporation left a residue that was crystallized from EtOH–Et_2O to give 5 as colorless needles: mp 175–176 °C; R_f 0.61 on TLC with 8% EtOH in $CHCl_3$; $[\alpha]^{22}_D$ +30.2° (c 0.43, MeOH); IR no OH bands, 1778 (lactone), 1742 (acetate), 1667 and 1643 cm^{-1} (olefins); chemical ionization MS (NH_3) *m/e* 370 (100%, MNH$_4^+$, $C_{18}H_{24}O_7$ requires 352), 353 (2, MH), 340 (10, MNH$_4$ − CH_2O), 338 (7, MNH$_4$ − MeOH), and 310 (3, MNH$_4$ − AcOH), and with isobutane *m/e* 353 (15, MH$^+$), 305 (4, MH − MeOOH), 293 (67, MH − AcOH), 262 (64, MH − AcOH − MeO), and 245 (100, MH − AcOH − MeOOH), but electron impact MS gave no useful spectrum.

Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 60.95; H, 6.89.

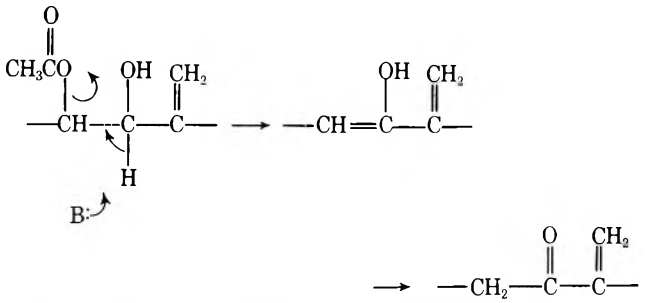
NaBH_4 Reduction of Peroxyferolide (1). A 350-mg sample of 1 in 45 mL of absolute EtOH was treated with 80 mg of $NaBH_4$ for 20 min. The mixture was neutralized with dilute HOAc and evaporated to dryness, and the residue was mixed with water and extracted with $CHCl_3$. The chloroform solubles were chromatographed on 14 g of silica gel with Me_2CO–$CHCl_3$ (1:3) and the effluent residue (200 mg) was crystallized to give 6 from Et_2O–$CHCl_3$, mp 165–166 °C, or from i-Pr_2O–MeOH, mp 132–133 °C: R_f 0.34 with 10% EtOH in $CHCl_3$; $[\alpha]^{22}_D$ −21.6° (c 0.51, MeOH); IR (KBr) 3450 (OH), 1765 (lactone), 1735 (acetate), and 1635 cm^{-1} (olefin); MS (CI, isobutane) *m/e* 325 (8%, MH, $C_{17}H_{24}O_6$ requires 324), 307 (3, MH − H_2O), 265 (100, MH − AcOH), and 247 (24, MH − H_2O − AcOH).

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.81; H, 7.49.

Elution of the column with Me_2CO–$CHCl_3$ (2:3) gave 28 mg of a minor polar compound 7 that was crystallized from i-Pr_2O–EtOH: mp 101–102 °C; R_f 0.24 on TLC with Me_2CO–$CHCl_3$ (2:3); $[\alpha]^{25}_D$ −30.9° (c 0.55, MeOH); IR (KBr) 3200–3350 (OH), 1745 (lactone), and 1625 (olefin); MS (CI, isobutane) 283 (33%, MH, $C_{15}H_{22}O_5$ requires 282), 265 (100, MH − H_2O), and 247 (17, MH − $2H_2O$).

Anal. Calcd for $C_{15}H_{22}O_5 \cdot \frac{2}{3}H_2O$: C, 61.20; H, 7.99. Found: C, 60.97; H, 8.05.

and original acetate, as the peak patterns associated with protons of these groups remained unaffected. There was, however, loss of the one-proton double doublet at 4.37 ppm in the transformation, and now the H-14 peaks became sharpened singlets. The UV and IR spectra, with intense ab-



sorption in the latter at 1670 cm^{-1}, suggested an α,β-unsaturated ketone, possibly arising from a 1-vinyl-1,2-glycol unit by elimination of acetate under basic conditions to form a pinacol rearranged product. The same reasoning was invoked for the conversion of verlotorin (4) to anhydroverlotorin.[7] Anhydroperoxyferolide was thus formulated as 3 with a ten-membered germacrane ring.

All efforts at gaining chemical support for the presence of a 1,2-glycol system were unsuccessful. These included acetonide (via acetone or 2,2-dimethoxypropane) and phenylborate ester preparation. However, treatment of peroxyferolide (1) with methyl iodide and silver oxide produced a monomethoxy derivative still containing seven oxygens, but no longer showing hydroxyl absorption in the IR spectrum. It was recovered unchanged after an acetylation attempt. Clearly the seventh oxygen was not hydroxyl. The methoxy derivative was formulated from evidence to follow as the methyl peroxide **5.**

On reduction of peroxyferolide (1) with sodium borohydride the major product contained one less oxygen and two additional hydrogens. The ^1H NMR spectrum showed no peaks for the H-13 protons, but instead a three-proton doublet at 1.32 ppm and an upfield shift for H-7, indicating the expected

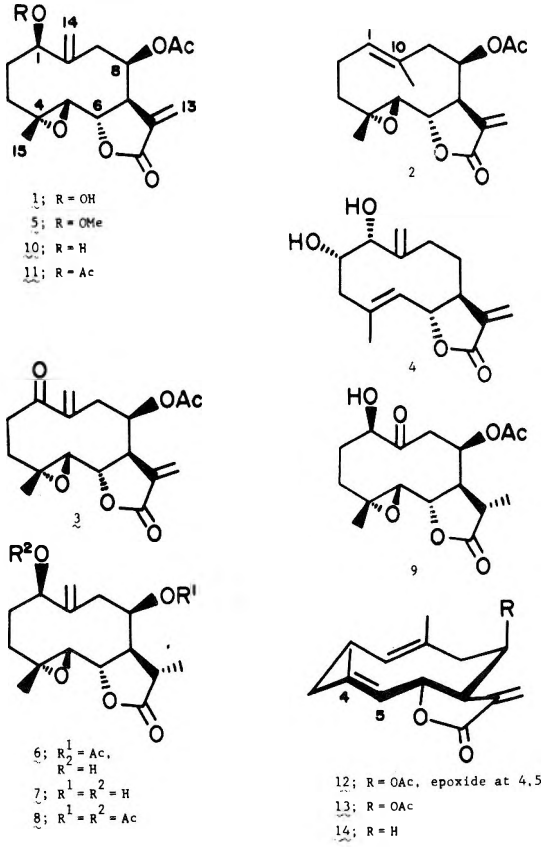


Table II. ^{13}C NMR Spectra of Peroxyferolide and Related Compounds[a]

Carbon atom	1[b]	2[b]	10[e]	11[e]
1	90.9 d	129.1 d	78.2 d	78.0 d
2	34.1 t[c]	44.0 t[c]	33.3 t[c]	33.5 t[c]
3	32.1 t[c]	36.4 t[c]	30.3 t[c]	31.2 t[c]
4	60.7 s	61.8 s	60.4 s	60.0 s
5	64.4 d	66.8 d	63.8 d	63.9 d
6	76.4 d	76.4 d	75.6 d	75.4 d
7	46.7 d	49.4 d	45.8 d	45.8 d
8	67.0 d	74.5 d	66.2 d	66.4 d
9	26.6 t[c]	24.5 t[c]	29.8 t[c]	27.8 t[c]
10	142.9 s	132.0 s	146.2 s	141.3 s
11	136.1 s	137.9 s	134.5 s	134.3 s
12	169.3 s	169.1 s	168.7 s	168.3 s
13	120.4 t	121.9 t	120.8 t[d]	119.4 t[d]
14	120.1 t	19.7 q	117.0 t[d]	120.9 t[d]
15	18.5 q	17.2 q	18.3 q	18.3 q
CH_3CO	20.5 q	20.6 q	20.6 q	21.0 q, 20.6 q
CH_3CO	170.2 s	169.9 s	169.9 s	169.8 s, 169.2 s

[a] Assignments of multiplets were made by single frequency off-resonance spin decoupling. Peak assignments were based on comparison with related compounds in our possession and by single-frequency irradiation of known proton resonances. [b] In Pyr-d_5. [c,d] Not designated, may be interchanged. [e] In $CDCl_3$.

reduction of the lactonic α-methylene. The remainder of the spectrum, except for the H-7 absorption as stated, stayed essentially unchanged; thus, the loss of oxygen was from a position little affecting the proton spectrum. When sodium borodeuteride was used, only two deuteriums were incorporated, at positions 11 and 13, confirming that additional carbons were not reduced and that the hydroxyl group was not formed from an unsaturated function. The evidence available refuted the presence of a glycol in peroxyferolide (1) and required consideration of a hydroperoxide. The borohydride product was formulated as **6** (stereochemical assignment at C-1 open) with the C-13 methyl placed α on the basis of similar reductions on related compounds.[6] A minor by-product of the borohydride reduction was assigned structure **7** on spectral evidence and by conversion to an acetate derivative **8** identical to the acetate prepared from **6.** With dihydrodeoxyperoxyferolide (**6**) it was possible to provide chemical proof for the exocyclic double bond to C-14, as ozonolysis of **6** gave formaldehyde (identified as the dimedone derivative) and the α-hydroxy ketone **9.**

Support for a hydroperoxide group in peroxyferolide (1) was obtained from the ^{13}C NMR spectrum (Table II), since three peaks were found in the methylene region at 34.1, 32.1, and 26.6 ppm, each appearing as triplets in off-resonance and undecoupled spectra. Only seven oxygenated carbons could be assigned, six of which corresponded to the partial structure from C-4 to C-8 previously established by the ^1H NMR experiments. The seventh oxygen-bearing carbon, uniquely located at 90.9 ppm, had to contain the two remaining oxygens. Chemical tests on peroxyferolide (1) for a hydroperoxide were positive; e.g., a deep blood-red color rapidly formed with ferrous thiocyanate,[8] and iodine was readily liberated from ethanolic potassium iodide. Furthermore, the characteristic loss of 16 mass units for hydroperoxides was observed in the mass spectrum,[9] and polarographic analysis in nonaqueous medium for peroxides and hydroperoxides[10] gave a half-wave potential of −0.66 V, a value within the range of −0.61 to −0.96 V reported for hydroperoxides. On mild reduction of peroxyferolide (1) with acidic potassium iodide, deoxyperoxyferolide (**10**) was formed, which was easily acetylated to **11.**

Table I. ^{1}H NMR Spectra of Peroxyferolide and Derivatives[a]

Registry no.	Compd	H-1	H-5	H-6	H-7	H-8	H-13	H-14	H-15	Miscellaneous
61228-73-7	1[b]	4.37 dd (9.9, 4.4)	2.98 d (9.4)	4.23 t (9.6, 9.4)	3.93 m (9.6, 3.5) 3.1, 3.1)	5.95 dq (11.4, 6.4, 3.1)	6.13 d (3.5) 5.53 d (3.1)	5.45 d (2.4) 5.33 br d (1.7)	1.53 s	10.64 br s[c], 2.84 m (H-9a), 2.65 m (H-9e), 2.03 s (Ac)
41059-80-7	2[b]	5.28 br d (11)	2.86 d (8.5)	4.24 dd (8.5, 7.8)	3.35 m (7.8, 3.4, 3.1, 0.9)	5.49 m	5.96 d (3.4) 5.54 d (3.1)	1.74 br s (~1)	1.29 s	1.99 s (Ac)
61228-74-8	3[d]		2.63 d (9.2)	4.18 t (9.0)	~3.2 m	5.53 dq (7.8, 3.7, 1.5)	6.33 d (3.5) 5.65 d (3.1)	6.2 s ($w_{1/2}$ = 1.2) 5.77 br s ($w_{1/2}$ = 2.2)	1.52 s	2.07 s (Ac)
63511-98-8	5[d]	4.47 dd (9.2, 4.0)	2.90 d (8.9)	4.21 t (8.9)	~3.7 m	5.97 dq (10.6, 5.4, 2.5)	6.30 d (3.3) 5.57 d (2.9)	5.48 br d (2.2) 5.17 br d (~1.5)	1.54 s	3.80 s (MeO), 2.06 s (Ac)
61228-75-9	6[d]	4.20 dd (9.4, 4.6)	2.79 d (9.2)	4.10 t (9.3)	~3.0 m	5.63 dq (10.8, 5.3, 2.2)	1.28 d (6.2)	5.41 d (2.6) 4.93 br d (1.8)	1.54 s	2.13 s (Ac) 1.87 br s (OH)[c]
63511-99-9	7[e]	4.0–4.6 m	2.82 d (9.0)	4.15 t (9.2)	~2.8	4.0–4.6 m	1.24 d (6.2)	5.30 d (2.5) 4.92 br q (~1)	1.52 s	
61228-76-0	8[d]	5.39 dd (9.0, 4.8)	2.83 d (9.2)	4.10 t (9.2)		5.58 dq (10.8, 5.0, 2.0)	1.28 d (6.2)	5.49 d (2.4) 5.02 br s	1.55 s	2.14 (Ac) 2.01 (Ac)
63512-00-5	9[d]	4.17 dd (6.2, 4.8)	2.65 d (9.0)	4.10 t (9.3)		5.50 m (8.8, 7.0, 2.8)	1.29 d (6.3)	absent	1.63 s	2.13 (Ac)
63512-01-6	10[b]	~4.2 m	2.97 d (9.1)	4.23 t (9.4)	3.90 m (9.4, 3.5, 3.2, 3.0)	5.92 dq (11.4, 6.4 3.0)	6.13 d (3.5) 5.52 d (3.2)	5.35 br d (2.4) 5.10 br d (2)	1.54 s	2.8 m (H-9a) 2.03 s (Ac)
63512-02-7	11[f]	5.42 dd[g] (9.5, 5.1)	2.93 d (9.5)	4.21 t (9.5)	3.67 m (9.5, 3.5, 3.2, ~3)	5.86 dq (11.4, 5.1, 2.5)	6.29 d (3.5) 5.54 d (3.2)	5.51 br d (2.5) 5.09 br d (~1)	1.56 s	2.06 and 2.03 (2 Ac)

[a] Spectra were determined in stated solvent at 60 or 90 MHz with Me_4Si as internal standard. Chemical shifts (δ) are in parts per million, coupling constants (J) in Hz are given in parentheses, and multiplicities are designated by the following symbols: s, singlet; d, doublet; m, multiplet with center given; q, quartet; t, triplet; and br, broadened signal. [b] In acetone-d_6 at 90 MHz. [c] D_2O exchangeable. [d] In $CDCl_3$ at 60 MHz. [e] In acetone-d_6 at 60 MHz. [f] In $CDCl_3$ at 90 MHz. [g] Partially obscured by other peaks.

the H_e pattern affected, but the 2.0–2.4-ppm region containing H_h was changed, as was the conversion of the one-proton split singlets at 5.45 and 5.33 ppm to sharp singlets. The alterations are consistent with the presence of an olefinic methylene adjacent to the aliphatic protons, H_g and H_h.

The partial structure of peroxyferolide (1) derived from NMR studies was in agreement with the arrangement of substituents observed for lipiferolide (2) from C-5 through C-8. The presence of a three-proton singlet at 1.53, although 0.24-ppm downfield from a similar peak of lipiferolide, was taken as an epoxide methyl with the difference resulting from the nature of the olefinic group. Thus, placement of an oxirane ring between C-4 and C-5, and assuming a normal isoprenoid skeleton, requires a methyl at C-4. This extends the similarity in structure to lipiferolide (2) to C-4 with the one-proton doublet at 2.98 ppm assigned H-5. The molecular formula of peroxyferolide (1) requires seven double-bond equivalents of which six are met by substituents of partial structure from C-4 through C-10. The remaining unsaturation equivalent must be from a ring, either carbocyclic or ether forming, since two oxygens still need to be accommodated, neither of which are associated with IR absorption in the carbonyl region.

The ^{1}H NMR analysis also provided stereochemical information. The large coupling constant of 9.6 Hz between H-6 and H-7 supports a trans-fused lactone, and, since all well-characterized sesquiterpene lactones have β side chains at C-7, the absolute stereochemistry at C-6 and C-7 is as drawn in **1**. Similarly, with $J_{7,8}$ = 3.1 Hz, a pseudo-equatorial H_8 is required that is further supported by the more downfield location of its pattern.[6]

Since hydroxyl absorption was observed for peroxyferolide (1) in the IR and ^{1}H NMR spectra, formation of an acetate with acetic anhydride and pyridine, and with acetylimidazole, was attempted. No acetylated product was formed, but, instead, an unstable derivative, anhydroperoxyferolide (3), was produced whose composition, $C_{17}H_{20}O_6$, corresponded to the loss of the elements of water. The ^{1}H NMR spectrum showed that the product retained the epoxide, unsaturated lactone,

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Isolation and Characterization of Peroxyferolide, a Hydroperoxy Sesquiterpene Lactone from *Liriodendron tulipifera*

Raymond W. Doskotch,* Farouk S. El-Feraly,[1a] Edward H. Fairchild, and Chin-Teh Huang[1b]

Division of Natural Products Chemistry, College of Pharmacy, Ohio State University, Columbus, Ohio 43210

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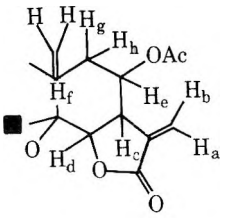
A naturally occurring germacranolide hydroperoxide, peroxyferolide, was assigned structure **1** from physical data, especially double-resonance ^1H NMR, and from chemical evidence. The allylic hydroperoxide function was supported by polarographic analysis, the preparation of anhydroderivative **3** under acetylation conditions, methylperoxyferolide (**5**) with methyl iodide and silver oxide, deoxyperoxyferolide (**10**) by mild reduction, and the presence of a characteristic absorption in the ^{13}C NMR. Formation of **1** from lipiferolide (**2**) by light-generated singlet oxygen confirmed the stereochemical assignments and established the configuration at the hydroperoxy-bearing carbon.

In screening ethanolic extracts of plants in a feeding test[2] for the larvae of the gypsy moth, *Lymantria dispar* L., it was found that the residue from the leaves of the tulip poplar, *Liriodendron tulipifera* L., showed antifeeding properties. On fractionating the crude extract a moderately active constituent,[3] peroxyferolide (**1**), was obtained and characterized to be the first naturally occurring germacranolide hydroperoxide[4] on the evidence reported herein. Previous work on this source had given lipiferolide (**2**) and epitulipinolide diepoxide (the 1,10-epoxide of **2**) as the major sesquiterpene components.[5]

Peroxyferolide (**1**) was isolated by repeated column chromatography and crystallization from ethanol–chloroform. Elemental and chemical ionization mass spectral analyses established the molecular formula as $C_{17}H_{22}O_7$, and the infrared spectrum suggested hydroxyl, α,β'-unsaturated γ-lactone, ester, and olefinic functions. The ^1H NMR spectrum (Table I) showed a pair of one-proton doublets at 6.13 and 5.53 ppm split by 3.5 and 3.1 Hz, respectively, which are characteristic of α-methylene γ-lactones, and confirmed by preparation of a crystalline pyrazoline derivative that was too unstable for proper characterization. A three-proton singlet at 2.03 ppm supported an acetate as the ester function. The remainder of the molecule was assumed to be sesquiterpenoid.

Double-irradiation experiments clarified the arrangement of the substituents about the α,β'-unsaturated γ-lactone as shown in A, in which ■ designates a quaternary carbon. Irradiation of the doublet for H_a at 6.13 ppm caused the multiplet at 3.93 ppm to be simplified to a pair of triplets with J = 9.6, 3.1, and 3.1 Hz, and irradiation at 5.53 ppm (H_b) showed a similar collapse with coupling now 9.6, 3.5, and 3.1 Hz, thus locating H_c at 3.93 ppm. Saturation of this signal not only converted the H_a and H_b doublets to singlets but also changed



A

the one-proton triplet at 4.23 ppm to a doublet (J = 9.6 Hz) and the saw-tooth multiplet of eight-peaks at 5.95 ppm to a pair of doublets (J = 11.4 and 6.4 Hz). The lactonic proton H_d was assigned at 4.23 ppm, and H_e on the acetate-bearing carbon at 5.95 ppm in keeping with the chemical shifts observed for similar protons in other sesquiterpene lactones. Irradiation at 4.23 ppm collapsed the multiplet at 3.93 ppm (H_c) to a broadened quartet ($J \approx 3$ Hz) and the doublet at 2.98 ppm for H_f to a singlet. The pattern and chemical shift of H_f suggested it was adjacent to a quaternary carbon and most probably on a carbon with an epoxide oxygen (vide infra). Similar decoupling of H_e (5.95 ppm) caused the expected collapse of the H_c pattern at 3.93 ppm to a pair of triplets and of a one-proton (H_g) multiplet centered at 2.74 ppm; the A doublet (J = 17.2 Hz) of an AB quartet, further split into five peaks ($J \approx 2$ Hz) to a doublet split into four peaks. In addition, a change between 2.0 and 2.4 ppm was observed, but the region consists of overlapping peaks and was not clearly analyzable. Irradiation at ~2.2 ppm affected the large coupling for the pattern at 2.74 ppm and thus the hidden pattern corresponds to the second methylene proton H_h. Furthermore, the H_e multiplet at 5.95 ppm was changed to a pair of doublets and the one-proton broadened doublet at 5.33 ppm to a sharp doublet, as would be expected on elimination of allylic coupling. Finally, on irradiation of H_g (2.74 ppm), not only was

°C (lit.[28] mp 98–98.5 °C); NMR (CCl_4) δ 2.4–2.7 (2 H, m, NCH_2), 2.33 (3 H, s, NCH_3), 0.7–1.7 (15 H, m, aliphatic CH); CIMS *m/e* (rel intensity) 144 (100), 130 (5).

Reduction of 4 using 2 equiv of Hydride per Mole of Acylguanidine. 4 (1.48 g, 6.12 mmol) was reduced with $LiAlH_4$ (3.12 mmol) at 0 °C for 4 h and then at 23 °C for 1 h. After workup, the resulting oil was distilled to yield 983 mg of a hygroscopic mixture: bp 110–115 °C (0.4 mm, Kugelrohr); NMR (CCl_4) δ 8.00 (1 H, t, $CONHCH_2N$, J = 6 Hz), 3.92 (2 H, d, $CONHCH_2N$, J = 6 Hz), 2.92 and 3.04 (equivalent singlets, dimethyloctanamide), 2.20 [m, $NCN(CH_3)_2$ and CH_2CO], 0.70–1.90 (m, aliphatic CH); CIMS *m/e* (rel intensity) 201 (100), 172 (15), 156 (25), 144 (30), 127 (1), rel intensities of 172 and 144 varied with time and temperature. The NMR sample was shaken with D_2O and the signal at δ 8.00 disappeared, while the previous doublet at δ 3.92 became a singlet at δ 3.92 (2 H).

The distilled product was found to contain three components by GC, identified as octanamide (**26**), *N,N*-dimethyloctanamide (**27**), and *N*-(dimethylaminomethyl)octanamide (**25**) by low-resolution GC/MS (ei). The empirical formulas were obtained from the mixture with a scanning high-resolution MS: first GC peak, *m/e* (rel intensity, molecular formula, Δmmu) 171 (3, $C_{10}H_{21}NO$, 0.3), 87 (100, C_4H_9NO, 0.3), 72 (40, C_3H_6NO, 2.8); second peak, 143 (1, $C_8H_{17}NO$, 0.0), 59 (100, C_2H_5NO, 2.7), 44 (21, CH_2NO, 0.4); third peak, 200 (1, $C_{11}H_{24}N_2O$, 0.4), 127 (40, $C_8H_{15}O$, 0.6), 57 (100, C_3H_7N, 3.6).[29] The mole fractions (from corrected GC and NMR integration) of each component were as follows: **26,** 0.12; **27,** 0.21; **25,** 0.67. Based on the 983 mg of distilled mixture, the yields were 10, 18, and 58%, respectively.

Reduction of 4 Using 1.3 equiv of Hydride per Mole of Acylguanidine. 4 (3.05 g, 12.6 mmol) was treated with $LiAlH_4$ (4.3 mmol) in 100 mL of ether as in the previous reduction, except that the time at 23 °C was 2 h. Workup and distillation gave 1.90 g of oil: bp 108–114 °C (0.45 mm, Kugelrohr); CIMS *m/e* (rel intensity) 201 (15), 172 (100), 156 (2), 144 (21), rel intensity varied with time and temperature; NMR and GC/MS showed the same products as before in the following proportions: **26,** 0.12; **27,** 0.78; **25,** 0.10. These mole fractions correspond to yields of 11, 69, and 9%, respectively.

***N*-(Dimethylaminomethyl)octanamide (25).** Octanamide[30] (300 mg, 2.10 mmol), formaldehyde (2.5 mL, aqueous, 33.3 mmol), dimethylamine (1.45 g, 32.2 mmol), and 20 mL of *tert*-butyl alcohol were heated for 2 h in a pressure vessel on a steam bath. The reaction mixture was cooled and evaporated to a dark yellow oil; CCl_4 (3 × 40 mL) was evaporated from the oil to remove H_2O and other volatile materials. The residue was dissolved in petroleum ether (5.0 mL, reagent), the solution was cooled and then filtered, the filtrate was evaporated, and the residue was distilled to give 222 mg (53%) of colorless oil: bp 115–120 °C (0.40 mm, Kugelrohr); NMR (CCl_4) δ 8.00 (1 H, t, NH, J = 6 Hz), 3.92 (2 H, d, $NHCH_2N$, J = 6 Hz), 2.20 [8 H, m, RCH_2CO and $N(CH_3)_2$], 0.70–1.90 (13 H, m, aliphatic CH); CIMS *m/e* (rel intensity) 201 (MH^+, 100), 156 (30), 144 (5), 127 (2); high-resolution MS, calcd for $C_{11}H_{24}N_2O$, *m/e* 200.1889; found, 200.1892.

2-Iminohexahydropyrimidine (29) Hydrochloride. β-Alacreatinine (**5**) hydrochloride (614 mg, 4.11 mmol) was reduced with $LiAlH_4$ (35.0 mmol) in 130 mL of THF. After 36 h, the reaction was worked up, and the filtrate was acidified (concentrated HCl) and evaporated to dryness. Crystallization from isopropyl alcohol/ether gave 156 mg (28%) of **29** hydrochloride, mp 153 °C (lit.[31a] mp 127–129 °C of a hydrated sample). Treatment of the metal salts by method B gave an additional 139 mg (25%), producing a total yield of 53%: NMR (D_2O) δ 3.37 (4 H, t, J = 6 Hz), 1.95 (2 H, quintet, J = 6 Hz); CIMS *m/e* 100 (MH^+ only); picrate, mp 183–184 °C (lit.[31b] mp 185–186 °C).

Reduction of Creatinine (6). A. With 5 equiv of Hydride per Mole of Acylguanidine. Creatinine (**6**) (496 mg, 4.38 mmol) was treated with $LiAlH_4$ (5.5 mmol, 25% molar excess) in 100 mL of THF for 30 h at 23 °C. Addition of *p*-toluenesulfonic acid hydrate (1.0 g, 6 mmol) and evaporation gave an oil, which was dried and shaken with 30 mL of ether to give 125 mg (29%) of mixed guanidine (**30**) and imidazole (**32**) salts: NMR (D_2O) δ 3.53 (4 H, s, guanidine CH_2CH_2), 2.83 (3 H, s, guanidine CH_3), 3.39 (3 H, s, imidazole CH_3), 6.74 (2 H, q, imidazole ring), 37 mol % **30** and 63 mol % **32** (by integration); CIMS ($NaOCH_3$ added) *m/e* (rel intensity) 100 (50), 98 (100).

PdO (100 mg) and PtO_2 (10 mg) were powdered together and then mixed with 50 mL of CH_3OH and the mixture of **30** and **32** tosylate salts. Shaking with hydrogen (40 psi, 20 °C) for 17 h followed by filtration, evaporation, and crystallization (ethanol/ether) gave 117 mg of (**30**) *p*-toluenesulfonate: mp 170–171 °C; NMR (D_2O) δ 7.56 (4 H, q, ar-H), 3.53 (4 H, s, CH_2CH_2), 2.83 (3 H, s, NCH_3), 2.34 (3 H, s, ar-CH_3); CIMS ($NaOCH_3$ added) *m/e* 100 (MH^+ only).

Anal. Calcd for $C_{11}H_{17}N_3O_3S$: C, 48.7; H, 6.3; N, 15.5. Found: C, 48.9; H, 6.1; N, 15.2.

B. With Excess Hydride. Creatinine (**6**) (1.00 g, 8.85 mmol) was reduced with $LiAlH_4$ (52.6 mmol) in 100 mL of THF for 28 h. After workup, the filtrate was acidified with 1 mL of acetic acid and stored at 0 °C. The precipitate from the workup was extracted by method A, and the resulting CH_2Cl_2 extract was combined with the THF filtrate for evaporation. Hydrogenation as above using 600 mg of PdO and 60 mg of PtO_2 gave 1.3 g (54%) of 2-imino-1-methylimidazolidine (**30**) *p*-toluenesulfonate, mp 170–171 °C, identical with the product from the previous reduction.

Reduction of Methylcreatinine (7). Methylcreatinine[10,11] (257 mg, 2.02 mmol) was reduced with $LiAlH_4$ (3.6 mmol) in 50 mL of THF for 10 h. After workup, the filtrate was acidified with concentrated HCl and evaporated to give a crude product with the following spectra: NMR (D_2O) δ 3.46 (4 H, s, uganidine CH_2CH_2), 2.87 (6 H, s, quanidine NCH_3), 6.75 (2 H, m, imidazole ring), 3.20 (6 H, s, imidazole NCH_3), 20 mol % 1,3-dimethyl-2-iminoimidazolidine (**31**) and 80 mol % 1,3-dimethyl-2-iminodihydroimidazole (**33**) (by integration); CIMS ($NaOCH_3$ added) *m/e* (rel intensity) 114 (15), 112 (100).

1,3-Dimethyl-2-iminoimidazolidine (31) *p*-Toluenesulfonate. Methylcreatinine (**7**) hydrogen sulfate[10] (704 mg, 3.13 mmol) was reduced with $LiAlH_4$ (22 mmol) in 90 mL of THF for 5 h. The product (**31**) was isolated in exactly the same manner as the monomethyl compound (**30**). Crystallization from isopropyl alcohol/ether gave 456 mg (51%) of *p*-toluenesulfonate: mp 180–181 °C; NMR (D_2O) δ 7.56 (4 H, q, ArH), 3.46 (4 H, s, NCH_2CH_2N), 2.87 (6 H, s, NCH_3), 2.34 (3 H, s, $ArCH_3$); CIMS ($NaOCH_3$ added) *m/e* 114 (MH^+ only).

Anal. Calcd for $C_{12}H_{19}N_3O_3S$: C, 50.5; H, 6.7; N, 14.7. Found: C, 50.6; H, 6.7; N, 14.7.

Registry No.—**1,** 5634-27-5; **2,** 63493-47-0; **3,** 63493-48-1; **4,** 63493-49-2; **5**·HCl, 15231-28-4; **7,** 34293-22-6; **7** sulfate, 63493-50-5; **9** HI, 63493-51-6; **9** acetate, 63493-52-7; **10,** 63493-53-8; **14,** 353-09-3; **15** acetate, 2439-10-3; **15** carbonate, 63493-54-9; **15** sulfate, 41197-06-2; **17** carbonate, 63493-55-0; **17** tosylate, 63493-56-1; **19,** 63493-57-2; **19** *p*-bromobenzenesulfonate, 63493-58-3; **19** carbonate, 63493-59-4; **19** acetyl derivative, 63493-60-7; **22,** 63493-60-7; **25,** 63493-61-8; **26,** 629-01-6; **27,** 1118-92-9; **29**·HCl, 26893-39-0; **30** tosylate, 63493-62-9; **31** tosylate, 63493-64-1; **33,** 59581-72-5; methyl laurate, 111-82-0; guanidine, 113-00-8; *N,N'*-dimethylguanidine hydrobromide, 13314-44-8; *N,N'*-dimethylguanidine, 3324-71-8; octanoyl chloride, 111-64-8; *N*-methyloctylamine piorate, 63493-65-2; formaldehyde, 50-00-0; dimethylamine, 124-40-3; *N,N,N',N'*-tetramethylguanidine, 80-70-6.

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(17) Melting points are uncorrected and were determined on a Thomas-Hoover apparatus; boiling points are uncorrected. IR spectra were obtained with a Perkin-Elmer 337 grating infrared spectrophotometer. UV spectra were recorded either with a Cary Model 14 or 15 spectrophotometer. NMR spectra were determined either with a Varian A-60A or T60 instrument using Me_4Si (δ 0) as an internal standard in nonaqueous media and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (δ 0) as an internal standard in D_2O. GC was performed on a Varian 2100 (FID) instrument with a 6 ft × 1/8 in. glass column packed with OV-225 (3% on Chromosorb W). Chemical ionization mass spectra (CIMS) were obtained with an AEI MS-902 instrument which had been modified for chemical ionization.[32] GC/MS (electron impact) were determined with an AEI MS-12 instrument. High-resolution mass spectra (ei) and microanalyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif. GC and CIMS work with nonvolatile guanidine salts was accomplished by adding a trace of $NaOCH_3$ just prior to analysis. Isobutane reactant was used for CIMS unless otherwise noted.

phase was decanted, the crystals were rinsed with hexane (30 mL), and the solid was dried to give 3.50 g (75%) of crude deliquescent solid, which was then azetropically dried with CH_2Cl_2 (100 mL), redissolved in 100 mL of CH_2Cl_2, and stored at 0 °C. Filtration, evaporation, and drying under vacuum over P_2O_5 gave 1.66 g (69%) of deliquescent partial hydrate: mp 99–107 °C; UV λ_{max} (0.01 N NaOH, C_2H_5OH) 209 nm (ϵ 14 000), λ_{max} (dioxane) 247 nm; NMR (CCl_4) δ 2.95 (6 H, s, $N(CH_3)_2$), 2.67 (3 H, s, NCH_3), 1.87 (3 H, s, $COCH_3$); CIMS *m/e* (rel intensity), 144 (MH^+, 100). 102 (1).

Anal. Calcd for $C_6H_{13}N_3O \cdot H_2O$: C, 48.8; H, 9.2; N, 28.5. Found: C, 48.5; H, 9.1; N, 28.5.

***N*-Octanoyl-*N',N',N'',N''*-tetramethylguanidine (4).** Octanoyl chloride (3.25 g, 20 mmol, freshly distilled, bp 194–196 °C) and *N,N,N',N'*-tetramethylguanidine (5.00 g, 43.5 mmol) were each dissolved in ethyl ether (50 mL each, anhydrous). To the guanidine solution, chilled in an ice bath, was slowly added the octanoyl chloride solution with stirring. A vigorous reaction ensued, precipitating the HCl salt of tetramethylguanidine (3.4 g, 22 mmol), which was removed by filtration, and the filtrate was evaporated. The oily residue was dissolved in 50 mL of CCl_4, washed twice with aqueous NaOH (20 mL each, pH 13), dried over K_2CO_3, filtered, and distilled to produce 4.30 g (89%) of colorless oil: bp 126–134 °C (0.05 mm, Kugelrohr): UV λ_{max} (0.01 N NaOH, C_2H_5OH) 239 nm (ϵ 14 700); NMR (CCl_4) δ 2.77 (12 H, s, NCH_3), 1.9–2.4 (2 H, m, $COCH_2$), 0.7–1.9 (13 H, m, aliphatic CH).

Anal. Calcd for $C_{13}H_{27}N_3O$: C, 64.7; H, 11.3; N, 17.4. Found: C, 64.6; H, 11.0; N, 17.6.

β-Alacreatinine [2-Amino-4-oxo-1,4,5,6-tetrahydropyrimidine (5)] Hydrochloride. β-Guanidinopropionic acid (**14**)[20] was cyclized with concentrated HCl as described,[21] producing 43% of **5**: mp 272–275 °C (lit.[21] mp 268–271 °C); UV λ_{max} (0.01 N NaOH, C_2H_5OH) 237 nm (ϵ 13 000) [lit.[6] UV 237 mm (13 100)]; NMR (D_2O) δ 3.80 (2 H, t, J = 7 Hz), 2.83 (2 H, t, J = 7 Hz).

Methylcreatinine [1,3-Dimethyl-2-imino-4-imidazolidinone (7)] Hydrogen Sulfate. Creatinine [2-amino-1-methyl-4-oxo-4,5-dihydroimidazole (**6**)] was methylated with dimethyl sulfate as described[10] to produce 89% of the hydrogen sulfate (**7**):[11] mp 118 °C (lit.[10] mp 118 °C); CIMS *m/e* 128 (MH^+), parent ion only.

General Procedure for Reduction of Acylguanidines. A 2.35 M homogeneous solution of $LiAlH_4$ in THF was prepared and assayed by the method described.[22] THF was distilled from $LiAlH_4$ under N_2 directly into a graduated cylinder with an outer ground glass top. This cylinder also had a side arm near the top fitted with a rubber septum for N_2 purging. After distillation, the ground joint was sealed with a second septum, and subsequent solvent transfers were made via a stainless steel cannula and positive N_2 pressure. THF thus prepared could be stored several weeks by sealing the punctured septa with unpunctured inverted septa. For reduction, starting material and a magnetic stir bar were added to a three-neck flask under N_2, the flask was fitted with a thermometer and a rubber septum, and dry THF was added by cannula. The system was cooled to −65 °C, the $LiAlH_4$ solution was added by syringe with stirring, and the temperature was maintained at −60 °C for 20 min, then at 0 °C for 30 min, and finally at 23 °C for the appropriate reaction time. Isolation of products proceeded by chilling, followed by addition of H_2O and aqueous NaOH as described.[23] After filtering off the metal salts small amounts of H_2O and CO_2(s) were added to the THF filtrate to protect the products as carbonate salts.

Isolation of Guanidines. Method A.[24] In a typical reduction of **6** (1.00 g, 8.85 mmol), all of the metal salts from the hydrolyzed reduction mixture were dissolved immediately in cold H_2O (12 mL, pH to 14)[25] contained in a glass-stoppered 100-mL flask, and aqueous NaOH (15 mL, 2 N, 0 °C) and benzyloxycarbonyl chloride (4 mL, 24 mmol, 0 °C) were added alternately in five portions over a period of 25 min with shaking and chilling after each addition of acid chloride. The mixture was then treated with CH_2Cl_2 (30 mL, 0 °C) and aqueous glycine (3.0 g in 20 mL, pH to 14, 0 °C), and the resulting two-phase system was stirred for 30 min at 0 °C, whereupon a second portion of CH_2Cl_2 (50 mL) was added. The organic phase was separated, the aqueous layer was extracted a second time (40 mL of CH_2Cl_2), and the combined extracts were washed with H_2O to pH 7. After drying with K_2CO_3, the CH_2Cl_2 extracts were combined with the THF filtrate from the reduction for subsequent evaporation and hydrogenolysis[26] (see reduction of **6** with excess hydride).

Method B.[24] In a typical reduction of **5** to **29**, a portion of the metal salts from the hydrolyzed reduction mixture (containing a maximum of 1.17 mmol of **29**) was dissolved in HCl (24 mL, 4 M). After chilling and neutralizing with 12 M NaOH to pH 7, the $Al(OH)_3$ was removed by centrifugation at 7700*g* (0 °C, 15 min). The supernatant was decanted, the $Al(OH)_3$ pellet was washed with 30 mL of H_2O, the $Al(OH)_3$ was spun down a second time, and the combined H_2O solutions were concentrated to 25–30 mL. Addition of 100 mL of isopropyl alcohol produced precipitation (mostly NaCl), and this mixture was heated to boiling followed by filtration and evaporation of the filtrate to dryness. The resulting solid residue was again suspended in 100 mL of hot isopropyl alcohol; filtration and evaporation to dryness gave 370 mg of a mixture of LiCl and **29**·HCl. A cation-exchange column was then prepared (12-mL bed, BioRad AG 50W-8X, hydrogen form, 200–400 mesh) and washed with HCl (500 mL, 1 M) and H_2O. The mixture of LiCl and **29**·HCl was washed onto the column with H_2O, washing until the eluent returns to the pH of distilled H_2O. Lithium was eluted first with HCl (~100 mL, 0.3 M); the guanidine was also eluted with HCl (~200 mL, increasing strength from 1 to 10 M). Evaporation to dryness, crystallization (isopropyl alcohol/ether), and drying over P_2O_5 produced 55 mg of **29**·HCl, mp 153 °C.

Dodecylguanidine (15) Acetate. Dodecanoylguanidine (**1**) (1.0 g, 4.15 mmol) was reduced with $LiAlH_4$ (53 mmol) in 120 mL of THF for 33 h. After decomposition (H_2O, NaOH) and filtration, the THF solution was acidified with 1 mL of acetic acid and chilled. Filtration produced 330 mg (60%) of acetate salt: mp 133–134 °C; CIMS *m/e* (rel intensity) 228 (MH^-, 100), 211 (5), 186 (1).

Anal. Calcd for $C_{15}H_{33}N_3O_2$: C, 62.7; H, 11.6; N, 14.6. Found: C, 62.9; H, 11.3; N, 14.8.

The filtrate (THF solution) was evaporated to an oil and the residue was suspended in hexane and filtered to yield 70 mg (15%) of crude salt. This material was primarily dodecylamine acetate: GC retention time (96 °C), 11 min 50 s (identical with authentic sample); CIMS *m/e* (rel intensity), 242 (8), 228 (4), 200 (2), 186 (100).

Dodecylguanidine (15) Sulfate. In a separate reduction of **1**, the guanidine product **15** was isolated as a carbonate salt: mp 91–95 °C dec; CIMS *m/e* (rel intensity) 228 (MH^+, 100), 211 (4), 186 (1). The carbonate salt was treated with 1 equiv of H_2SO_4 to give the sulfate: mp 250–260 °C dec, mmp with authentic **15** sulfate[27] was undepressed; IR (KBr) 3480, 3160, 2920, 2880, 1630, 1470, 1380, 1120, 1060, 980, 720, 620 cm^{-1}, identical with IR obtained from authentic sample.

Reduction of Dodecylguanidine (15) Sulfate. 15 sulfate (500 mg, 1.81 mmol) was treated with $LiAlH_4$ (26 mmol) in THF (50 mL) for 21 h. Isolation gave dodecylamine in 15% yield.

***N,N'*-Dimethyl-*N''*-dodecylguanidine (17) Tosylate.** *N*-Dodecanoyl-*N',N''*-dimethylguanidine (**2**) (1.00 g, 3.71 mmol) was reduced with $LiAlH_4$ (24 mmol) in 100 mL of THF for 8 h. After workup, the THF filtrate was treated with H_2O (0.5 mL, 28 mmol) and CO_2 (s, ~1 g). Chilling (0 °C, 12 h) produced a crude carbonate, mp 96–110 °C dec. This material was converted to 985 mg (62%) of tosylate: mp 85–87 °C; NMR (HBr salt in $CDCl_3$) δ 3.4 (2 H, m, NCH_2), 3.0 (6 H, s, $2NCH_3$), 0.7–1.8 (23 H, m); CIMS *m/e* (rel intensity) 256 (MH^+, 100), 225 (8), 186 (2), 71 (3), 32 (10).

Anal. Calcd for $C_{22}H_{41}N_3O_3S$: C, 61.8; H, 9.7; N, 9.8. Found: C, 62.1; H, 9.5; N, 9.9.

***N*-Ethyl-*N',N',N''*-trimethylguanidine (19) *p*-Bromobenzenesulfonate.** *N*-Acetyl-*N',N',N''*-trimethylguanidine (**3**) (593 mg, 4.02 mmol, ¼ hydrate) was reduced with $LiAlH_4$ (13.2 mmol) in 30 mL of THF for 4 h. After workup, a carbonate, prepared by the method used for compound **17**, was isolated and melted at 73–75 °C dec. The carbonate was treated with *p*-bromobenzene sulfonic acid to give 870 mg (59%) of salt: mp 97–98 °C from ethanol/ether; NMR (D_2O) δ 7.73 (4 H, q, ArH), 3.28 (2 H, q, NCH_2CH_3, J = 7 Hz), 2.96 [6 H, s, $N(CH_3)_2$], 2.90 (3 H, s, NCH_3), 1.20 (3 H, t, NCH_2CH_3, J = 7 Hz); CIMS (NaOH added) *m/e* (rel intensity) 130 (MH^+, 100), 99 (3), 85 (12).

Anal. Calcd for $C_{12}H_{20}BrN_3O_3S$: C, 39.4; H, 5.5; N, 11.5; Br, 21.8. Found: C, 39.4; H, 5.5; N, 11.5; Br, 21.9.

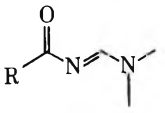
A sample of pure **19** *p*-bromobenzenesulfonate was converted to the free base (ion exchange)[5] and then to the carbonate: CIMS (CH_4 reactant) *m/e* (rel intensity) 130 (MH^+, 100), 99 (9), 85 (16), 46 (6), 32 (1).

Acetylation of *N*-Ethyl-*N',N',N''*-trimethylguanidine (19). Purified **19** carbonate (200 mg, ~1.2 mmol) was mixed with 30 mL of acetic anhydride and heated for 6 h (100 °C, N_2). Evaporation and distillation of the resulting oil (45 °, 0.05 mm, Kugelrohr) gave product with the following spectra: UV λ_{max} (0.01 N NaOH, C_2H_5OH) 225 nm (ϵ 8000); NMR (CCl_4) δ 3.05 (2 H, q, NCH_2CH_3, J = 7 Hz), 2.86 (3 H, s, NCH_3), 2.82 [6 H, s, $N(CH_3)_2$], 1.83 (3 H, s, $COCH_3$), 1.09 (3 H, t, NCH_2CH_3, J = 7 Hz).

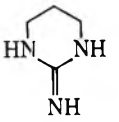
Reduction of Octanoyl-*N,N'*-tetramethylguanidine (4) with excess $LiAlH_4$. **4** (2.4 g, 10 mmol) was reduced with $LiAlH_4$ (26.3 mmol) for 1 h using 50 mL of Et_2O instead of THF. After workup, the Et_2O filtrate was evaporated to give *N*-methyloctylamine, which was converted to 2.25 g (60%) of *N*-methyloctylamine picrate: mp 96–98

methylamide ion attacks either 4 or 28 to produce 27. The primary amide 26 probably arises from 25, undergoing a reverse Mannich during the isolation.

Reduction of the three cyclic substrates, 5, 6, and 7, to the corresponding guanidines, 29, 30, and 31, was complicated by



28



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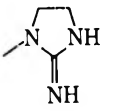
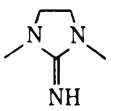


30



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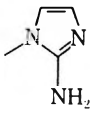
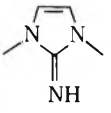
occlusion of nearly half of the product in the metal salts formed during isolation. To overcome this problem, two general methods were developed which allow separation of the highly water soluble guanidines from metal salts. The physical purification method (method B) relies on precipitation of Al^{3+} and Na^+ ions, followed by removal of Li^+ via ion-exchange chromatography. Method B, when applied to the isolation of 29, increased the yield to 53% from 28% obtained using conventional methods.

The derivatization method (method A) employs a digestion of the mixed salts in aqueous alkali, followed by acylation with excess benzyloxycarbonyl chloride. Excess acid chloride is then destroyed by adding glycine before extraction of the guanidine derivative with CH_2Cl_2. The extract is then combined with the filtrate from the reduction and the combined material is subjected to hydrogenolysis. This isolation scheme greatly increased yields of both 30 and 31. The reason for including the filtrate in the hydrogenation is that reduction of 6 with $LiAlH_4$ produces a mixture of the guanidine 30 and the imidazole 32. Similarly, 7 produces both 31 and 33. After



32



33

finding that 32 could be converted to 30 by catalytic hydrogenation, it became obvious that the hydrogenation step served a dual purpose, i.e., removal of the benzyloxycarbonyl group and the reduction of the 2-aminoimidazoles to 2-iminoimidazolidines.

Summary

A critical point to consider in the $LiAlH_4$ reduction of acylguanidines is the electron density on the metalated acylguanidine in the reduction medium. This electron density depends primarily on the number of NH protons which are replaced by Al (with hydrogen evolution) and will have an effect on both the rate and the stoichiometry. Quantitation of the hydrogen evolved in the reaction of $LiAlH_4$ with both 1 and 6 clearly indicated that all available NH protons are removed under reduction conditions. The hydrogen evolution is somewhat slower with 5, but this is probably due to formation of a precipitate, presumably a polyaluminate.

Two factors emerge, then, which suggest an approximate reaction time. Compounds 1, 5, and 6 are reduced at relatively slow rates; 1 is slow because it has a formal −4 charge, and 6 and 7 are slow because they both give precipitates. Reduction of 4 is very fast (homogeneous and no NH protons) and the reductions of 2, 3, and 7 are moderately rapid (homogeneous with one or two NH protons). In addition to the proper reaction time, the use of THF, room temperature, excess $LiAlH_4$, and extraction of the metal salts during isolation all favor increased yields.

Classically, conversion of a carboxyl group to an alkylguanidine requires preparation of an amide, reduction to an amine, and reaction with a reagent such as *S*-methylisothiourea.[7] The same conversion may now be accomplished more directly by preparing and reducing the appropriate acylguanidine. From another point of view, the sequence of acylation and reduction allows the selective alkylation of an already existing guanidine, a manipulation with no previous parallel.

Experimental Section[17]

Dodecanoylguanidine (1). Methyl laurate (26.0 g, 122 mmol)[18] and ethanol (50 mL, absolute) were mixed with guanidine free base (7.3 g, 124 mmol, freshly prepared by ion exchange)[5] and allowed to stand (23 °C, under dry N_2) for 12.5 h. Evaporation of the ethanol, addition of ether (30 mL, anhydrous) and chilling gave a cake of crystals to which was added hexane (150 mL, reagent), and the flask was stoppered and shaken vigorously. The mixture was then chilled, filtered, and dried to give 20.0 g (68%) of crude product, mp 101–104 °C (lit.[4] mp 80–82 °C). This crude material was crystallized from acetone to produce 14.1 g (48%) of colorless crystals: mp 110–111 °C; UV λ_{max} (0.01 N NaOH, C_2H_5OH) 232 nm (ϵ 16 000), λ_{max} (dioxane) 237 nm; NMR ($CDCl_3$) δ 6.10 (4 H, s, NH), 2.0–2.4 (2 H, m, $COCH_2$), 0.7–1.9 (21 H, m, aliphatic CH); CIMS *m/e* (relative intensity) 242 (MH^+, 100), 200 (56), 83 (2), 60 (4).

Anal. Calcd for $C_{13}H_{27}N_3O$: C, 64.7; H, 11.3; N, 17.4. Found: C, 64.7; H, 10.9; N, 17.3.

***N*-Dodecanoyl-*N'*,*N''*-dimethylguanidine (2).** *N*,*N'*-Dimethylguanidine hydrobromide[19] (6.45 g, 38.4 mmol) was converted to the free base by ion exchange[5] under N_2 before adding methyl laurate (10.5 mL, 42.7 mmol). The reaction mixture was left at room temperature for 26 h, at which time UV and TLC showed that it was predominantly acylguanidine. A column of neutral alumina (300 g, activity IV, 100–200 mesh, BioRad) was prepared in hexane, and the reaction mixture was washed onto it with five 10-mL portions of hexane. Separation of three components was monitored by TLC (silica gel, acetone). The first component (ester) eluted from the column with 500 mL of 3:1 hexane/benzene, an intermediate fraction of 300 mL of acetone followed, and the third fraction (375 mL of acetone) removed all of the product. Evaporation of this third fraction gave 6.5 g of oil which was dried under vacuum over P_2O_5, yielding 5.2 g (50%) of slowly deliquescing crystals: mp 38 °C; UV λ_{max} (0.01 N NaOH, C_2H_5OH) 237 nm (ϵ 15 300), λ_{max} (dioxane) 242 nm; NMR (CCl_4) δ 2.84 (6 H, s, NCH_3), 2.0–2.3 (2 H, m, $COCH_2$), 0.7–1.8 (21 H, m, aliphatic CH).

Anal. Calcd for $C_{15}H_{31}N_3O$: C, 66.9; H, 11.6; N, 15.6. Found: C, 66.8; H, 11.5; N, 15.3.

***N*,*N*,*N'*-Trimethylguanidine (9) Acetate.** A quaternary ammonium cation-exchange resin (36 mL, 44 mequiv OH^- form, 20–50 mesh, BioRad) was converted to the acetate form by soaking with two portions of aqueous acetic acid (60 mL, 1 N). A column was then prepared and washed with 100 mL of H_2O. *N*,*N*,*N'*-Trimethylguanidine (9) hydriodide[7,8] (5.00 g, 21.8 mmol) was dissolved in 10 mL of H_2O and applied to the column. Elution with 150 mL of H_2O followed by evaporation gave 4.64 g of hygroscopic oil, which on drying at 23 °C (0.05 mm) for 12 h gave 3.48 g (99%) of deliquescent crystals, used without purification for the next step.

***N*,*N'*-Diacetyl-*N*,*N''*,*N''*-Trimethylguanidine (10).** *N*,*N*,*N'*-Trimethylguanidine (9) acetate (1.98 g, 12.3 mmol) was stirred with acetic anhydride (50 mL) under N_2 at 100 °C for 40 min. Excess acetic anhydride was then evaporated, finally at 60 °C (1 mm) for 30 min to remove the last traces of anhydride, producing 2.26 g of crude oil. This material was distilled through a short Vigreux column to give 2.13 g (95%) of colorless oil: bp 120–125 °C (0.025 mm); UV λ_{max} (C_2H_5OH) 205 nm (ϵ 5750), 257 (14 400); NMR (CCl_4) δ 3.01 (6 H, s, $N(CH_3)_2$), 2.91 (3 H, s, NCH_3), 2.04 (3 H, s, $COCH_3$), 1.99 (3H, s, $COCH_3$).

Anal. Calcd for $C_8H_{15}N_3O_2$: C, 51.9; H, 8.2; N, 22.7. Found: C, 51.7; H, 8.0; N, 22.5.

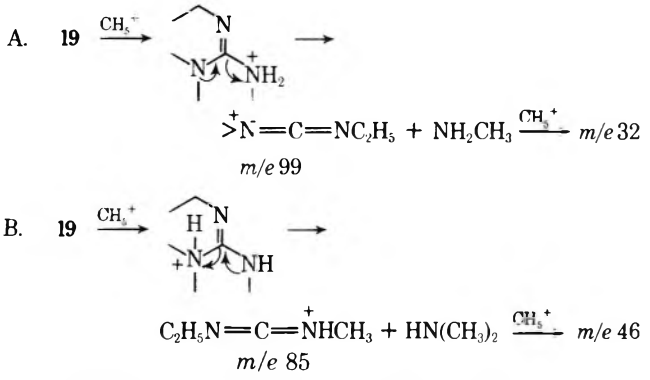
***N*-Acetyl-*N'*,*N'*,*N''*-trimethylguanidine (3).** *N*,*N'*-Diacetyl-*N*,*N''*,*N''*-trimethylguanidine (10) (6.00 g, 32.4 mmol) was mixed with 50 mL of methanol and quaternary ammonium ion-exchange resin (60 mL, 84 mequiv, BioRad AG1-X8 hydroxide form, 20–50 mesh, washed with 4 × 100 mL of methanol) and allowed to stand at room temperature. After 20 h, the reaction was diluted with 500 mL of methanol and stirred for 10 min, the methanol was decanted, the resin was washed again with 150 mL of methanol, and the combined methanol extracts were evaporated. The resulting oil was azeotropically dried (evaporate 100 mL of CCl_4; 100 mL of 1:1 benzene/CH_2Cl_2) and mixed with benzene (7.0 mL) and CH_2Cl_2 (1.0 mL). After chilling (0 °C, 3 days), layering with petroleum ether (20 mL), and chilling again (0 °C, 4 days), the monoacetic product crystallized. The liquid

Table I. Spectral (UV and NMR) Characterization of Acetyltetraalkylguanidines

Compd	UV absorption, λ_{max} (ϵ) in ethanol (OH^-)	NMR absorption δ, in CCl_4
N-Acetyl-*N'*-ethyl-*N,N''*-trimethylguanidine (**22**)	225 nm (8000)	1.09 (t, CH_2CH_3) 3.05 (q, CH_2CH_3) 1.83 (s, $CH_3C{=}O$) 2.82 (s, $2NCH_3$) 2.86 (s, $AcNCH_3$)
N'-Acetyl-*N,N,N'',N''*-tetramethylguanidine[c]	238 nm (15 100)	1.90 (s, $CH_3C{=}O$) 2.80 (s, $4NCH_3$)
N-Acetyl-*N,N',N'',N''*-tetramethylguanidine[a]	225 nm (8950)	1.85 (s, $CH_3C{=}O$) 2.80 (s, $3NCH_3$) 2.85 (s, $AcNCH_3$)

[a] Data from ref 6.

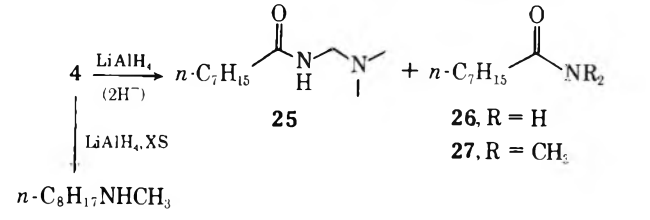
Scheme I. CIMS Fragmentation of *N*-Ethyl-*N',N',N''*-trimethylguanidine (19)



C. Similarly, **20** → *m/e* 85 and 46; 71 and 60

the presence of **19** and the absence of **20**. By establishing the structure of **19**, we have also established the structure of **3**.

In anticipation of a rapid reduction, octanoyl-*N,N'*-tetramethylguanidine (**4**) was treated with excess $LiAlH_4$ for 1 h in ether to produce *N*-methyloctylamine (**24**) in 60% yield. A stoichiometric reduction ($2H^-$, 0.5 mol of $LiAlH_4$/mol of acylguanidine) was then carried out with the hope of arresting the reduction of **4** at the guanidine stage. Instead of a guanidine, the reaction product consisted of a mixture of compounds **25, 26,** and **27**. A third reduction was performed using less $LiAlH_4$ ($1.3H^-$, 0.33 mol of $LiAlH_4$/mol of acylguanidine) in the hope of isolating an acylamidine. Instead, the same three products were obtained as in the previous reduction; only the relative yields had changed (see Table II).



Although the production of **25, 26,** and **27** in the second and third reductions was unexpected, the data substantiating these results is clear. Initially, the CIMS indicated only the presence of **25, 26,** and **27** plus two other ions, *m/e* 156 and 127, which turned out to be fragments of **25**.

NMR data supplied the first clues to the structure of **25**, notably, the coupling of the NH proton to the NCH_2N methylene, which was erased by exchanging the NH proton for deuterium. Two examples of acylaminals such as **25** have been reported,[14,5] both of which were prepared by condensation of formaldehyde, a primary amide, and a secondary amine. Using this approach, an authentic sample of **25** was prepared for comparison with the reduction product, thus establishing its structure.

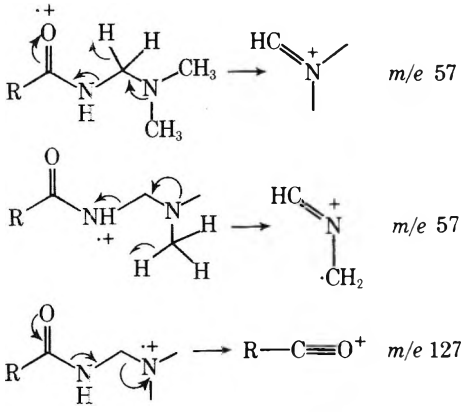
Table II. Distribution of Products from the Reduction of *N*-Octanoyl-*N',N',N'',N''*-tetramethylguanidine (4) with Varying Amounts of Lithium Aluminum Hydride

Product	Amount of lithium aluminum hydride: Excess	2 equiv[a]	1.3 equiv[b]
24[c]	60%		
25[d]		58%	9%
26[d]		10%	11%
27[d]		18%	69%

[a] $2H^-$ or 0.5 mol of $LiAlH_4$/mol of **4**. [b] $1.3H^-$ or 0.33 mol of $LiAlH_4$/mol of **4**. [c] Isolated yield. [d] Yields from GC and NMR integration; tertiary mixture was distilled, but components were not separated.

Since the reduction products from the limited $LiAlH_4$ reductions of **4** could be distilled without any change in the NMR or CIMS, the mixtures were analyzed by GC/MS and high-resolution mass spectrometry (both with electron impact sources). The first and second GC peaks eluted had parent ions of *m/e* 171 and 143, respectively, as well as all the fragments predicted by structures **26** and **27**, including McLafferty rearrangements (giving the base peaks) and α cleavage.[16] The third GC peak gave a weak parent (*m/e* 200) and the two other ions, *m/e* 127 and 57 (base), which can be explained by the following fragmentations (Scheme II). Authentic **25** and

Scheme II



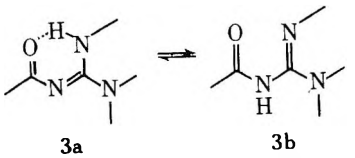
26 gave GC/MS retention times and fragmentation patterns which correspond to the second and third GC/MS peaks from the reduction mixtures. Finally, all the molecular formulas for the three parent ions and their electron impact MS fragments were obtained from a computerized high-resolution scan over the entire mass range of a reduction mixture (see Experimental Section).

Although the reduction of **4** to **24** and **25** can be easily explained, the formation of **26** and **27** is more difficult to rationalize. The formation of **24** and **25** probably arises from conjugate addition, followed by elimination of metalated dimethylamide ion, to give the intermediate acylamidine **28**. This species is probably extremely labile to reduction, since as little as 1.3 equiv of hydride/mol of **4** failed to show any evidence of **28**. In the presence of excess $LiAlH_4$, **28** can undergo conjugate addition of hydride, elimination of dimethylamide ion, further conjugate addition to the *N*-methylamide, and finally, reduction to amine **24**. With 2 equiv of H^-, this process stops at the acylaminal (**25**) stage, and with 1.3 equiv of H^- the reduction rate is slow enough that di-

Peracetylation of the trimethylguanidine by heating with acetic anhydride gave the diacetylguanidine **10** in excellent yield. Initial attempts to convert **10** to the monoacetylguanidine **3** were based on a procedure for converting diacetylguanidine to monoacetylguanidine via ethanolysis.[9] With **10**, however, solvolysis required reflux for 3 days and a complex mixture of products was obtained.

In a second approach to the monodeacetylation of **10** to **3**, we employed a quaternary ammonium hydroxide resin for both practical and theoretical reasons. The practical advantage of the resin over metal hydroxides arises from the relative ease of product isolation. Alkaline cleavage was chosen over acid, since hydroxide attack on **10** should give **3** rather than **11**, as the unconjugated tetrahedral intermediate **12** is of higher energy than **13**. Furthermore, **13** proceeds to a resonance stabilized anion which **12** does not.

Having thus rationalized that hydrolysis of diacetylguanidine **10** should result in the acyliminoguanidine **3** rather than the acylaminoguanidine **11**, we were surprised to find that the product from hydroxide cleavage of **10** showed λ_{max} 209 nm, consistent with an acylaminoguanidine,[6] i.e., structure **11**. This discrepancy between the predicted and observed UV absorption was resolved, however, when it was found that **3** gave a bathochromic shift of 35 nm (to λ_{max} 247 nm) by changing the solvent from ethanol to dioxane. Similar solvent changes with **1** and **2** gave bathochromic shifts of only 5 nm, implying that **3** exhibits unusual properties and may even exist as the more polar deconjugated tautomer **3b** in protic solvents.



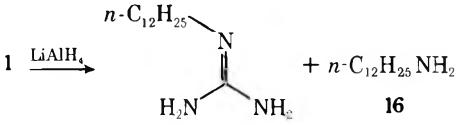
3a **3b**

Changing to an aprotic solvent would then favor the intramolecularly hydrogen-bonded tautomer **3a**. Experiments on the reduction product of **3** (discussed later) further substantiate our structure assignment.

β-Alacreatinine (**5**) hydrochloride was obtained from β-guanidinopropionic acid (**14**) which, in turn, was prepared from β-alanine and, finally, methylcreatinine [1,3-dimethyl-2-imino-4-imidazolidinone, (**7**)] was obtained by methylation of creatinine (**6**) with dimethyl sulfate.[10] This methylation of **6** gives a good yield, and the incorrect structure (CH_3 on exo nitrogen) assigned to methylcreatinine in ref 10 was subsequently corrected to structure **7**.[11]

Reductions. Since the reduction of each substrate had some unique features, we will consider them separately before discussing the more general aspects of the reaction. One common problem, however, was the tendency of the alkylguanidine products to be overreduced and form amines. Good yields required controlled reaction times, and these varied individually from 4 to 36 h.

The first substrate, dodecanoylguanidine (**1**), chosen for its solubility in THF, was reduced smoothly to dodecylguanidine (**15**), accompanied by dodecylamine (**16**). Reaction monitoring

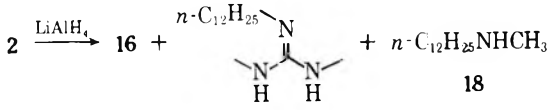


15 **16**

by GC on OV-225 was sufficient to set an approximate reaction time which was then verified by three reductions; 33 ± 5 h represents the optimum time under the conditions reported. An attempt at shortening this reaction time by heating to reflux in THF produced a drastic increase in amine formation; therefore, all subsequent reductions were conducted at 23 °C. Attempts to minimize the formation of amine by using only a slight excess of $LiAlH_4$ and longer reaction times led to lower yields. Although the acetate salt is the most convenient form for isolation, the sulfate was superior for characterization.

To determine whether amine **16** was formed by reduction of guanidine **15** or by conjugate addition of H^- to **1**, **15** was treated with $LiAlH_4$. The amount of amine **16** formation (15% by GC) in this reduction suggested that all or most of the amine **16** formed in the reduction of **1** comes from subsequent reduction of **15**; the best yield of **15**, 60%, was accompanied by 15% of **16**.

Reduction of *N*-dodecanoyl-*N'*,*N''*-dimethylguanidine (**2**) to the trialkylguanidine **17** also proceeded in good yield and could be monitored by TLC with good resolution of **2**, dodecylamine (**16**), and *N*-dodecyl-*N'*,*N''*-dimethylguanidine (**17**). The ratio of **16** to **18** (about 2:1) would be expected from a

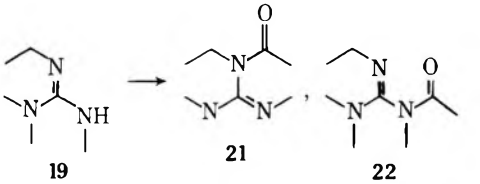


17 **18**

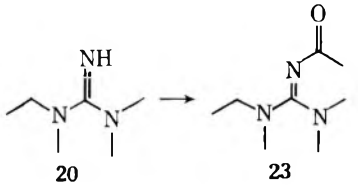
purely random breakup of the intermediate aluminum complex followed by reduction of the resulting metalated amidine. Although **17**·HI has been reported,[12] we found **17** was more conveniently characterized as its tosylate.

N-Acetyl-*N'*,*N'*,*N''*-trimethylguanidine (**3**) was reduced rapidly to *N*-ethyl-*N'*,*N'*,*N''*-trimethylguanidine (**19**). Since we sought further evidence for the structure of **3**, two experiments were undertaken to confirm the structure of **19**. The first was derivatization of **19**; the second was a CIMS fragmentation study.

The competing structure for the monodeacetylation product of **10** would be **11**, in which the remaining acetyl group is on a methylated nitrogen, rather than **3**, in which the acetylated nitrogen bears no methyl. If **10** cleaves to **3** and is reduced to **19**, then acetylation should give **21** and/or **22**, both



19 **21** **22**



20 **23**

of which are tetraalkylacylaminoguanidines (nonconjugated). If **10** cleaves to **11**, which is then reduced to **20**, acetylation of **20** would give a tetraalkylacyliminoguanidine **23** (conjugated). It was found that acetylation of **19** gave a compound whose NMR and UV are consistent only with structure **22** (Table I), a nonconjugated derivative. Molecular models of **21** and **22** show extreme crowding in the coplanar conformation. Structure **22** appears slightly less crowded and is probably formed preferentially for steric reasons.

As further evidence, the assigned structure of **19** was supported by its fragmentation in the CIMS. To maximize the fragmentation, CH_4 reagent gas was used, since this gives the high-energy protonating species, CH_5^+.[13] The possible fragmentation patterns for **19** and **20** are shown in Scheme I. The fragments *m/e* 85 and 46 are predicted for both **19** and **20**, and both were observed. In addition, both *m/e* 99 and 32 were observed and *m/e* 71 and 60 were not, clearly demonstrating

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Reduction of Acylguanidines to Alklyguanidines with Lithium Aluminum Hydride

Jay F. Stearns and Henry Rapoport*

Department of Pharmaceutical Chemistry, University of California, San Francisco, California and Department of Chemistry, University of California, Berkeley, California 94720

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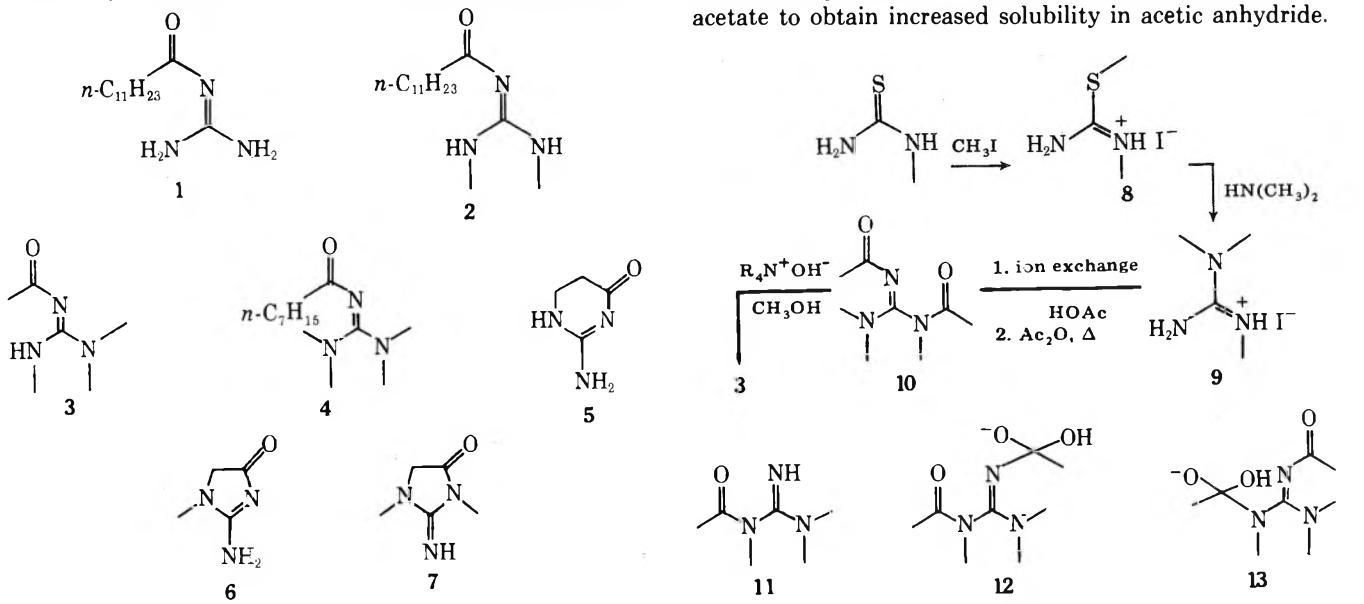
Six acylguanidines bearing different alkylation patterns, namely dodecanoylguanidine (**1**), *N*-dodecanoyl-*N'*,*N''*-dimethylguanidine (**2**), *N*-acetyl-*N'*,*N'*,*N''*-trimethylguanidine (**3**), β-alacreatinine (**5**), creatinine (**6**), and methylcreatinine (**7**), have been reduced to the corresponding alkylguanidines with lithium aluminum hydride in yields ranging from 51 to 62%. A seventh reduction substrate, *N*-octanoyl-*N'*,*N'*,*N''*,*N''*-tetramethylguanidine (**4**), gave only nonguanidine reduction products resulting from cleavage of the guanidine moiety, including *N*-(dimethylaminomethyl)octanamide (**25**). Syntheses of the various substrates are described and reaction mechanisms and general synthetic utility are discussed.

Although a literature search revealed no examples of reduction of an acylguanidine with lithium aluminum hydride ($LiAlH_4$), a statement[1] that the guanidine group is inert to $LiAlH_4$ suggested to us that the reduction of an acylguanidine to an alkylguanidine might be possible. The utility of such a conversion is illustrated by the occurrence of the alkylguanidine moiety in a wide variety of biological systems and the presence of the guanidine group in antihypertensive drugs such as clonidine[2] and guanethidine.[3]

Results and Discussion

Preparation of Reduction Substrates. The acylguanidines **1–7**, selected because they represent a broad range of substitution patterns, were in most cases easily prepared. Compounds **1**[4] and **2** were prepared by acylating the appropriate guanidine free base with methyl dodecanoate following the general procedure for acylating guanidines with esters.[5] To acylate the *sym*-tetramethylguanidine and prepare substrate **4**, the acid chloride was required. Compounds **1**, **2**, and **4** displayed the spectral properties expected for such acylguanidines.[6]

Considerable difficulty was encountered in the preparation of *N*-acetyl-*N'*,*N'*,*N''*-trimethylguanidine (**3**), the major problem being the selective conversion of **10** to **3**. The preparation of **9** proceeded according to conventional methods,[7,8] and then **9** hydriodide was converted by ion exchange to the acetate to obtain increased solubility in acetic anhydride.



p-methoxybenzaldehyde, 11 g of sodium hydroxide, 100 mL of water, and 80 mL of ethanol was stirred for 20 h at room temperature. After the addition of 200 mL of water, the reaction mixture was extracted with ether. The ethereal extract was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent and unreacted *p*-methoxybenzaldehyde gave 19 g of compound **3** as a yellow oil, which was used in the following reaction without purification. A part of the product was purified by preparative thin-layer chromatography on silica gel (ether–benzene, 1:2) for the spectral data and microanalysis: UV (MeOH) 323 nm; IR ($CHCl_3$) 1633 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.63–1.53 (4 H, m, cyclopropyl protons), 1.43 (3 H, s, CH_3), 3.81 (3 H, s, CH_3O), 6.70 (1 H, d, J = 14 Hz, –CH=CH–), 7.64 (1 H, d, J = 14 Hz, –CH=CH–), 6.90 (2 H, d, J = 8 Hz, aromatic β protons), 7.45 (2 H, d, J = 8 Hz, aromatic α protons); MS *m/e* 216 (M^+).

Anal. Calcd for $C_{14}H_{16}O_2 \cdot 0.25H_2O$: C, 76.25; H, 7.54. Found: C, 76.10; H, 7.39.

3-(4-Methoxyphenyl)-1-methylcyclopropylpropanone (4). A suspension of 18 g of compound **3** and 10 g of Raney nickel (W_2) in 400 mL of ethanol was shaken under a current of hydrogen for 24 h. After removal of the catalyst, the ethanol was evaporated off to give a pale yellow oil, which was distilled to afford 18 g (81.35% yield based on compound **2**) of compound **4** as a colorless oil: bp 115 °C (0.4 mmHg); IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.48–1.23 (4 H, m, cyclopropyl protons), 1.29 (3 H, s, CH_3), 2.41–3.08 (4 H, m, –CO–CH_2CH_2Ar), 3.72 (3 H, s, CH_3O), 6.76 (2 H, d, J = 9 Hz, aromatic β protons), 7.60 (2 H, d, J = 9 Hz, aromatic α protons); MS *m/e* 218 (M^+).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.70; H, 8.36.

2-Bromo-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (5). To a solution of 5 g of compound **4** in 200 mL of ether was added in small portions 7.5 g of pyridinium hydrobromide perbromide under ice cooling and the resulting mixture was stirred for 4 h at the same temperature. After filtration, the filtrate was washed with saturated aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 7.5 g of bromide **5** as a yellow oil, which was used in the following reaction without further purification because of its instability. A part of this product was purified by preparative thin-layer chromatography on silica gel ($CHCl_3$) for spectral data and microanalysis: IR ($CHCl_3$) 1685 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.6–1.3 (4 H, m, cyclopropyl protons), 1.35 (3 H, s, CH_3), 2.8–3.7 (2 H, m, $ArCH_2$–), 3.76 (3 H, s, CH_3O), 4.47 (1 H, q, J = 6 and 9 Hz, –CHBr–), 6.8 (2 H, d, J = 8 Hz, aromatic β protons), 7.1 (2 H, d, J = 8 Hz, aromatic α protons); MS *m/e* 296 (M^+), 298 (M^+ +2).

Anal. Calcd for $C_{14}H_{17}O_2Br$: C, 56.58; H, 5.77. Found: C, 56.45; H, 5.87.

2-Benzylamino-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone)6). A solution of 7.5 g of bromide **5** and 11.3 g of benzylamine in 200 mL of methanol was refluxed for 5.5 h. After removal of methanol, the residue was dissolved in 100 mL of 10% hydrochloric acid, whose solution was washed with *n*-hexane. The aqueous layer was basified with 10% ammonium hydroxide solution and extracted with ether. The ethereal layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent and unreacted benzylamine afforded a yellow oil, which was purified by column chromatography on 100 g of silica gel. Elution with hexane–benzene (2:3) gave 5.6 g (75.6% based on compound **4**) of benzylamino derivative **6** as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.5–1.2 (4 H, m, cyclopropyl protons), 1.23 (3 H, s, CH_3), 2.68–3.0 (2 H, m, >$CHCH_2$Ar), 3.3–3.75 (3 H, m, –$CHCH_2$– and >NCH_2Ar), 3.8 (3 H, s, CH_3O), 6.8 (2 H, d, J = 8 Hz, aromatic β protons), 7.1 (2 H, d, J = 8 Hz, aromatic α protons), 7.2 (5 H, s, aromatic protons); MS *m/e* 323 (M^+). Hydrochloride formed colorless crystals: mp 163–164 °C.

Anal. Calcd for $C_{21}H_{25}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 68.31; H, 7.38; N, 3.80. Found: C, 68.10; H, 7.23; N, 3.83.

1-Benzyl-2-(4-methoxybenzyl)-4-methylpiperidin-3-one (7). A solution of 325 mg of benzylamino derivative **6** hydrobromide and 130 mg of potassium iodide in acetonitrile was heated at 140–145 °C in a sealed tube for 3 days. After filtration of inorganic compound, the solvent was distilled off and the residue was dissolved in 20 mL of 10% hydrochloric acid, whose solution was washed with *n*-hexane. The aqueous layer was basified with 10% ammonium hydroxide solution and extracted with ether. The ethereal layer was washed with saturated aqueous sodium thiosulfate solution and saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded a yellow oil, which was subjected to column chromatography on 10 g of silica gel. Elution with benzene gave a solid, which was recrystallized from benzene–hexane to afford 185 mg (71.2%) of **7** as colorless needles, mp 104–105 °C: IR ($CHCl_3$) 1710 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6.5 Hz, CH_3), 1.5–3.6 (8 H, m, methylene and methine protons), 3.73 (2 H, s, >NCH_2Ar), 3.78 (3 H, s, CH_3O), 6.78 (2 H, d, J = 9 Hz, aromatic β protons), 7.03 (2 H, d, J = 9 Hz, aromatic α protons), 7.21 (5 H, s, aromatic protons); MS *m/e* 323 (M^+).

Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.20; H, 7.73; N, 4.13.

1-Benzyl-3-hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidine (8). (A) From 7. To a solution of methylmagnesium iodide (prepared from 85 mg of Mg turnings and 500 mg of methyl iodide) in 5 mL of dry ether was added dropwise a solution of 100 mg of **7** in 5 mL of dry ether and stirred for 5 h at room temperature. The reaction mixture was poured into 10 mL of ice–water and extracted with ether. The ethereal layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent afforded a yellow oil, which was subjected to column chromatography on 2 g of silica gel. Elution with benzene–ethyl acetate (95:5) gave 62 mg (59%) of **8** as a colorless oil, which was identical with **8** obtained from **9** as below in its IR, NMR spectrum, and mixture melting point.

(B) From 1-Benzyl-5-hydroxy-6-(4-methoxybenzyl)-4,5-dimethylpiperidin-2-one (9). A solution of 1.3 g of amide **9** in 25 mL of dry xylene was added to a solution of 12 g of 70% sodium bis(2-methoxyethoxy)aluminum hydride in 15 mL of dry xylene, and the resulting mixture was heated under reflux for 4 h under a current of nitrogen. After the reaction mixture was acidified with 10% hydrochloric acid, the organic layer separated was extracted with water. Both aqueous layers were combined and basified with 10% ammonium hydroxide solution and extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a yellow oil, which was subjected to column chromatography on 20 g of silica gel. Elution with benzene–ethyl acetate (95:5) afforded 662 mg (50.3%) of **8** as a colorless oil: IR ($CHCl_3$) 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 4.0 Hz, CH_3CH<), 1.25 (3 H, s, $CH_3C(OH)$<), 3.8 (3 H, s, CH_3O), 6.8 (2 H, d, J = 8 Hz, aromatic β protons), 7.6 (2 H, d, J = 8 Hz, aromatic α protons), 7.65 (5 H, s, aromatic protons). Hydrochloride: mp 180–182 °C.

Anal. Calcd for $C_{22}H_{29}NO_2 \cdot HCl \cdot 0.5\ H_2O$: C, 68.64; H, 8.06; N, 3.64. Found: C, 68.68; H, 7.94; N, 3.71.

1-Benzyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (10). A solution of 30 mg of carbinol **8** in 5 mL of 50% sulfuric acid was heated at 80 °C for 2 days under stirring. The reaction mixture was basified with 10% ammonium hydroxide solution and extracted with ether. The ethereal layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent gave a yellow oil, which was purified by preparative thin-layer chromatography on silica gel (petroleum ether–ether, 3:1) to afford 23 mg (81%) of **10** as a colorless oil: NMR ($CDCl_3$) δ 1.63 (6 H, s, 2× CH_3), 3.58 (2 H, s, >NCH_2Ar), 3.77 (3 H, s, CH_3O), 6.66 (2 H, d, J = 9.1 Hz, aromatic β protons), 7.08 (2 H, d, J = 9.1 Hz, aromatic α protons), 7.1 (5 H, s, aromatic protons). Hydrochloride, mp 152–153 °C (lit.,[27] mp 152–154 °C) identical with an authentic sample[27] in its IR, NMR spectrum, and mixture melting point.

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Registry No.—**1**, 359-83-1; **2**, 1567-75-5; **3**, 63215-74-7; **4**, 63181-46-4; **5**, 63181-47-5; **6**, 63181-48-6; **6** HCl, 63181-49-7; **6** HBr, 63197-36-4; **7**, 63181-50-0; **8**, 63181-51-1; **8** HCl, 63181-52-2; **9**, 63181-53-3; **10**, 22185-48-4; **10** HCl, 23909-52-6; *p*-methoxybenzaldehyde, 123-11-5; benzylamine, 100-46-9.

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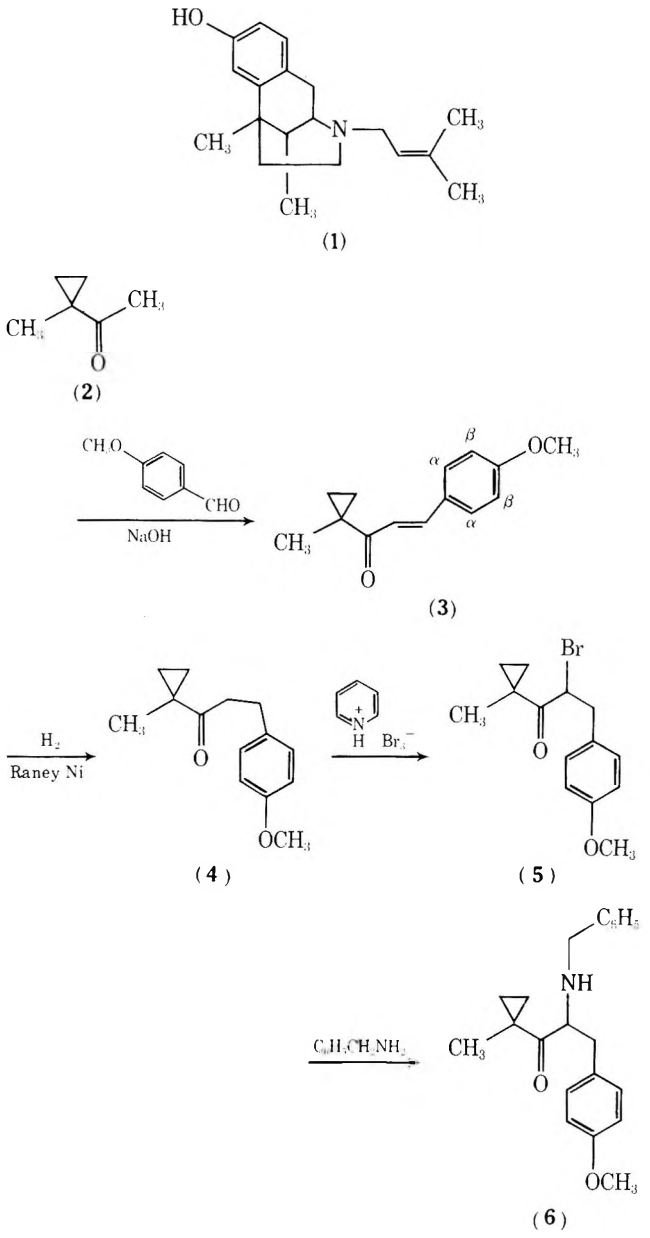
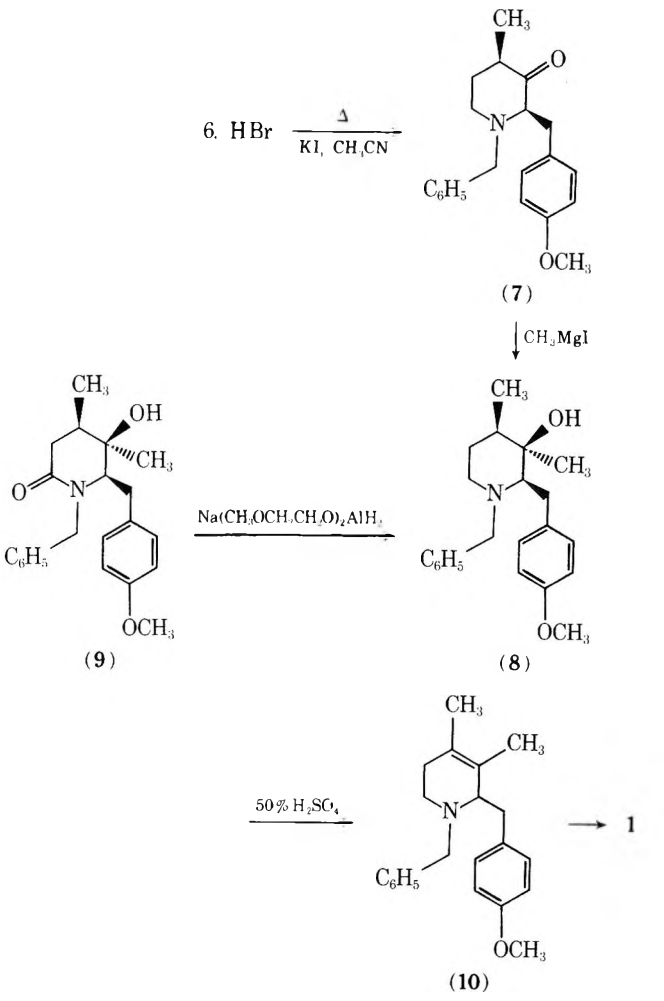
Scheme I



Scheme II



aminomethyl cyclopropyl ketones and this prompted us to examine its possible use for the synthesis of more complex objectives.

Since pentazocine (1), 1,2,3,4,5,6-hexahydro-8-hydroxy-6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocine, was first synthesized by Archer et al.,[20] many kinds of synthetic methods[21-24] for this compound 1 have been reported because of its nonnarcotic analgesic activity. Herein we wish to report a simple and novel synthesis of pentazocine (1) by using the thermal rearrangement of aminomethyl cyclopropyl ketone 6 as a key reaction.

The key compound 6 in our synthesis was prepared as follows. Condensation of 1-acetyl-1-methylcyclopropane (2)[25,26] with *p*-methoxybenzaldehyde in the presence of sodium hydroxide, followed by the catalytic hydrogenation of the resulting styril ketone 3, afforded the cyclopropylpropanone 4 in 81.35% overall yield. Bromination of the compound 4 with pyridinium hydrobromide perbromide in ether gave the bromide 5 [*m/e* 296 (M^+), 298 ($M^+ + 2$), ν_{max} ($CHCl_3$) 1685 cm^{-1}, δ ($CDCl_3$) 4.47 (1 H, q, J = 6 and 9 Hz, -CO-CHBr-)], which was subsequently treated with benzylamine in methanol to afford the key intermediate 6 in 75.6% yield (based on the propanone 4).

Next, thermolysis of compound 6 was carried out to proceed smoothly in high yield. A solution of hydrobromide of the compound 6 in acetonitrile was heated at 140–145 °C in a sealed tube in the presence of potassium iodide to give the piperidone 7 in 71.2% yield as a single product. The relative configuration between methyl and *p*-methoxybenzyl groups was assigned to be cis tentatively at this stage and this was confirmed by a subsequent transformation to the piperidin-3-ol 8, which was in turn derived from the known compound 9.[22] At first the piperidone 9[22] was reduced with sodium bis(2-methoxyethoxy)aluminum hydride to afford 8.

Finally, the piperidone 7 was treated with methylmagnesium iodide in ether to furnish the piperidin-3-ol 8 in 59% yield, which was shown to be identical with the authentic sample obtained above in its IR ($CHCl_3$) and NMR ($CDCl_3$) spectral comparisons and mixture melting points. The dehydration was effected by treating the piperidin-3-ol 8 with 50% sulfuric acid to give the olefinic compound 10 as a single product in 81% yield. Our product 10 was found to be identical with the authentic sample[27] in its IR ($CHCl_3$), NMR ($CDCl_3$) spectrum, and mixture melting point. Since this olefin 10 had been transformed to pentazocine (1),[27] this work constitutes a novel synthesis of pentazocine (1). Thus, we could demonstrate the thermal rearrangement of aminomethyl cyclopropyl ketone as a useful reaction for the synthesis of the compounds which contain a piperidine ring.

Experimental Section

Melting points are uncorrected. NMR spectra were taken with a JNM-PMX-60 spectrometer (tetramethylsilane as an internal reference), IR spectra with a Hitachi 215 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

3-(4-Methoxyphenyl)-1-methylcyclopropyl-2-propenone (3). A solution of 10.5 g of 1-acetyl-1-methylcyclopropane (2), 14.6 g of

Orleans, La., a sample of versicolorin C derived from versiconal acetate from Dr. R. J. Cole, National Peanut Research Laboratory, Dawson, Ga., and a sample of versiconol from Dr. Y. Hatsuda, University of Tottori, Japan. We also wish to thank Dr. R. J. Cole for a prepublication copy of his paper on the carbon NMR of versiconal acetate. We thank Mr. T. Glass for obtaining the NMR spectra, and Miss Sue Ellen Jolly for assistance in the preparation of versicolorin A. This work was supported, in part, by contract 223-74-2146 from the Food and Drug Administration, Washington, D.C.

Registry No.—**3**, 6807-96-1; **4**, 10048-13-2; **6a**, 63324-95-8; **7b**, 63324-96-9; **9**, 22268-13-9; **10**, 63358-82-7; **12a**, 63324-97-0; **13**, 63324-98-1; **14b**, 63324-99-2; **16**, 63325-00-8; **17**, 63325-01-9; **18**, 6795-16-0; **19**, 63325-02-0; sodium borohydride, 16940-66-2.

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Studies on the Syntheses of Heterocyclic Compounds. 726.[1] Thermal Rearrangement of Aminomethyl Cyclopropyl Ketones and a Novel Synthesis of Pentazocine

Tetsuji Kametani,* Hideharu Seto, Hideo Nemoto, and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

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Thermal rearrangement of the hydrobromide of 2-benzylamino-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**6**), obtained from 1-acetyl-1-methylcyclopropane (**2**) through 3-(4-methoxyphenyl)-1-methylcyclopropyl-2-propenone (**3**), 3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**4**), and 2-bromo-3-(4-methoxyphenyl)-1-methylcyclopropylpropanone (**5**), gave 1-benzyl-2-(4-methoxybenzyl)-4-methylpiperidin-3-one (**7**) in 71.2% yield, which was transformed to 1-benzyl-1,2,5,6-tetrahydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (**10**) by Grignard reaction, followed by dehydration of the resulting 1-benzyl-3-hydroxy-2-(4-methoxybenzyl)-3,4-dimethylpiperidine (**8**). Since **10** had been converted to pentazocine (**1**), this work constitutes a novel synthesis of pentazocine (**1**).

The susceptibility of cyclopropane rings with suitable activating groups to several kinds of nucleophiles has been well documented[2–7] since the studies of Bone and Perkin.[8,9] Recently, Danishefsky reported[10–13] the nucleophilic homoconjugate reactions of cyclopropanes with two geminal activating groups and an enhanced activation of cyclopropanes with cyclic acylal. On the other hand, the acid-catalyzed thermal rearrangement of cyclopropylimines, which was originally reported by Cloke,[14,15] has been shown to be a useful reaction for the synthesis of Δ^1- or Δ^2-pyrrolines,[16–18] and aminomethyl cyclopropyl ketones have been transformed to 3-ketopiperidine rings.[19] In contrast to the well-studied thermal rearrangement of cyclopropylimines, there have been very limited studies regarding the thermal rearrangement of

with that of the hemiacetal **12a**. Its IR spectrum showed no hydroxyl stretching band: $[\alpha]^{27}_D$ −184° (c 6.9, $CHCl_3$); mass spectrum *m/e* 370 (M^+, 45), 342 (22), 341 (100), 325 (11), 313 (16), 297 (35), 295 (13), 285 (28); ^1H NMR ($CDCl_3$) δ 13.28, 13.20 (1 H, 2s, 3-OH), 7.46 (1 H, t, *J* = 8 Hz, H-5), 6.84–6.64 (2 H, m, H-4 and H-6), 6.50 (1 H, 2d, H-14), 6.36 (1 H, 2s, H-11), 5.34 (1 H, m, H-17), 4.18 (1 H, m, H-15), 4.00 (3 H, s, H-18), 3.84–3.16 (2 H, two overlapping q, $-OCH_2-$), 2.40 (2 H, m, H-16), 1.14, 0.89 (3 H, 2s, $-CH_3$). Decoupling experiments indicated that the signals at 4.18 and 6.50 ppm arose from protons on adjacent carbons, as did the signals at 5.34 and 2.40 ppm.

Reduction of Sterigmatocystin Hemiacetal with Sodium Borohydride. Sterigmatocystin hemiacetal (300 mg) was dissolved in tetrahydrofuran (300 mL) and 0.05 M phosphate buffer, pH 7.2 (80 mL), at 0 °C. The cold solution was treated dropwise over 3 h with 50 mL of buffer solution containing 90 mg of $NaBH_4$. The reaction mixture was then diluted with 50 mL of water, adjusted to pH 6 with dilute HCl, and extracted with ethyl acetate. The organic extract was washed, dried, and evaporated to yield a crude product which consisted almost completely of two new products. These products were separated by PTLC using solvent system B.

Sterigmatodiol (16). The more polar of the two products (120 mg) had mp 208–210 °C after crystallization from acetone, and $[\alpha]^{25}_D$ −8° (c 2.4, CH_3SOCH_3). It showed: λ_{max} 232 nm (ε 27 000), 249 (29 000), 331 (16 000); ν_{max} 3400 (OH), 1645, 1605 cm^{-1}; mass spectrum *m/e* 346 (M^+, 54) 316 (20), 315 (70), 297 (20), 285 (77), 283 (20), 271 (100); ^1H NMR (CD_3COCD_3) δ 7.56 (1 H, t, *J* = 8 Hz, H-5), 6.90 (1 H, d, *J* = 8 Hz, H-4), 6.66 (1 H, t, *J* = 8 Hz, H-6), 6.46 (1 H, s, H-11), 4.16–3.96 (3 H, m, H-14 and -15), 3.90 (3 H, s, H-19), 3.58 (2 H, t, *J* = 7 Hz, H-17); the signal for H-16 was concealed under the solvent peak; ^{13}C NMR (CD_3SOCD_3) δ 180.7, 163.6, 161.2, 159.7, 157.2, 154.3, 135.9, 110.0, 108.5, 107.9, 106.1, 103.7, 95.7, 63.5, 59.9, 55.8, 42.0–37.0 (solvent), 34.9, 33.2.

Anal. Calcd for $C_{18}H_{18}O_7$: C, 62.4; H, 5.2. Found: C, 62.6; H, 5.3.

Partially Reduced Hemiacetal (14b). The less polar of the two reduction products described above (80 mg) had mp 223–226 °C after crystallization from acetone. It showed: λ_{max} 232 (ε 22 000), 249 (ε 29 000), 325 (15 000); ν_{max} 3410, 3260, 1640, 1610 cm^{-1}; mass spectrum *m/e* 344 (M^+, 38), 326 (70), 314 (22), 313 (100), 297 (20), 285 (60), 283 (42), 255 (20), 253 (27), 169 (21), 149 (27), 131 (22), 119 (33); ^1H NMR (CD_3SOCD_3) δ 13.15 (1 H, s, 3-OH), 7.54 (1 H, t, *J* = 8 Hz, H-5), 6.84 (1 H, d, *J* = 8 Hz, H-4), 6.63 (1 H, d, *J* = 8 Hz, H-6), 6.30 (1 H, s, H-11), 5.64–5.42 (1 H, m, H-17), 5.2–4.8 (1 H, m, H-15), 3.83 (3 H, s, H-18), 4.0–3.7 (2 H, m, H-14), 2.28–2.44 (m, H-16, partially concealed under the solvent peak); ^{13}C NMR (CD_3SOCD_3) δ 180.6, 161.1 (2 overlapping signals), 160.0, 156.2, 154.5, 136.0, 110.3, 108.1, 106.2, 102.0, 95.9, 93.2, 62.7, 56.2, 42.0–37.0 (solvent), 32.5, 30.2.

Dihydrosterigmatocystin (18). Sterigmatocystin (400 mg) was hydrogenated in ethyl acetate (50 mL) over 10% Pd/C at room temperature for 4 h. The product was recovered in the usual manner and recrystallized from acetone to give dihydrosterigmatocystin, mp 226–227 °C (lit. 230 °C).[36]

Its UV and IR spectra were as expected; its mass spectrum showed *m/e* 326 (M^+, 100), 308 (20), 297 (26); ^1H NMR ($CDCl_3$) δ 13.04 (1 H, s, 3-OH), 7.36 (1 H, t, *J* = 8 Hz, h-5), 6.70 (1 H, d, *J* = 8 Hz, H-4), 6.62 (1 H, d, *J* = 8 Hz, H-6), 6.42 (1 H, d, *J* = 5 Hz, H-14), 6.24 (1 H, s, H-11), 4.16 (2 H, m, H-17), 3.93 (3 H, s, H-18), 3.63 (1 H, q, *J* = 7 Hz, H-15), 2.30 (2 H, m, H-16); ^{13}C NMR (CD_3SOCD_3) δ 180.0, 165.5, 162.8, 161.1, 154.3, 153.6, 135.6, 113.3, 110.2, 108.0, 105.8, 105.4, 90.0, 67.0, 56.3, 43.2, 42.0–37.0 (solvent), 30.5.

Isodihydrosterigmatocystin (17) The hemiacetal **14b** (20 mg) was treated with concentrated HCl (1 mL) in tetrahydrofuran (50 mL) for 4 h under reflux. Workup in the usual way yielded a homogeneous product, which was crystallized from ethyl acetate to give the product **17**, mp 226–227 °C, $[\alpha]^{27}_D$ −1.7° (c 2.4, $CHCl_3$). Its UV absorption was essentially identical with that of dihydrosterigmatocystin, but its IR spectrum showed differences in the fingerprint region: mass spectrum *m/e* 326 (M^+, 100), 308 (33), 297 (32), 283 (70), 265 (30); ^1H NMR ($CDCl_3$) δ 12.96 (1 H, s, 3-OH), 7.36 (1 H, t, *J* = 8 Hz, H-5), 6.69 (1 H, d, *J* = 8 Hz, H-4), 6.62 (1 H, d, *J* = 8 Hz, H-6), 6.20 (1 H, s, H-11), 5.79 (1 H, d, *J* = 2 Hz, H-17), 4.19 (2 H, ABX, J_{AB} = 8 Hz, J_{AX} = 3 Hz, J_{BX} = 0 Hz, H-14), 3.90 (3 H, s, H-18), 3.88 (1 H, m, H-15), 2.20 (2 H, m, H-16); ^{13}C NMR (CD_3SOCD_3) δ 180.1, 160.8, 160.2, 158.1, 154.1, 135.3, 109.8, 108.2, 107.8, 105.7, 99.3, 95.7, 78.7, 55.8, 42.0–37.0 (solvent), 31.5, 28.7.

Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.3, H, 4.3. Found C, 66.3; H, 4.4.

Methylation of 14b. The partially reduced sterigmatocystin hemiacetal **14b** (15 mg) in ethyl acetate (50 mL) was treated with excess diazomethane in alcohol-free ether for 2 h at 0 °C. The resulting solution was evaporated to dryness, and the product crystallized from ethyl acetate to yield the ether **18** as pale yellow crystals, mp 202–204 °C, $[\alpha]^{27}_D$ +8.5° (c 2.2, CH_3SOCH_3). The material had: λ_{max} 231 nm (ε 21 000), 250 (27 000), 329 (13 000); IR ν_{max} 3480, 1660, 1610 cm^{-1}; mass spectrum *m/e* 358 (M^+, 100), 340 (14), 328 (18), 327 (43), 300 (15), 299 (65), 285 (44), 273 (14), 272 (61), 255 (15), 254 (20), 242 (14), 226 (15); ^1H NMR ($CDCl_3/CD_3SOCD_3$) δ 13.02 (1 H, br s, -OH), 7.51 (1 H, t, *J* = 8 Hz, H-5), 6.82 (1 H, d, *J* = 8 Hz, H-6), 6.64 (1 H, d, *J* = 8 Hz, H-4), 6.50 (1 H, s, H-11), 5.64 (1 H, br d, *J* = 4 Hz, H-17), ~4.8 (1 H, br s, H-15), ~4.0 (2 H, complex, H-14), 3.80 (6 H, s, 2 OCH_3), and 2.2 (2 H, complex, H-16).

Anal. Calcd for $C_{19}H_{18}O_7 \cdot 0.5H_2O$: C, 62.1; H, 5.2. Found: C, 62.3; H, 5.1.

Versicolorin A Hemiacetal (6a). Versicolorin A[20] (150 mg) was heated under reflux for 24 h in acetone (150 mL) containing 1.5 mL of 10% H_2SO_4. The reaction mixture was cooled, evaporated in vacuo to remove most of the acetone, diluted with H_2O (100 mL), and extracted with 5 × 50 mL of ethyl acetate. The combined extracts were washed, dried, and evaporated to yield a crude essentially homogeneous product which was crystallized from acetone to give orange-red crystals of the hemiacetal **6a** (90 mg), mp 269–270 °C. The material had: λ_{max} 223 nm (ε 25 000), 255 (15 000), 266 (18 000), 291 (25 000), 317 (11 000), 456 (6100); ν_{max} 3440, 3240, 1610 cm^{-1}; mass spectrum *m/e* 356 (M^+, 18), 355 (27), 328 (60), 310 (67), 309 (73), 300 (74), 299 (100), 285 (40); ^1H NMR (CD_3COCD_3) δ 7.18 (1 H, d, *J* = 2 Hz, H-8), 7.05 (1 H, s, H-4), 6.61 (1 H, d, *J* = 2 Hz, H-10), 6.49 (1 H, d, *J* = 6 Hz, H-15), 5.7–5.5 (1 H, m, H-18), 4.3–4.0 (1 H, m, H-16); signals for H-17 were concealed under the solvent peak.

Reduction of Versicolorin A Hemiacetal with Sodium Borohydride. Versicolorin A hemiacetal (80 mg) was dissolved in a mixture of tetrahydrofuran (80 mL) and 0.05 M phosphate buffer, pH 7.2, 40 mL. The solution was cooled to 0 °C and treated dropwise over 2 h with a cold solution of sodium borohydride (20 mg) in 4 mL of buffer. The reaction mixture was then diluted with water, adjusted to pH 6 with dilute HCl, and extracted with 5 × 50 mL of ethyl acetate. The extract was washed, dried, and evaporated to give a crude product which consisted largely of two new materials, which were separated by PTLC with solvent system A.

Versiconol (9). The more polar of the two reduction products was identified as versiconol (**9**). The material (10 mg) had mp 263–265 °C after crystallization from acetone, undepressed in admixture with authentic material, mp 262–266 °C, $[\alpha]^{27}_D$ 0 ± 5 (c 0.4, dioxane). The TLC behavior of the isolate and of authentic versiconol in solvent system A were identical. The material had: λ_{max} 224 nm (ε 22 000), 262 (7900), 296 (9400), 318 (11 000), 460 (2300); ν_{max} 3420, 1620 cm^{-1}; mass spectrum *m/e* 342 (M − 18, 10), 340 (42), 312 (40), 311 (58), 298 (25), 297 (100); using chemical ionization the sample showed *m/e* 361 (MH^+, 11), 344 (13), 343 (55), 342 (20), 341 (100); ^1H NMR (CD_3COCD_3) δ 7.24 (2 H, br, H-4 and H-5), 6.64 (1 H, d, *J* = 2 Hz, H-10), 4.2–3.8 (3 H, complex, H-15 and H-16), 3.4 (2 H, t, *J* = 6 Hz, H-18).

Partially Reduced Versicolorin A Hemiacetal (7b). The less polar of the two products from the reaction described was crystallized from acetone to give orange-red crystals (15 mg), mp >305 °C dec. The material had: λ_{max} 223 nm (ε 24 000), 255 (12 000), 267 (14 000), 318 (9000), 453 (7200); ν_{max} 3580, 3150, 1620 cm^{-1}; mass spectrum *m/e* 340 (M − 18, 84), 312 (63), 311 (92), 297 (100); ^1H NMR (CD_3SOCD_3) δ 12.62 (1 H, br s, -OH), 11.94 (1 H, br s, -OH), 6.98 (1 H, d, *J* = 2 Hz, H-8), 6.88 (1 H, s, H-4), 6.48 (1 H, d, *J* = 2 Hz, H-10), ~5.5 (1 H, m, H-15), 3.8–3.0 (3 H, m, H-16 and H-18).

Isoversicolorin C (10). Treatment of the partially reduced hemiacetal **7b** with concentrated HCl (0.5 mL) in tetrahydrofuran (20 mL) under reflux for 2 h, followed by the usual workup, yielded isoversicolorin C (**10**) as the only organic reaction product. The material had mp >350 °C after recrystallization from acetone, and λ_{max} 222 nm (ε 25 000), 255 (14 000), 265 (16 000), 294 (18 000), 318 (15 000), and 463 (6500).

It showed IR absorption at ν_{max} 3380, 1605 cm^{-1}, and its mass spectrum had *m/e* 340 (M^+, 62), 312 (20), 312 (43), 311 (100), 298 (20), 297 (84); ^1H NMR (CD_3SOCD_3) δ 12.40 and 11.94 (2 H br s, 2 -OH), 7.02 (1 H, d, *J* = 2 Hz, H-8), 6.91 (1 H, s, H-4), 6.50 (1 H, d, *J* = 2 Hz, H-10), 5.98 (1 H, br s, H-18), 4.14 (2 H, m, H-15), 3.72 (1 H, br s, H-16), 2.20 (2 H, br s, H-17). Decoupling experiments indicated that the H-17 protons at 2.20 ppm were coupled to the H-18 proton at 5.98 and the H-16 proton at 3.73 ppm; the latter was also shown to be coupled to the H-15 protons at 4.14 ppm.

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The calculated shifts of compounds **14a** and **14b** were obtained by correcting the shifts of the model compounds in an appropriate fashion. Thus, the hydroxyl-bearing C-10 of structure **14b** was assumed to have the same shift as C-10 of structure **16**, while the "alkoxyl" substituted C-10 of structure **14a** was approximated by C-10 of structure **18**. The difference in chemical shift between these two carbons is in line with previous studies of substituent effects on aromatic systems,[32] and tends to support the assumptions made. In particular, the ring strain inherent in structure **17** makes this compound unsuitable for model purposes, since corrections for ring strain are difficult to estimate in compounds of this type. The other key assignment is of C-14 in structures **14a** and **14b**. In the case of **14a**, the shift of carbon-14 in compound **16** was taken as the best available model, since the differences in structure between **16** and **14a** occur at C-17, which should have a minimal effect on the shift of C-14. In the case of structure **14b**, the shift of C-17 of compound **18** was taken as a reference, and was then corrected by the difference in chemical shift between C-14 and C-17 of compound **16** to correct for the fact that the α carbon in **14b** is benzylic.

A comparison of the observed shifts for C-10 and C-14 of compound **14** with those calculated for structures **14a** and **14b** clearly indicates that structure **14b** offers the best agreement between theory and experiment. However, in view of the approximate nature of the calculations used to obtain the shifts for compounds **14a** and **14b**, it was deemed desirable to carry out a structural proof by chemical means also. A sample of compound **14** was thus treated with diazomethane to yield one major product. The product had a molecular weight (MS) of 358, and its ^{1}H NMR spectrum showed the presence of an additional methoxyl group. The presence of a signal in the ^{1}H NMR spectrum for a chelated proton at 13.0 ppm indicated that the hydroxyl group at carbon 3 was still intact, and the product was thus formulated as the ether **19**. Since only structure **14b**, and not **14a**, would be expected to undergo methylation with diazomethane, this work supports the assignment of structure **14b** to the partially reduced sterigmatocystin hemiacetal.

The reason for the preferential formation of **14b** over the other possible structures **14a**, **15a**, and **15b** is not clear, but it must lie either in the stability of the various ring systems involved in the tautomeric equilibria or in some special kinetic effect. If the former is the correct explanation, it would require (contrary to our earlier expectations) that the equilibrium between the reducible forms **12b–d** of the hemiacetal of sterigmatocystin must lie in favor of **12d** under the conditions of the experiment. Reduction of **12d** to **14** would then allow a new equilibrium to be established, which must lie in favor of **14b** rather than **14a**. An explanation based on a special kinetic effect seems less probable, although it cannot be completely excluded.

Having established the pathway taken by the reduction of the hemiacetal of sterigmatocystin, we turned our attention to the conversion of versicolorin A hemiacetal into its reduction products. Treatment of versicolorin A (**3**) with acid yielded the hemiacetal **6a** as the major isolable product, and reduction of this compound with sodium borohydride under the conditions previously established for the sterigmatocystin case yielded a mixture of two products, which were separated by PTLC.

The more polar of the two was assigned the versiconol structure **9** on the basis of its spectroscopic properties and by analogy with the corresponding compound from sterigmatocystin. A direct comparison of our sample with authentic versiconol showed that the two compounds had the same R_f on TLC and the same melting point, but that they differed in the fingerprint region of their infrared spectra, which were obtained as KBr pellets. The reason for this difference is presumably because our sample had undergone essentially complete racemization during the reduction process.

The second, less polar, product was shown from its mass spectrum to be a partially reduced derivative of the hemiacetal **6a**, and its ^{1}H NMR spectrum indicated that it possessed structure **7a**, **7b**, **8a**, or **8b**. The absence of any absorptions assignable to aldehyde protons indicated that the compound existed in the hemiacetal form, while the presence of signals for *two* chelated hydroxyl groups indicated that cyclization to the C-1 hydroxyl group, as for example in structure **7c**, had *not* occurred.

Conversion of the partially reduced hemiacetal to a stable acetal was effected by treatment with dilute acid. The spectroscopic properties of the resulting product, and especially its ^{1}H NMR spectrum, showed that it had the isoversicolorin C structure (**10**) rather than the versicolorin C structure (**11**), and the partially reduced material must thus possess the structure **7a** or **7b**. It was not possible to do a ^{13}C NMR study of the structure of this latter material, but by analogy with the sterigmatocystin case we can assign the structure **7b** to it.

The discovery that reduction of the hemiacetal **6a** yields none of the desired product **8** (or at least, none isolable by us) prevented us from achieving our initial objective of the synthesis of the acetate **2c**. However, since a crucial part of the initial structural assignment of "versiconal acetate" was its conversion to versicolorin C (**11**) in acid, it became important to confirm that this conversion did in fact yield versicolorin C and not an isomer such as isoversicolorin C (**10**). We thus compared a sample of the product from acid treatment of "versiconal acetate" with authentic versicolorin C (**11**) and isoversicolorin C (**10**), and were able to show that the retention time on HPLC[33] matched that of versicolorin C and differed from that of isoversicolorin C. This work thus offers further support, in an indirect way, for the formulation of versiconal acetate as **2b**. This conclusion has been confirmed and extended by a recent study of the ^{13}C NMR spectrum of versiconal acetate.[34]

The sterigmatocystin and versicolorin derivatives described here should be handled with extreme caution because of their structural relationship to the known carcinogens aflatoxin B_1 and sterigmatocystin.

Experimental Section[35]

Sterigmatocystin Hemiacetal (12a). Sterigmatocystin (1.0 g) was heated for 12 h under reflux in acetone (200 mL) containing 10% H_2SO_4 (10 mL). The reaction mixture was cooled, the yellow-green precipitate collected, and the filtrate concentrated, diluted with water, and extracted with ethyl acetate. The combined extracts were washed, dried, evaporated, and combined with the precipitate to yield crude product, which was recrystallized from acetone to yield 400 mg of hemiacetal, mp 210–212 °C, $[\alpha]^{27}_D$ −7° (*c* 1.4, CH_3SOCH_3). The isolated material had: λ_{max} 232 nm (ϵ 28 000), 249 (34 000), 327 (17 000); ν_{max} 3400 (OH), 1650, 1625 cm^{-1}; mass spectrum *m/e* 342 (M^+, 16), 325 (17), 324 (80), 313 (19), 306 (31), 296 (20), 295 (49), 278 (22), 277 (20), 267 (23), 266 (21), 265 (27), 181 (34), 169 (35), 152 (24), 151 (23), 149 (40); ^{1}H NMR (CH_3SOCH_3) δ 13.48, 13.40, 13.30 (1 H total area, 3s, 3-OH), 9.36, 9.50 (0.05 H total area, 2s), 7.51 (1 H, t, J = 8 Hz, H-5), 6.82 (1 H, d, J = 8 Hz, H-6), 6.62 (1 H, d, J = 8 Hz, H-4), 6.45 (1 H, s, H-11), 6.50–6.32 (1 H, m, H-14), 5.56–5.38 (1 H, m, H-17), 4.18–4.00 (1 H, m, H-15), 3.84 (3 H, s, H-18), 2.20 (2 H, m, H-16) ppm; in $CDCl_3$ solution the signal for H-14 appeared as a doublet (J = 2 Hz) at 6.53 ppm.

Anal. Calcd for $C_{18}H_{14}O_7 \cdot 0.5H_2O$: C, 61.7; H, 4.3. Found: C, 61.9; H, 4.4.

Sterigmatocystin Ethoxyacetal (13). Extraction of the hemiacetal as described above was inadvertently carried out on one occasion with a batch of ethyl acetate containing a small amount of ethanol. The crude product was shown by TLC in system A to contain two products, which were separated by PTLC in the same solvent system. The more polar of the two compounds was sterigmatocystin hemiacetal (**12a**), and the less polar was a new product identified as the ethoxyacetal **13**. The material had mp 189–192 °C after recrystallization from acetone, and had a UV spectrum essentially identical

Scheme III

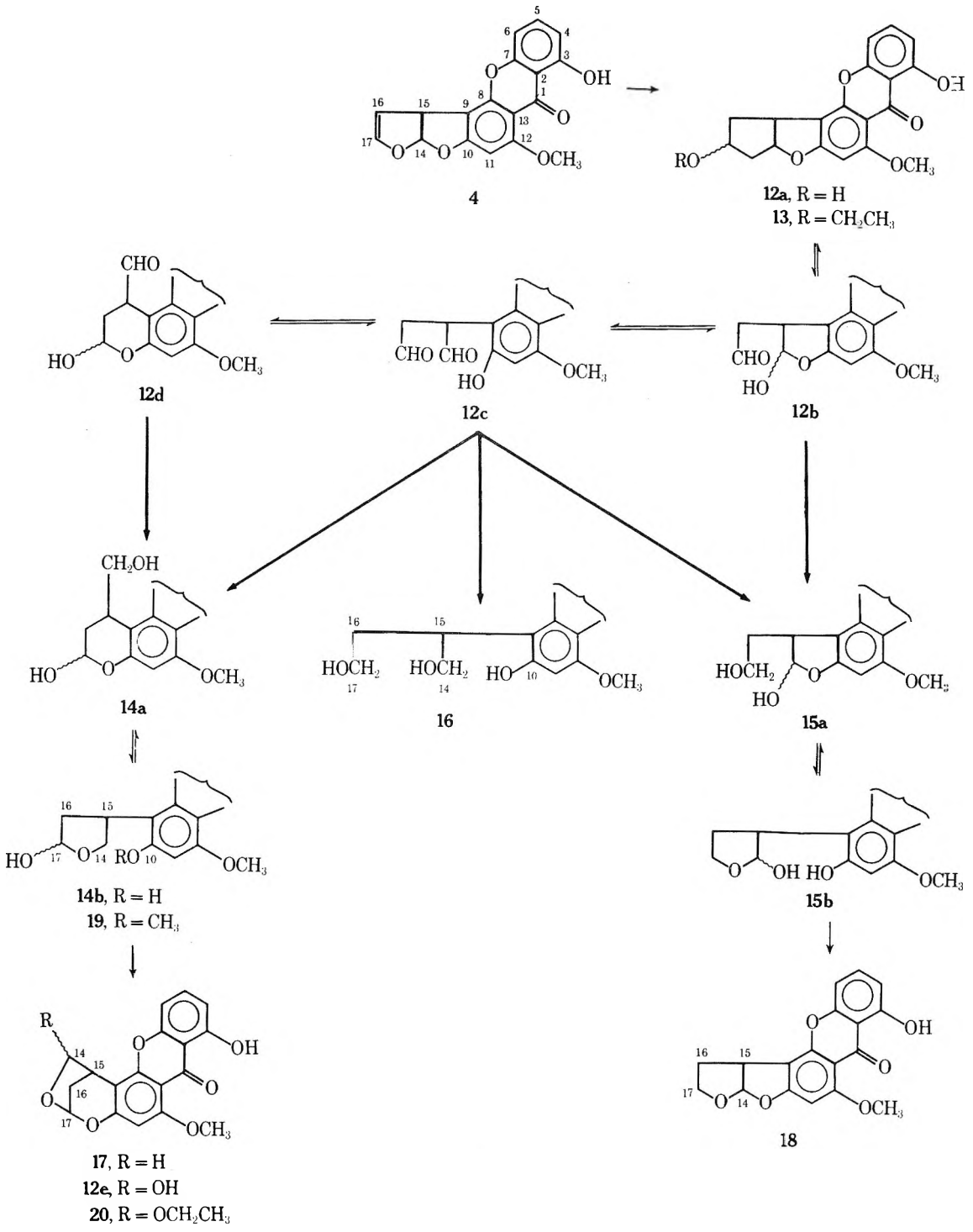


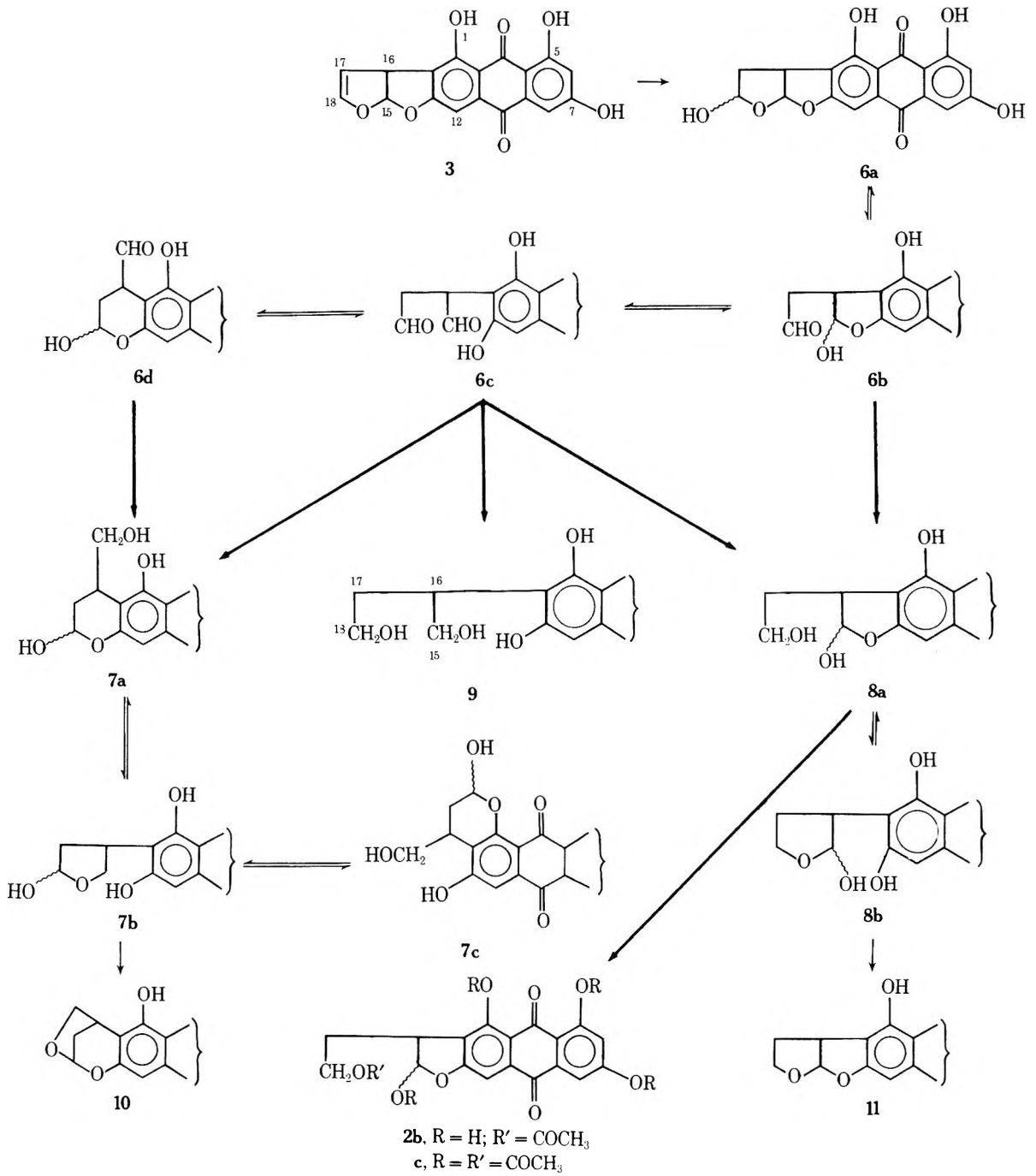
Table I. Carbon-13 Chemical Shifts for Some Sterigmatocystin Derivatives[a,b]

Carbon	16	17	18	14a, calcd	14b, calcd	14, expt
10	159.7	158.1	165.6	165.7	159.7	160.0
14	59.9	78.7	113.3	59.9	33.4	62.7
15	34.9	28.7	43.2	33.4	33.6	30.2
						32.5
16	33.2	31.5	30.5	35.8	38.7	*c*
17	63.5	99.3	67.0	99.3	99.3	95.9
				95.7	95.7	92.8
18	55.8	55.9	56.3	56.6	56.6	56.1

[a] In parts per million downfield from Me_4Si. [b] In $(CD_3)_2SO$ solution. [c] Peak hidden under the solvent peaks.

the literature assignments in $CDCl_3$. The carbons at positions 15 and 17 in compound 14 each appeared to give rise to two signals of diminished intensity, presumably because of the existence of two epimers of this structure. The assignment of these signals should be regarded as tentative, since there was insufficient material available to permit any decoupling techniques to be used in this case, but differences of 2–4 ppm for the corresponding carbons in epimeric carbohydrates have been observed and thus tend to support the assignments.[30,31] The assignment for C-14 in compound 14 is secure, since it is the only possible signal in that range, while the assignment for C-10 must lie in the range 161.1–160.0 ppm, and better agreement with the spectra of previously assigned compounds is obtained when the value of 160.0 ppm is used for this carbon.

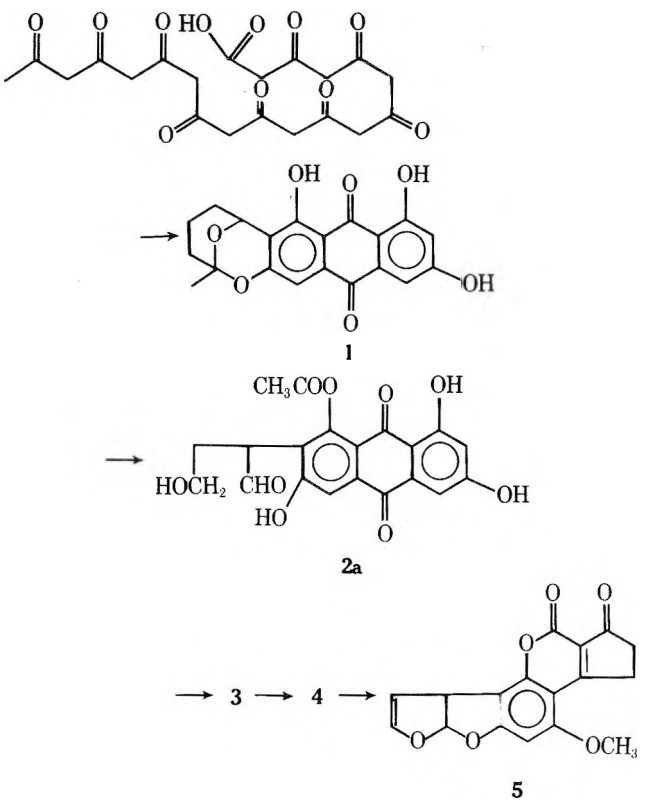
Scheme II



dihydrosterigmatocystin (**17**) followed from its ^{1}H NMR spectrum and from spin decoupling experiments. The latter showed that the one-proton multiplet at 5.79 ppm (H-17) was coupled with the two-proton multiplet at 2.20 ppm (H-16), which in turn was coupled with the one-proton multiplet at 3.88 ppm (H-15). Coupling between H-15 and H-14 could not be demonstrated by these experiments because of the similarity of their chemical shifts, but the pattern observed for H-14 at 4.19 ppm is consistent with these protons being coupled to one proton only at H-15; a dihedral angle between H-15 and one of the H-14 protons of nearly 90° explains the negligible coupling between them. This evidence can only be satisfied by the assignment of structure **17** to the compound, to which we have given the trivial name isodihydrosterigmatocystin. It follows from this that PRSTHA must have the structure **14a** or **14b**, since a rearrangement of the Cannizzaro type, which would be required to give isodihydrosterigmatocystin from structures **15a** or **15b**, is highly unlikely under the acidic conditions used.

A distinction between structures **14a** and **14b** for PRSTHA could not be made on the basis of its ^{1}H NMR spectrum, since as has been noted this was poorly resolved and complicated by the existence of two epimers. A distinction was made, however, on the basis of the ^{13}C NMR spectrum of compound **14** in comparison with the model compounds **16–18**. The ^{13}C NMR spectra of sterigmatocystin (**4**) and dihydrosterigmatocystin (**18**) have been published previously,[28,29] with some differences in assignments. Fortunately, the disputed assignments do not affect our conclusions, and we have chosen to use the values of Steyn[28] as the basis of our assignments. Assignments for carbons 10 and 14–18 of compounds **16, 17,** and **18,** together with predicted assignments for structures **14a** and **14b** and the experimental values for compound **14,** are given in Table I. The chemical shift assignments of compounds **16** and **17** were made on the basis of gated decoupling experiments, which revealed both directly bonded and long-range carbon–proton couplings of the indicated carbons, while the assignments of compound **18** are taken by comparison with

Scheme I



bisfuran ring system as sterigmatocystin and the aflatoxins B_1 and G_1, and it has been shown that two carbon atoms derived from the methyl groups of acetate have become linked in these molecules.[8,14] Since averufin is produced by a normal head-to-tail condensation of acetate units,[15] it follows that the conversion of averufin to versicolorin A involves a rearrangement of some type, and we[16] and others[6,3,17] have proposed possible pathways for this rearrangement. One possible intermediate in this conversion of averufin to versicolorin A has been identified as a yellow pigment,[18] which appears to be identical with a compound assigned the tentative structure of "versiconal acetate" (**2a**).[19] Because of the importance of "versiconal acetate" as a possible intermediate in the biosynthesis of the aflatoxins, and because of certain ambiguities in the original structural study, we undertook to attempt a synthesis of a derivative of versiconal acetate that could be used for purposes of structural confirmation. This paper describes the results of our studies.

An analysis of the spectral data in the original publication on "versiconal acetate" indicated to us that structure **2b** represented a probable structure of the compound. Our proposed pathway for the preparation of the acetylated derivative of this compound (**2c**) is shown in Scheme II. Acid treatment of versicolorin A, available from a mutant strain of *Aspergillus parasiticus*,[20] would yield the hemiacetal **6a**, which might be expected to exist in aqueous solution in equilibrium with the tautomers **6b–d**, in addition to other possible tautomers involving the peri hydroxyl group at position 1.[21] Reduction of this tautomeric mixture with a limited quantity of sodium borohydride[22] would be expected to yield a mixture of the two possible dihydro derivatives **7** and **8**, together with the fully reduced tetrahydro derivative versiconol (**9**), which has previously been isolated from *A. versicolor*.[23] Although the relative probabilities of reduction of tautomers **6b** and **6d** could not be predicted with confidence, it seemed reasonable to assume that these would be proportional to their relative concentrations in the reaction mixture, and an analogy from carbohydrate chemistry suggested that the dihydrofuran form **6b** should be preferred over the dihydropyran form **6d**.[24] Reduction should thus occur to yield the desired products **8a** and **8b** in reasonable yield. Acetylation of the anticipated mixture of these products would then yield at least some of the desired acetate **2c**, unless the equilibrium between the two forms favored **8b** to the exclusion of **8a**.

In view of the complexity of the possible products resulting from the reduction of versicolorin A hemiacetal **6a**, and because our supply of this compound was limited, the corresponding reduction of the hemiacetal derivative **12a** of sterigmatocystin (**4**) was studied first. Sterigmatocystin and its derivatives also have the advantage of being less polar than versicolorin A and its derivatives, and thus more readily handled by conventional techniques than the latter. The possible reduction products of the hemiacetal of sterigmatocystin (**12a**) are analogous to the versicolorin A derivatives, and are outlined in Scheme III.

Treatment of sterigmatocystin (**4**) with dilute sulfuric acid in acetone resulted in its smooth conversion to a hydrated product which consisted of a mixture of at least three isomers. The product had ultraviolet and infrared absorption spectra and a mass spectrum consistent with its formulation as a hydrate of sterigmatocystin, but its ^1H NMR spectrum showed a more complex pattern than would have been predicted for a single compound of structure **12a**. Thus, three signals were observed for the proton of the chelated hydroxyl group, and while the presence of two of these signals could be rationalized by the existence of both epimers of structure **12a** the presence of the third signal and weak absorptions due to aldehyde protons demand that the compound exists to some extent in one or more of the open-chain forms **12b–d**, with additional possible contributions from the hydrates of these structures.

Treatment of the hemiacetal **12** with ethanol under acidic conditions resulted in its conversion to a mixture of two epimeric ethoxy acetals (**13**). The spectroscopic data for the mixture support the assignment of structure **13** as opposed to possible alternate structures; in particular, spin-decoupling experiments exclude structure **20**, based on assignments of H-17 at 6.50 ppm and H-14 at 5.34 ppm for this hypothetical compound. By implication, therefore, the hemiacetal also exists largely as the tautomer **12a**; a recent paper describes the preparation of the hemiacetal of 5-methoxysterigmatocystin, and proposes a structure corresponding to **12a** for it.[26]

Reduction of the hemiacetal **12a** with a limited amount of sodium borohydride in tetrahydrofuran–pH 7.2 phosphate buffer yielded only two isolable products. The more polar of the two was identified on the basis on its spectral data as the sterigmatocystin analogue of versiconol (**9**), and was given the trivial name of sterigmatodiol (**16**). The low optical rotation observed for this and several of the other compounds studied is attributed to the occurrence of partial racemization during the reduction process; an analogous racemization of aflatoxin B_{2a} under basic conditions has been previously reported.[27] The second reduction product was identified as a partially reduced sterigmatocystin hemiacetal (PRSTHA) by its mass spectral parent ion peak at m/e 344. The ^1H NMR spectrum of the isolated material, like that of compound **12a**, was rather ill-defined, but it did indicate the absence of any open-chain tautomers by the lack of any aldehyde absorption. The spectra were not capable, however, of differentiating between the possible structures **14a**, **14b**, **15a**, and **15b**.

Treatment of PRSTHA with dilute acid effected its smooth conversion into a new product, which lacked any hemiacetal group and which thus gave a clean, well-resolved ^1H NMR spectrum. This compound had the molecular weight and a similar mass spectrum to dihydrosterigmatocystin (**18**), prepared by hydrogenation of sterigmatocystin (**4**), but a direct comparison of samples showed that they were not identical. Assignment of the structure of the new compound as iso-

m, $w_{1/2}$ = 9.5 Hz, 3-H), and 4.22 (1H, t, J = 3.5 Hz, 3-H). *m/e* (M^+) 400.3335 (calcd 400.3331), 382 ($M^+ - H_2O$), 364 ($M^+ - H_2O$), 152 ($M^+ - C_{18}H_{32}$), and 134 ($M^+ - C_{18}H_{32} - H_2O$).[9]

1-Ketoprevitamin D_3 3-Acetate (6b). A solution of 50 mg of 1-ketoprevitamin D_3 (**6a**) in 4 mL of methylene chloride was treated with 10 mg of 4-(dimethylamino)pyridine and 15 mg of acetic anhydride at room temperature for 2 h. The reaction mixture was evaporated and the residue was chromatographed on silica gel. Elution with ether gave 45 mg of 1-ketoprevitamin D_3 3-acetate (**6b**). UV λ_{max} 287, 236 nm (ϵ 10 000, 9500) and on addition of iodine and exposure to sunlight λ_{max} 320 nm (ϵ 22 000). NMR δ 0.69 (3H, s, 18-H), 1.74 (3H, s, 19-H), 1.99 (3H, s, acetate methyl), 5.45 (1H, m, 9-H), 5.90 and 6.08 (2H, ABq, J = 12 Hz, 6-H and 7-H), 5.04 (1H, heptet, J = 8.5 Hz and 4.0 Hz, 3-H). *m/e* (M^+) 440.3277 (calcd 440.3279), 396 ($M^+ - C_2H_4O$), 380 ($M^+ - C_2H_4O_2$) 220, 202.[9]

Reduction and Hydrolysis of 1-Ketoprevitamin D_3 3-Acetate (6b). A solution of 40 mg of 1-ketoprevitamin D_3 3-acetate (**6b**) in 3 mL of methanol was treated with 20 mg sodium borohydride at 0 °C for 30 min, extracted with ether, and washed with brine.

The ether extract was dried over magnesium sulfate and evaporated at 0 °C to dryness. The residue was chromatographed on silica gel. Elution with a mixture of ether–hexane (4:6) gave 25 mg of 1β-hydroxyprevitamin D_3 3-acetate (**10b**). UV λ_{max} 259 nm (ϵ 10 000) and on addition of iodine and exposure to sunlight: λ_{max} 272, 282, and 292 nm (ϵ 22 000, 25 000, 21 000). A solution of 20 mg (**10b**) in methanol was treated at 0 °C with a solution of 40 mg of potassium hydroxide in 1 mL of methanol for 4 h. The reaction mixture was extracted with ether and water and washed with brine. The ether extract was dried over magnesium sulfate and evaporated at 0 °C to dryness. The residue was chromatographed on silica gel. Elution with ether gave 15 mg of material which was identical with 1β-hydroxyprevitamin D_3 (**10a**).

1β-Hydroxyvitamin D_3 3-Acetate (5b). A solution of 10 mg of 1β-hydroxyprevitamin D_3 3-acetate (**10b**) in 2 mL of isooctane was heated under nitrogen atmosphere at 70 °C for 3.5 h. The solvent was evaporated to dryness and the residue was chromatographed on silica gel. Elution with a mixture of ether–hexane (4:6) gave 7 mg of 1β-hydroxyvitamin D_3 3-acetate (**5b**). UV λ_{max} 264 nm (ϵ 18 000) and on addition of iodine and exposure to sunlight λ_{max} 272 nm (ϵ 22 000). NMR δ 0.54 (3H, s, 18-H), 1.98 (3H, s, methyl acetate), 4.90 (1H, m, 19Z-H), 5.29 (1H, m, 19E-H), 5.87 and 6.15 (2H, ABq, J = 11.5 Hz, 6-H and 7-H), 3.97 (1H, quartet J = 9Hz and J = 4 Hz, 1-H), 4.82 (1H, heptet J = 9 Hz and J = 4 Hz 3-H).

1-Ketotachysterol$_3$ (9). A solution of 50 mg of 1-ketoprevitamin D_3 (**6a**) in 10 mL of ether was treated with 0.1 mL of 5% iodine solution in ether and exposed to visible light for 30 min. The ether solution was washed with water and evaporated under vacuum to give 35 mg of 1-ketotachysterol$_3$ (**9**). UV λ_{max} 320 nm (ϵ 22 000). NMR δ 0.70 (3H, s, 18-H), 1.82 (3H, s, 19-H), 4.1 (1H, m, 1-H), 5.77 (3H, m, 6-H, 7-H and 9-H).

Acknowledgment. We are indebted to Dr. Z. V. I. Zaretskii for the mass spectra determinations and to Mr. E. Berman for the NMR spectra. We thank United States–Israel Binational Science Foundation, Jerusalem, for financial support.

Registry No.—**2,** 41294-56-8; **5a,** 63181-13-5; **5b,** 63181-14-6; **6a,** 63181-15-7; **6b,** 63181-16-8; **8,** 41461-13-6; **9,** 63181-17-9; **10a,** 63181-18-0; **10b,** 63181-19-1; 1α,3β-dihydroxycholesta-5,7-diene, 43217-89-6.

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(6) The comparatively short wavelength absorption in **6a**, as well as in the other previtamin D_3 derivatives, indicates that the triene system in these compounds is not planar as in their respective tachysterol derivatives. The ring A of previtamin is probably tilted considerably in one or both directions; G. M. Sanders, J. Pot, and E. Havinga, *Fortschr. Chem. Org. Naturst.*, **27,** 131 (1969).
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(9) Full mass spectral data will be published elsewhere by Dr. Z. V. I. Zaretskii.

Reduction of Sterigmatocystin and Versicolorin A Hemiacetals with Sodium Borohydride[1]

Paul N. Chen,[2] David G. I. Kingston,*[2] and John R. Vercellotti[3]

Departments of Chemistry and Biochemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

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Reduction of sterigmatocysin or versicolorin A hemiacetals with a limited amount of sodium borohydride yielded two major products in each case. The hemiacetal derived from sterigmatocystin gave a new diol as the complete reduction product and a new hemiacetal as a partial reduction product, and the structure of this new hemiacetal was established by ^{13}C NMR spectroscopy and by chemical conversions. The hemiacetal derived from versicolorin A behaved similarly. The bearing of this work on the structure of versiconal acetate, isolated from *Aspergillus flavus*, is discussed.

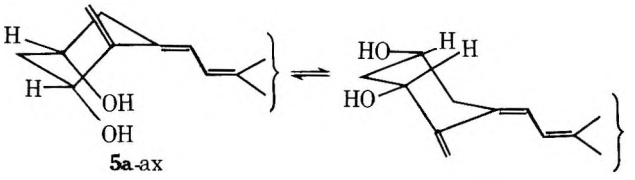
The aflatoxins and the related sterigmatocystins are a group of toxic and carcinogenic metabolites of certain strains of the fungi *Aspergillus flavus, Aspergillus parasiticus,* and *Aspergillus versicolor,* and have aroused considerable interest because of their widespread occurrence in human and animal foodstuffs.[4,5] Previous theoretical proposals and experimental studies on the biosynthesis of these compounds have indicated that the most probable biosynthetic pathway lies from acetate through the anthraquinones averufin (**1**) and versicolorin A (**3**) to sterigmatocystin (**4**) and thence to aflatoxin B_1 (**5**) (Scheme I).[6-13] The conversion of averufin to versicolorin A is of considerable interest, since the latter contains the same

epimer 8 only by the chemical shift of the protons at C_1 and C_3.

Reduction of the ketone **6a**, with lithium aluminum hydride proceeded differently from that with sodium borohydride, resulting in a mixture of both C_1 epimers **10a** and 8 in a ca. 2.8:1 ratio. The formation of the 1α-hydroxyprevitamin D_3 (8) in the lithium aluminum hydride reduction may be explained by the coordination of the aluminum atom to the hydroxy function which allows an attack of the hydride from the sterically hindered α side of the molecule.

Heating 1β-hydroxyprevitamin D_3 (**10a**) at 70 °C for 3.5 h gave a mixture containing the starting material and 1β-hydroxyvitamin D_3 (**5a**) (λ_{max} 264 nm; ϵ 18 000) in a 1:4 ratio (as established by the NMR spectrum of the total product mixture). The NMR spectrum of **5a** was similar to that of its C_1 epimer, the 1α-hydroxyvitamin D_3 (**1**), but for the signals of the protons at C_1 and C_3, while the mass spectra of both compounds were practically identical. 1β-Hydroxyvitamin D_3 (**5a**) isomerized with visible light in the presence of iodine to 1β-hydroxy-5,6-*trans*-vitamin D_3 (λ_{max} 272 nm; ϵ 22 000).

1β-Hydroxyvitamin D_3 (**5a**) exists as other vitamin D derivatives as a mixture of two chair conformers, which in solution are in dynamic equilibrium.[8] This equilibration can be deduced from its NMR spectrum in a nonpolar solvent (carbon tetrachloride), where the protons at C_1 and C_3 appear at 4.22 and 3.96 ppm as two triplets with J = 3.6 Hz and with half-height width, $w_{1/2}$ = 9.5 Hz. These triplets are due to two vicinal interactions, one axial:equatorial ($J_{ax:eq} = J_{eq:ax}$ = ca. 3.6 Hz) and the other representing an average between axial:axial and equatorial:equatorial coupling (J = 3.6 Hz). Using $J_{ax:ax}$ = 11 Hz, $J_{eq:eq}$ = 3 Hz,[3] and the experimental value J = 3.6 Hz we have calculated the ratio of the two conformers **5a-ax** and **5a-eq** to be 9:1. The strong preference for



5a-ax **5a**-eq

a conformation having the hydroxyl group in diaxial orientation is due to an intramolecular hydrogen bonding between these groups. This internal H bonding breaks down in H-bonding solvents, as the following NMR data show. Upon addition of acetone-d_6 to the carbon tetrachloride solution of **5a** both signals shifted to a higher field appearing at 3.79 and 4.02 ppm, the former as a heptet (J = 8.4 Hz and ca. 4.0 Hz) and the latter as a broad multiplet ($w_{1/2}$ = 17 Hz). These NMR data indicated that the intermolecular hydrogen bonding becomes predominant and the compound assumes mainly the conformation in which both hydroxyl groups are equatorial, the ratio of **5a-ax:5a-eq** being 3:7.

Additional information about the hydrogen bonding of the two hydroxyl groups at C_1 and C_3 can be gained from the NMR spectrum of 1β-hydroxyvitamin D_3 3-acetate (**5b**).

This compound was synthesized from **6a** by acylation with 4-(dimethylamino)pyridine and acetic anhydride resulting in the ketoacetate **6b** (λ_{max} 287, 236 nm; ϵ 10 000, 9500). Reduction with sodium borohydride in methanol yielded 1β-hydroxyprevitamin D_3 3-acetate (**10b**) (λ_{max} 259; ϵ, 10 000) which on hydrolysis gave 1β-hydroxyprevitamin D_3 (**10a**). The acetate (**10b**) isomerized to tachysterol derivative **11b** with iodine and sunlight (λ_{max} 272, 282, 292 nm; ϵ 22 000, 25 000, 21 000).

Heating **10b** at 70 °C for 3.5 h gave 1β-hydroxyvitamin D_3 3-acetate (**5b**) (λ_{max} 264; ϵ 18 000). The NMR spectrum in carbon tetrachloride was similar to that of **10a** except for the signals of the protons at C_1 and C_3 which appeared at 4.2 ppm (quartet, J = 9 Hz and ca. 4.0 Hz) and 4.88 ppm (heptet, J = 9 Hz and ca. 4.0 Hz), respectively, indicating that **5b** exists mainly in the diequatorial conformation, the ratio of **5b-eq: 5b-ax** being 8:2.

Preliminary biological assays in chicks indicated that 1β-hydroxyvitamin D_3 (**5a**) as well as its 3-acetate **5b** are devoid of any activity in inducing calcium transport and mobilization in the body.[1] Thus it appears that the high physiological activity of C_1-hydroxylated vitamin D_3 derivatives is limited to compounds possessing this function in the α-configuration.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Bruker 270 MHz using carbon tetrachloride as a solvent and cyclohexane-d_{12} as an internal lock. All chemical shifts are reported in δ values relative to tetramethylsilane standard. The ultraviolet spectra were taken on a Cary 118 spectrophotometer, using ether as a solvent. Mass spectra were recorded on Varian MAT 731 high resolution mass spectrometer.

1α-Hydroxyprevitamin D_3 (8). A solution of 400 mg of 1α,3β-dihydroxycholesta-5,7-diene in 250 mL of dry ether was irradiated at 0 °C under a nitrogen atmosphere with 3000-Å light (Rayonet) using 0.4% solution of sodium nitrate as a filter. The solvent was evaporated and the residue was chromatographed on Sephadex LH-20. Elution with a mixture of chloroform–hexane (6.5:3.5) gave 100 mg of 1α-hydroxyprevitamin D_3 (**8**). UV λ_{max} 259 nm (ϵ 10 000). NMR δ 0.71 (3H, s, 18-H), 1.70 (3H, s, 19-H), 5.50 (1H, m, 9-H), 5.68 and 5.86 (2H, ABq, J = 12 Hz, 6-H and 7-H), 4.02 (1H, m, $w_{1/2}$ = 9.4 Hz, 1-H), 3.89 (1H, m, $w_{1/2}$ = 17.2 Hz, 3-H). *m/e* (M^+) 400.3297 (calcd 400.3330, 382 ($M^+ - H_2O$), 364 ($M^+ - 2H_2O$), 152 ($M^+ - C_{18}H_{32}$) and 134 ($M^+ - C_{18}H_{32} - H_2O$).[9]

1-Ketoprevitamin D_3 (6a).[1] A solution of 100 mg of 1α-hydroxyvitamin D_3 (**1**) in 10 mL of dry ether was treated at room temperature with 350 mg of freshly prepared manganese dioxide for 6 h. The reaction mixture was filtered through a celite column and the filtrate was evaporated to dryness at room temperature. Chromatography on silica gel using an ethyl acetate–chloroform mixture (3:7) resulted in 35 mg of 1-ketoprevitamin D_3 (**6a**). UV λ_{max} 287, 236 nm (ϵ 10 000, 9500). NMR δ 0.74 (3H, s, 18-H) 1.69 (3H, s, 19-H), 5.99 and 6.13 (2H, ABq, J = 11 Hz, 6-H and 7-H), 5.51 (1H, m, 9-H) and 4.02 (1H, heptet, J = 8.6 and 4.3 Hz, 3-H). *m/e* (M^+) 398.6349 (calcd 398.3174), 380 ($M^+ - H_2O$), 157 ($M^+ - C_{16}H_{31} - H_2O$).[9]

A solution of 100 mg of 1α-hydroxyprevitamin D_3 (**8**) in 10 mL of ether was treated with 650 mg of freshly prepared manganese dioxide for 6 h. Isolation as above resulted in 85 mg of 1-ketoprevitamin D_3 (**6a**).

1β-Hydroxyprevitamin D_3 (10a).[1] A solution of 50 mg of 1-ketoprevitamin D_3 (**6a**) in 20 mL of methanol was treated with 85 mg of sodium borohydride at 0 °C for 30 min, extracted with ether, and washed with brine. The ether extract was dried over magnesium sulfate and evaporated at 0 °C to dryness. The residue was chromatographed on silica gel. Elution with a mixture of ethyl acetate–chloroform (3:7) gave 35 mg of 1β-hydroxyprevitamin D_3 (**10a**). UV λ_{max} 259 nm (ϵ 10 000), and on addition of iodine and exposure to sunlight λ_{max} 272, 282, 292 nm (ϵ 22 000, 25 000, 21 000). NMR δ 0.70 (3H, s, 18-H), 1.70 (3H, s, 19-H), 5.56 (1H, s, 9-H), 5.78 and 5.94 (2H, AB q, J = 11.5 Hz, 6-H and 7-H), 5.93 (1H broad s, $w_{1/2}$ = 11Hz, 3-H), and 4.22 (1H, m, $w_{1/2}$ = 10.5 Hz 1-H). *m/e* (M^+) 400.3333 (calcd 400, 3333), 382 ($M^+ - H_2O$), 364 ($M^+ - 2H_2O$), 152 ($M^+ - C_{18}H_{32}$), and 134 ($M^+ - C_{18}H_{32} - H_2O$).

A solution of 100 mg of 1-ketoprevitamin D_3 (**6a**) in 10 mL of anhydrous ether was treated with 20 mg of lithium aluminum hydride at 0 °C for 3 h with stirring. The reaction mixture was then triturated with saturated sodium sulfate solution followed by filtration and the residue was evaporated to dryness. Chromatography on silica gel and elution with a mixture of ethyl acetate chloroform (3:7) gave 1β-hydroxyprevitamin D_3 (**10a**) and 1α-hydroxyprevitamin D_3 (**8**) in a 2.8:1 ratio (60% yield).

1β-Hydroxyvitamin D_3 (5a).[1] A solution of 30 mg of 1β-hydroxyprevitamin D_3 (**10a**) in 10 mL isooctane was heated under nitrogen atmosphere at 70 °C for 3.5 h. The solvent was evaporated to dryness and the residue was chromatographed on silica gel. Elution with ether gave 25 mg of 1β-hydroxyvitamin D_3 (**5a**). UV λ_{max} 264 nm (ϵ 18 000) and on addition of iodine and exposure to sunlight λ_{max} 272 nm (ϵ 22 000). NMR δ 0.54 (3H, s, 18-H), 5.19 (1H, m, 19E-H), 4.88 (1H, m, 19Z-H), 5.92 and 6.29 (2H, ABq, J = 11.5 Hz, 6-H and 7-H), 3.96 (1H,

Conformational Equilibria in Vitamin D. Synthesis of 1β-Hydroxyvitamin D_3[1]

Mordechai Sheves, Noga Friedman, and Yehuda Mazur*

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

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1 β-Hydroxyvitamin D_3 was prepared from 1α-hydroxyvitamin D_3 by oxidation to 1-ketoprevitamin D_3, followed by sodium borohydride reduction and subsequent thermal isomerization. The conformational equilibria in 1β-hydroxyvitamin D_3 were established using ^1H NMR technique. These data indicate that in nonpolar solvent this compound assumes mainly the conformation in which hydroxy groups are both axial, while in H-bonding solvent mainly the conformation where these groups are both diequatorial.

1α,25-Dihydroxyvitamin D_3, **1** (C_{25}-OH), is a natural hormone,[2] inducing the formation of calcium binding proteins, responsible for the calcium transport and its mobilization in the body. A number of other vitamin D_3 analogs, like 1α-hydroxyvitamin D_3 (**1**),[3] dihydrotachysterol$_3$ (**2**), 5,6-transvitamin D_3 (**3**), 1α-hydroxy-3-deoxyvitamin D_3 (**4a**), its 3α-methyl analog (**4b**)[3] and their respective 25-hydroxy derivatives[2] exert in various degrees similar biological activity in vivo. One of the common features in all these compounds is the presence of a hydroxy function at C_1 having an α configuration.[4]

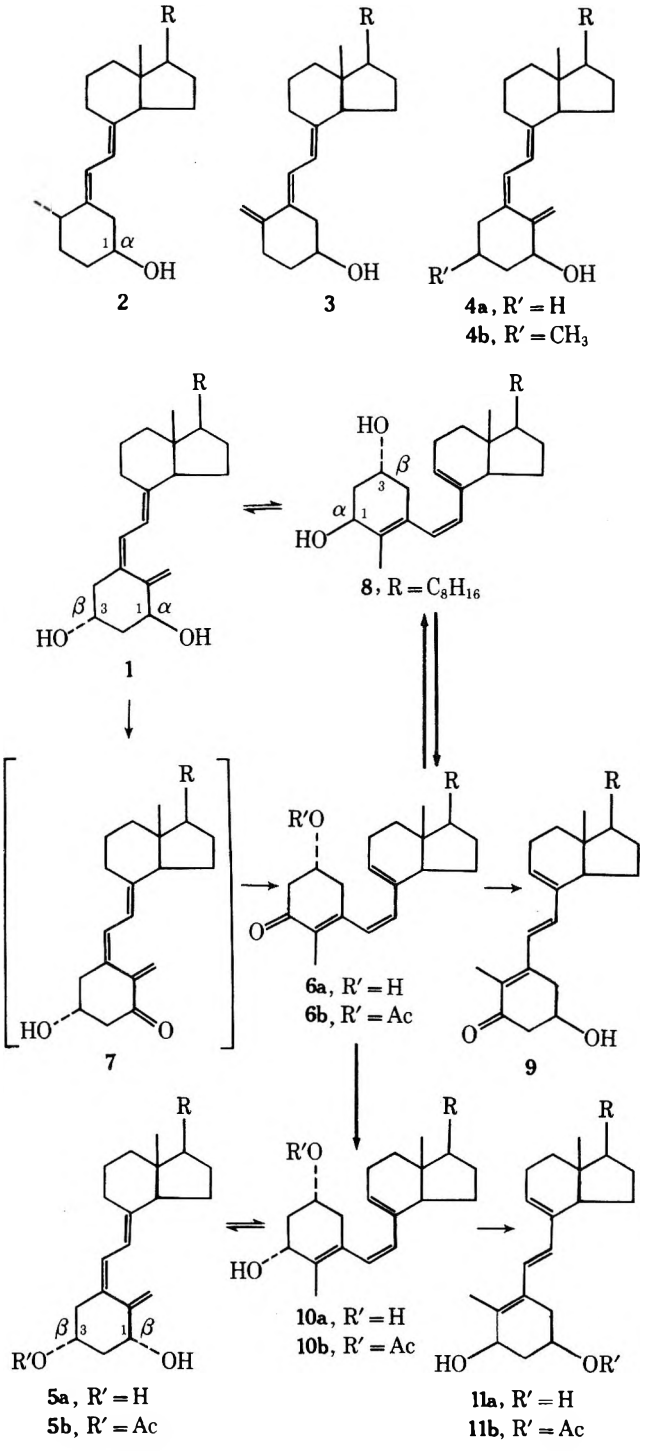
In order to establish whether this 1α-hydroxy substituent is essential for the hormonal activity of the vitamin D_3 analogs, we have synthesized 1β-hydroxyvitamin D_3 (**5a**) the C_1 epimer of 1α-hydroxyvitamin D_3 (**1**) and evaluated its biological activity.[1]

The starting material, 1α-hydroxyvitamin D_3 (**1**), was oxidized with freshly prepared active manganese dioxide in ether resulting in the ketone **6a**. The spectral data indicated that this ketone possessed the previtamin D and not the vitamin D skeleton. Thus its NMR spectrum showed three vinylic protons due to the endocyclic 5(10),6,8-triene system (AB quartet of the two protons at C_6 and C_7 and a broad singlet of the proton at C_9) instead of the four protons of 1-ketovitamin D_3 (**7**) exocyclic 5,7,10(19)-triene system. The UV spectrum of **6a** exhibited two bands at λ_{max} 236 and 287 nm (ε 9500, 10 000) the latter indicating an extension of conjugation of the previtamin chromophore by 28 nm (1α-hydroxyprevitamin D_3 (**8**) absorbs at λ_{max} 259 nm; ε 10 000) in accord with the assigned structure.[5] Furthermore, on exposing **6a** to sunlight in the presence of iodine the UV spectrum changed; the two bands were replaced by one appearing at higher wavelength with enhanced intensity (λ_{max} 320 nm; ε 22 000). This UV change was indicative of a C_6–C_7 double bond $Z \rightleftarrows E$ isomerization, with a formation of tachysterol$_3$ derivative, **9**, possessing an extended planar conjugated 1-keto-triene chromophore.[6]

Oxidation of 1α-hydroxyprevitamin D_3 (**8**)[7] with an active manganese dioxide resulted also in 1-ketoprevitamin D_3 (**6a**). This oxidation, however, proceeded at a faster rate than the corresponding oxidation of 1α-hydroxyvitamin D_3 (**1**) and gave the ketone in higher yield.

The formation of 1-ketoprevitamin (**6a**) instead of 1-ketovitamin **7** from **1** implied that the thermal equilibrium **6a** $\rightleftarrows$ **7** is totally on the side of the 1-ketoprevitamin D_3 (**6a**) differing thus from the equilibrium vitamin $D_3 \rightleftarrows$ previtamin D_3 which is predominant on the side of the vitamin. This shift in the position of the equilibrium is consistent with the increased stability due to the linearly conjugated carbonyl system present in the ketone **6a**.

Reduction of ketone **6a** with sodium borohydride in methanol resulted in a single product 1β-hydroxyprevitamin D_3 (**10a**) which had a UV spectrum identical with 1α-hydroxyprevitamin D_3 (**8**) and isomerized with iodine and light to a tachysterol derivative **11a** (λ_{max} 272, 282, 292 nm; ε 22 000, 25 000, 21 000). The NMR of **10a** differed from that of its C_1



trate was lyophilized. The residue was dissolved in 200 mL of $CHCl_3$, and the insoluble material was removed by filtration. Evaporation of the filtrate under reduced pressure gave 2.66 g (80%) of syrupy residue, homogeneous by TLC on SiO_2 (R_f 0.50; cyclohexane–ethyl acetate–EtOH, 5:3:2): ^1H NMR ($CDCl_3$) δ 1.32 (d, 3 H, J = 6.0 Hz, CH_3C), 3.43 (s, 3 H, CH_3O), 3.55 (s, 3 H, CH_3O), 3.2–4.0 (m, 4 H, CHO), 4.83 (d, 1 H, J = 1.0 Hz, H-1).

Methyl 2-*O*-Methyl-3,4-di-*O*-acetyl-α-L-rhamnoside (4b). **4a** (1 g) was converted to its diacetate by the standard acetic anhydride–pyridine procedure. The product was a syrup, weight 0.88 g. This material was chromatographed on 88 g of silica gel, eluting with $CHCl_3$–$CH_3COOC_2H_5$ (95:5) and collecting 128 10-mL fractions. As a result of weight analysis fractions 40–60 were combined and evaporated to dryness under reduced pressure, weight 0.73 g. Crystallization from ether–Skellysolve B gave 0.27 g, mp 68–71 °C. The crystalline material was sublimed under a pressure of 0.5 mm and a bath temperature of 60–62 °C: yield 0.24 g; mp 70–72 °C (lit.[20] 70–71 °C); R_f 0.45 (SiO_2; $CHCl_3$–$CH_3COOC_2H_5$, 9:1); $[\alpha]_D$ −71° (*c* 2, CH_3OH) (lit.[20] −69°); IR (Nujol) 1740, 1235, 1220, 1150, 1170, 1140, 1125, 1105, 1070, 1050, 975, 965, 930, 915, 910, 885, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, CH_3C), 2.06 and 2.10 (2s, 6 H, CH_3CO), 3.42 (s, 3 H, CH_3O), 3.50 (s, 3 H, CH_3O), 3.63 (d of d, 1 H, J = 2.0 and 3.2 Hz, H-2), 3.80 (m, 1 H, H-5), 4.73 (d, 1 H, J = 2.0 Hz, H-1), 5.10–5.30 (m, 2 H, H-3 and H-4); mass spectrum m/e 245 (M − CH_3O).

Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30. Found: C, 52.42; H, 7.23.

Methyl 2-*O*-Methyl-3-*O*-(*p*-nitrobenzoyl)-α-L-rhamnoside (4c) and Methyl 2-*O*-Methyl-3,4-di-*O*-(*p*-nitrobenzoyl)-α-L-rhamnoside (4d). A solution of 209 mg of **4a** and 500 mg of *p*-nitrobenzoyl chloride in 10 mL of pyridine was allowed to stand at room temperature for 72 h. Water (1 ml) was added and the solution was allowed to stand for 0.5 h, after which it was poured into CH_2Cl_2. The pyridine was removed by thorough washing with 1 N HCl. This was followed by washing with 1 N $NaHCO_3$ solution and water. The CH_2Cl_2 solution was dried ($MgSO_4$), filtered, and evaporated to dryness, leaving an oily residue (375 mg). The product was chromatographed on 40 g of silica gel using gradient elution with benzene–ether (98:2 to 8:2). The eluate was analyzed by TLC on SiO_2 (benzene–ether, 8:2), combining the fractions containing a faster moving material (R_f 0.64) and the fractions containing a slower moving material (R_f 0.28). Evaporation of the R_f 0.64 fractions gave **4d** (72 mg) as indicated by its ^1H NMR: ($CDCl_3$) δ 1.33 (d, 3 H, J = 6.5 Hz, CH_3C), 3.50 (s, 3 H, CH_3O), 3.52 (s, 3 H, CH_3O), 3.87 (m, 1 H, H-2), 3.9–4.3 (m, 1 H, H-5), 4.87 (d, 1 H, J = 2.0 Hz, H-1), 5.62 (m, 2 H, H-3 and H-4), 8.21 (s, 8 H, aromatic).

Evaporation of the R_f 0.28 fractions gave **4c** (233 mg), which was crystallized from benzene–ether and from ether–methylene chloride: mp 139–139.5 °C; IR (Nujol) 3470, 1725, 1605, 1525, 1490, 1345, 1275, 1185, 1120, 1115, 1100, 1050, 1040, 885, 835, 725, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, 3 H, J = 5.8 Hz, CH_3C), 3.37 (s, 3 H, CH_3O), 3.42 (s, 3 H, CH_3O), 3.68 (q, 1 H, J = 2.0 and 3.2 Hz, H-2), ~3.75 (m, 1 H, H-2 or H-4), 3.80 (m, 1 H, H-2 or H-4), 4.73 (d, 1 H, J = 2.0 Hz, H-1), 5.27 (q, 1 H, J = 9.5 and 3.2 Hz, H-3), 8.22 (m, 4 H, aromatic).

Anal. Calcd for $C_{15}H_{19}NO_8$: C, 52.78; H, 5.61. Found: C, 52.77; H, 5.21.

Methyl 2,4-Di-*O*-methyl-α-L-rhamnoside (4e). The filtrate from crystallization of **2a** after methanolysis of 5.0 g of **1b** was evaporated under reduced pressure until the CH_3OH was removed. The residue was mixed with a solution of 75 mL of pyridine in 500 mL of water, and the resulting solution was stirred overnight with 125 mL of Dowex 2 (OH^-). The resin was removed by filtration, and the filtrate was concentrated to a syrup by distillation under 25–30 mm at 45 °C. Water (50 ml) was added to the residue, and the solution was adjusted to pH 9.0 with 1.0 N NaOH solution. The basic solution was extracted with three 50-mL portions of $CHCl_3$. The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure, leaving a mobile liquid, weight 1.01 g, homogeneous by TLC (R_f 0.60; SiO_2; cyclohexane–ethyl acetate–ethanol, 5:3:2). The liquid was chromatographed on 50 g of silica gel, eluting with Skellysolve B–acetone (4:1) until 92 5-mL fractions were collected. Fractions 40–62 (weight maximum) were combined and evaporated under reduced pressure to give a residue weighing 0.93 g. Distillation gave 0.30 g of colorless liquid: bp 82 °C (0.3 mm); $[\alpha]_D$ −67.7° (c 2, CH_3OH) (lit.[21a] −66.6°); $[\alpha]_D$ −56.0° (*c* 2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3 H, J = 6.4 Hz, CH_3C), 3.35 (s, 3 H, CH_3O), 3.49 (s, 3 H, CH_3O), 3.57 (s, 3 H, CH_3O), 2.74 (d, 1 H, J = 8.8 Hz, OH), 2.97 (t, 1 H, J = 9.0 and 8.3 Hz, H-4), 3.45 (d of d, 1 H, J = 3.7 and 1.5 Hz, H-2), 3.55 (m, 1 H, H-5), 3.80 (m, 1 H, J 9.0, 8.8, and 3.7 Hz, H-3), 4.71 (d, 1 H, J = 1.5 Hz, H-1); mass spectrum m/e 175.0978 (M − CH_3O) (calcd for $C_8H_{15}O_4$, 175.0970).

Anal. Calcd for $C_9H_{18}O_5$: C, 52.40; H, 8.80. Found: C, 51.90; H, 9.87.

Registry No.—**1a,** 11033-34-4; **1b,** 54526-94-2; **1c,** 63493-71-0; **2a,** 57847-74-2; **2b,** 57847-75-3; **2c,** 63493-72-1; **3a,** 63493-73-2; **3b,** 63493-74-3; **4a,** 59013-63-7; **4b,** 63527-42-4; **4c,** 63493-75-4; **4d,** 63493-76-5; **4e,** 35939-75-4; *p*-nitrobenzoyl chloride, 122-04-3.

References and Notes

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1035, 960, 755 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.43 (s, 3 H, CH_3C), 3.48 (s, 3 H, CH_3O), 3.62 (d, 1 H, J = 3.0 Hz, H-8), 3.90 (s, 3H, CH_3O), 5.24 (d, 1 H, J = 3.0 Hz, H-7), 6.75 (d, 1 H, J = 2.5 Hz, H-3), 7.10 (d, 1 H, J = 2.5 Hz, H-1), 8.00 (s, 1 H, H-11); mass spectrum m/e 414.09538 (15.7; calcd for $C_{21}H_{18}O_9$, 414.09508), 340.05633 (− $CH_3OCHCHOH$, 29.4; calcd for $C_{18}H_{12}O_7$, 340.05830), 326.04236 (− $CH_3OCHC(OH)$-CH_3, 97.2; calcd for $C_{17}H_{10}O_7$, 326.04265), 298.04748 (− CH_3O-$CHC(OH)CH_3CO$, 36.4; calcd for $C_{16}H_{10}O_6$, 298.04773).

Anal. Calcd for $C_{21}H_{18}O_9$: C, 60.87; H, 4.38. Found: C, 60.14; H, 4.77.

(b) From Steffimycin B (1b). **1b** (5 g) was treated with acidic methanol as above, except that heating was continued for 48 h only. The first fraction weighed 2.2 g. A second fraction of 1.6 g was obtained by concentration and refrigeration of the filtrate from the first fraction. These fractions were combined and chromatographed on 360 g of silica gel using cyclohexane–ethyl acetate–ethanol (6:3:1) as the eluting system and collecting 486 10-mL fractions. Fractions 290–486 were combined and concentrated under reduced pressure. The residue was recrystallized from acetone, yield 1.07 g, mp 253–256 °C. The product had the same R_f (0.38) on TLC (SiO_2, cyclohexane–ethyl acetate–ethanol, 5:3:2) as did **2a**. Its IR spectrum was the same as that of **2a**, and a mixture melting point was not lowered.

7-Deoxysteffimycinone (2b). **1a** (1 g) was dissolved in CH_3OH, and 300 mg of 10% Pd/C was added. The mixture was shaken under hydrogen at an initial pressure of 45 psi for 93 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was pratitioned between CH_2Cl_2 and H_2O, and the two-phase system was filtered. The water layer was removed, and the organic layer was washed with water, a solution containing an excess of $FeCl_3$ in 1 N HCl, and again with water. The organic phase was removed and concentrated to dryness under reduced pressure. The residue was chromatographed on 100 g of silica gel using CH_2Cl_2–CH_3OH (97:3) for elution, which was continued until the material having R_f 0.40 (SiO_2; CH_2Cl_2–CH_3OH, 97:3) had been eluted. The fractions containing this material were combined and evaporated to dryness under reduced pressure, weight 160 mg. Recrystallization from CH_3OH gave 85 mg, mp 191–194 °C. Two recrystallizations from EtOH gave: mp 191.5–194 °C; UV (EtOH) λ_{max} 213 nm (ϵ 25 700), 236 (ϵ 27 400), 258 sh (ϵ 19 520), 274 sh (ϵ 21 400), 283 (ϵ 23 450), 458 (ϵ 14 800); UV (0.01 N methanolic KOH) λ_{max} 230 sh nm (ϵ 25 650), 268 (ϵ 23 700), 514 (−11 670); IR (Nujol) 3500, 1705, 1675, 1620, 1605 sh, 1560, 1305, 1240, 1160, 1100, 965, 755 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.33 (s, 3 H, CH_3C), 3.22 (m, 2 H, CH_2), 3.37 (s, 3 H, CH_3O), 3.77 (m, 1 H, H-8), 3.90 (s, 3 H, CH_3O), 6.74 (d, 1 H, J = 2.5 Hz, H-3), 7.17 (d, 1 H, J = 2.5 Hz, H-1), 8.02 (s, 1 H, H-7); mass spectrum m/e 398.09730 (calcd for $C_{21}H_{18}O_8$, 398.1002), 324 (98.5), 323 (100), 310 (9.8), 295 (39.8), 282 (20.1).

Anal. Calcd for $C_{21}H_{18}O_8$: C, 63.31; H, 4.55. Found: C, 63.52; H, 4.57.

4,6-Di-*O*-methylsteffimycin (1c). **1a** (1g, 1.67 mmol) was dissolved in 100 mL of acetone, and the air above the solution was displaced with N_2. K_2CO_3 (1 g) was added, followed by 650 mg (4.7 mmol) of $(CH_3)_2SO_4$, and the mixture was heated under reflux for 20 h. Water was added, and the reaction mixture was stirred for 45 min. The acetone was removed by evaporation under reduced pressure. The residue was mixed with CH_2Cl_2, and the mixture was extracted with 5% NaOH solution. The CH_2Cl_2 solution was washed with a saturated ammonium chloride solution and dried ($MgSO_4$). After filtration, the solution was evaporated to dryness under reduced pressure, leaving a residue which was crystallized from CH_3OH. The product obtained was chromatographed on 100 g of silica gel using CH_2Cl_2–CH_3OH (95:5). The fractions containing the first color maximum off the column were combined and evaporated to dryness under reduced pressure. The residue (500 mg) was recrystallized three times from CH_3OH: yield 307 mg; mp 220–224 °C; R_f 0.39 (SiO_2; $CHCl_3$–CH_3OH, 9:1); UV (EtOH) λ_{max} 248 nm (ϵ 25 890), 283 sh (ϵ 16 860), 396 (ϵ 5240); IR (Nujol) 3635, 3570, 3510, 3400, 1705, 1670, 1650, 1590, 1555, 1370, 1340, 1320, 1285, 1275, 1235, 1090, 1050, 1025, 980, 950, 910, 840, 815, 740 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.30 (d, 3 H, J = 6.0 Hz, CH_3CH), 1.43 (s, 3 H, CH_3C), 3.35 (s, 3 H, CH_3O), 3.53 (s, 3 H, CH_3O), 3.68 (d, 1 H, J = 2.2 Hz, H-8), 3.93 (s, 6 H, CH_3O), 3.98 (s, 3 H, CH_3O), 4.68 (d, 1 H, OH), 4.90 (d, 1 H, OH), 5.15 (d, 1 H, J = 2.2 Hz, H-7), 5.42 (d, 1 H, J = 2.2 Hz, anomeric), 5.55 (s, 1 H, OH), 6.84 (d, 1 H, J = 2.5 Hz, H-3), 7.14 (d, 1 H, J = 2.5 Hz, H-1), 8.22 (s, 1 H, H-11); mass spectrum m/e 602 (M^+, 4.5), 472 (9.0), 442 (21.6), 426 (89.1), 383 (100), 352 (82.9).

Anal. Calcd for $C_{30}H_{34}O_{13}$: C, 59.79; H, 5.69. Found: C 59.84; H 5.93.

4,6-Di-*O*-methylsteffimycinone (2c). **2a** (100 g, which also contained considerable **1a**) was dissolved in 3.5 mL of acetone, and 77.0 g of K_2CO_3 and 57 mL of $(CH_3)_2SO_4$ were added. The mixture was stirred and heated under reflux under N_2 for 21.5 h. After the reaction mixture had cooled to room temperature it was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 containing a small amount of CH_3OH and washed with three portions of 5% NaOH solution. The CH_2Cl_2 solution was washed with H_2O and dried (Na_2SO_4). Filtration and evaporation under reduced pressure gave 105 g. This material was chromatographed in two portions, 34 and 71 g. The smaller portion was chromatographed on 2.4 kg of silica gel, eluting with 10 L of CH_2Cl_2–CH_3OH (98:2), 10 L (97:3), and 4 L (96:4). The second fraction removed from the column (as indicated by TLC) was isolated by evaporation under reduced pressure, yield 17.5 g. The larger fraction was purified similarly to give 36.0 g. These fractions were combined and recrystallized from CH_2Cl_2–CH_3OH, yield 42.5 g, mp 232.5–234.5 °C. A small sample was recrystallized from acetone for analysis: R_f 0.32 (SiO_2; $CHCl_3$–CH_3OH, 95:5), 0.46 (SiO_2; $CH_3COOC_2H_5$–C_2H_5OH–H_2O, 92:5:3); UV (EtOH) λ_{max} 248 nm (ϵ 25 640), 283 sh (ϵ 18 560), 395 (ϵ 10 060); IR (Nujol) 3470, 3420, 1705, 1675, 1660, 1590, 1555, 1370, 1340, 1320, 1285, 1250, 1195, 1170, 1150, 1095, 1040, 1025, 975, 955, 905, 860, 835, 740 cm^{-1}; ^1H NMR (DMF-d_7) δ 1.43 (s, 3 H, CH_3C), 3.59 (s, 3 H, CH_3O), 3.77 (d, 1 H, J = 2.5 Hz, H-8), 4.09 (s, 6 H, $2CH_3O$), 4.09 (s, 3 H, CH_3O), 5.44 (d, J = 2.5 Hz, H-7), 7.01 (d, 1 H, J = 2.5 Hz, H-3), 7.26 (d, 1 H, J = 2.5 Hz, H-1), 8.44 (s, 1 H, H-11); mass spectrum m/e 442.1267 (calcd for $C_{23}H_{22}O_9$, 442.1264).

Anal. Calcd for $C_{23}H_{22}O_9$: C, 62.44; H, 5.02. Found: C, 62.28; H, 5.14.

Steffimycinol (3a). **2a** (16 g) was reduced in four equal batches as follows: a solution of 4.0 g (9.7 mmol) of **2a** in 200 mL of 0.2 N NaOH solution was stirred while adding dropwise over 0.5 h a solution of 280 mg (7.6 mmol) of $NaBH_4$ in 40 mL of 0.2 N NaOH solution. Stirring was continued for another 0.5 h, followed by addition of 50 mL of 2 N HCl. The resulting mixture was extracted with one 200-mL portion and two 100-mL portions of EtOAc. The extracts were combined, dried ($MgSO_4$), filtered, and evaporated to dryness under reduced pressure. Sixteen grams of **2a** gave 13.2 g of residue. This material (10.8 g) was deposited from solution on 37 g of silica gel, which was added to the top of a column containing 1080 g of silica gel packed in $CHCl_3$–CH_3OH (97:3). Elution was done with the same solvent system until those fractions containing **3a**, as determined by TLC (R_f 0.18; SiO_2; $CHCl_3$–CH_3OH, 95:5), were eluted. Those fractions containing pure **3a**, also determined by TLC, were combined and evaporated to dryness under reduced pressure: yield 3.7 g (23%); mp 230 °C dec; UV (EtOH) λ_{max} 227 nm (ϵ 35 400), 269.5 (ϵ 21 250), 285 sh (ϵ 17 150), 435 (ϵ 13 200); IR (Nujol) 3600, 3560, 3300, 1675, 1605, 1570, 1565, 1395, 1300, 1275, 1255, 1215, 1160, 1100 cm^{-1}; ^1H NMR (Me_2SO-d_6–D_2O) δ 1.38 (s, 3 H, CH_3C) 3.32 (d, 1 H, J = 6.0 Hz, H-8), 3.63 (s, 3 H, CH_3O), 3.83 (s, 3 H, CH_3O), 4.42 (s, 1 H, H-10), 4.95 (d, 1 H, J = 6.0 Hz, H-7), 6.65 (d, 1 H, J = 3.0 Hz, H-3), 7.00 (d, 1 H, J = 3.0 Hz, H-1), 7.80 (s, 1 H, H-11); mass spectrum m/e 416 (M^+, 1.3), 398 (14.9), 328 (100), 310 (90.2), 299 (22.6), 282 (21.8).

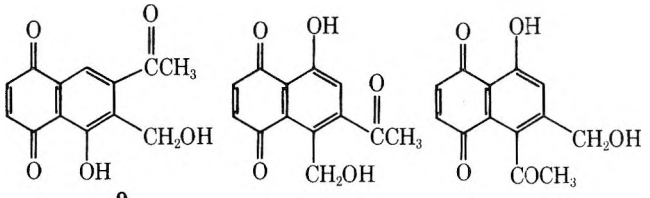
Anal. Calcd for $C_{21}H_{20}O_9$: C, 60.57; H, 4.85. Found: C, 60.55; H, 4.97.

7-Deoxysteffimycinol (3b). A solution of 2.0 g (4.8 mmol) of **2a** in 100 mL of 0.2 N NaOH solution was stirred while adding dropwise 920 mg (24.2 mmol) of $NaBH_4$ dissolved in 46 mL of 0.2 N NaOH solution. Stirring was continued 1 h after addition was completed. EtOAc (150 mL) and 35 mL of 2 N HCl were added. The organic layer was removed, and the aqueous layer was extracted with two 100-mL portions of ethyl acetate. The organic layers were combined, dried ($MgSO_4$), and evaporated to dryness under reduced pressure, weight 1.53 g. Material prepared in this way (2.2 g) was recrystallized twice from $CHCl_3$–CH_3OH (97:3) by dissolving in ~900 mL and concentrating: yield, 1.12 g; mp 274–276 °C; R_f 0.44 (SiO_2, $CHCl_3$–CH_3OH; 95:5); UV (EtOH) λ_{max} 226 nm (ϵ 34 000), 249 sh (ϵ 17 550), 273 (ϵ 24 500), 435 (ϵ 13 500); IR (Nujol) 3490, 1660, 1625, 1610, 1560, 1390, 1315, 1300, 1275, 1240, 1210, 1190, 1095, 970, 805, 785, 760 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.37 (s, 3 H, CH_3C), 3.33 (m, 5 H, H-7, H-8, OH), 3.44 (s, 3 H, CH_3O), 392 (s, 3 H, CH_3O), 4.33 (s, 1 H, H-10), 6.85 (d, 1 H, J = 2.6 Hz, H-3), 7.17 (d, 1 H, J = 2.6 Hz, H-1), 7.87 (s, 1 H, H-11); mass spectrum m/e 400.1172 (calcd for $C_{21}H_{10}O_8$, 400.1158), 350 (32.9) 339 (49.7), 325 (45.7), 312 (100), 284 (70.9).

Anal. Calcd for $C_{21}H_{20}O_8$: C, 63.00; H, 5.04. Found: C, 62.51; H, 4.99.

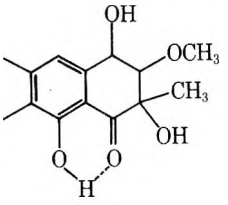
Methyl 2-O-Methyl-α-L-rhamnoside (4a). The filtrate after crystallization of **2a** derived from 10 g of **1a** was mixed with 150 mL of pyridine, and 1 L of H_2O was added. The solution was extracted repeatedly with 200-mL portions of CH_2Cl_2 until the red color was removed. The aqueous solution was stirred overnight with 300 mL of Dowex 2 (OH^-). The resin was removed by filtration, and the fil-

proton which gives rise in the ^1H NMR spectrum to a singlet at δ 7.92 in DMF-d_7. Since the carbonyl group in ring A is no longer present, the downfield position of this proton arises from its position α to the anthraquinone carbonyl, and the linear tetracyclic system must be the correct one. Furthermore, a structure such as 8 would be expected to have both anthraquinone carbonyl groups hydrogen bonded, as is the case in tetrangulol.[18] The ^{13}C NMR spectrum of **2a** provides some evidence bearing on this point. Using values taken from the literature for the chemical shifts in the ^{13}C NMR spectrum of naphthoquinone, and using correction values obtained from Stothers,[17] it can be estimated that the unsubstitued α carbon in **9** would have a chemical shift of δ 117.8 in its ^{13}C NMR spectrum. The corresponding values for the unsubstituted β carbons in **10** and **11** would be δ 119.4 or 124.2 for **10** and δ



122.6 or 127.4 in **11**. The values for the unsubstitued aromatic carbon atom in ring B of **1a** and **2a** are δ 115.2 and 115.3, respectivley. This would be more consistent with the linear tetracyclic system, as in **2a**.

It then remains to establish the orientation of ring A. The frequency of 1710 cm^{-1} found for the ketonic carbonyl in the infrared spectrum of **1a** is higher than would be expected for a carbonyl group attached to an aromatic ring. If the carbonyl group is peri to the hydroxyl group in ring B, as in **12**, hydro-



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gen bonding would be expected, making such a high infrared carbonyl frequency even more surprising. Consequently, this piece of evidence would better fit the **2a** orientation. A number of aglycones contain the C-6, C-7 dihydroxyl arrangement indicated in **2a**. In such cases, the proton at C-7 shows chemical shifts of δ 5.10–5.45 in ^1H NMR spectra.[13d,15c] In steffimycinone, the corresponding resonance is at δ 5.25, which argues strongly for a similar relationship in **2a** and requires that the ketonic carbonyl be at C-10. Bell[19] has shown that metal hydride reduction of phenolic carbonyl compounds leads to reduction to methylene if the carbonyl is ortho or para to the phenolic hydroxyl, but only to a hydroxyl group if the relationship is meta. Reduction of **2a** using an excess of sodium borohydride gave a new compound (**3b**), in which two transformations were evident. In the ^1H NMR spectrum of **3b** the resonance at δ 5.25 had disappeared, showing that the secondary hydroxyl group in ring A was now absent. In addition, the infrared spectrum of **3b** did not have a bond for the ketonic carbonyl. A new singlet at δ 4.33 in the ^1H NMR spectrum of **3b** could only arise by reduction of the ketonic carbonyl to a hydroxyl group. In view of Bell's findings, the only relationship of the substituents in rings A and B which could give such a reduction would be that indicated in **2a**, which must represent the structure of steffimycinone aside from stereochemistry at the asymmetric carbon atoms. At present, very little can be deduced about these configurations. A coupling constant of 3.0 Hz between protons at C-7 and C-8 would suggest that they cannot be diaxial, and therefore the hydroxyl at C-7 and the methoxyl at C-8 cannot both be equatorial.

As previously mentioned, acidic methanolysis of **1a** and **1b** gave, in addition to **2a, 4a** and **4e**, respectively. The molecular formulas of the two antibiotics, when compared to that of **2a**, indicated that the products, taking into account the addition of CH_3OH, would have molecular formulas of $C_8H_{16}O_5$ (**4a**) and $C_9H_{18}O_5$ (**4b**). Such formulas suggested that these compounds were sugars, as did their ready removal by acidic methanolysis. The ^1H and ^{13}C NMR spectra of **4a** showed quite clearly that it was an eight-carbon compound having a CH_3C and two CH_3O groups, an anomeric carbon and proton, four carbon atoms substituted by oxygen and carrying protons, and suggested a rhamnose configuration. Acetylation formed a diacetate, which was found to be identical with the diacetate of methyl 2-*O*-methyl-α-L-rhamnoside by comparison of its melting point, rotation, and ^1H NMR spectrum with the same properties reported in the literature.[20] The infrared and mass spectra were also consistent with such a structure. Thus, steffimycin must have the structure, aside from stereochemistry, represented by **1a**. Keller-Schierlein et al.[14,20] have proposed that the configuration at C-1 of the sugar in aranciamycin is β on the basis of a ^1H NMR chemical shift at δ 5.49 appearing as a singlet. An almost identical resonance (δ 5.43) occurs in the spectrum of **1a**, but it is not well resolved and appears to be a doublet with a small coupling constant. This may be evidence for an α configuration at C-1 in the sugar in **1a**, as is the case in most anthracyclines.

In view of the structure of **4a** and the differences and similarities observed between **4a** and **4e**, it seemed probable that **4e** was an *O*-methyl analogue of **4a** with methylation having occurred at the oxygen on C-3 or C-4. It was also possible that **4e** was either α- or β-methyl 3,4-di-*O*-methyl-rhamnoside. A comparison of the rotation of **4e** in $CHCl_3$ and CH_3OH with values reported in the literature[21] gave methyl 2,4-di-*O*-methyl-α-L-rhamnoside as the closest match. The ^1H NMR spectrum of **4e** substantiates the identity. Three singlets (δ 3.35, 3.49, and 3.57) show the presence of three methoxyl groups. A doublet at δ 4.71 (J = 1.5 Hz) represents the anomeric hydrogen, which is coupled to a proton at C-2 (δ 3.45, J = 1.5 and 3.7 Hz) which resonates as a doublet of doublets. In such case, the H-1, H-2 relationship is ee or ea, as is the relationship of H-2 to H-3 (δ 3.80). The latter gives rise to six lines with J values of 3.7 (H-2, H-3), 9 (H-3, H-4), and 8.8 Hz (H-3 and OH). The hydroxyl proton has a chemical shift of δ 2.74 (d, J = 8.8 Hz). The proton on C-4 resonates as a triplet at δ 2.97 (J = 8.3 and 9 Hz), with the smaller coupling constant arising from coupling with a proton on C-5 appearing as a multiplet at δ 3.55. These coupling constants establish that the H-3, H-4 protons are aa, as are H-4 and H-5. The proton on C-5 is coupled with the CH_3C proton, which shows as a doublet (δ 1.29, J = 6.4 Hz). This spectrum establishes that **4e** is methyl 2,4-di-*O*-methylrhamnoside and the rotation establishes that it is α-L. The structure of steffimycin B can then be depicted as **1b**, although again stereochemistry is not completely established, but must be the same as in **1a**.

Experimental Section

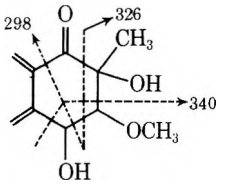
Steffimycinone (2a). (a) From Steffimycin (1a). A solution of 5 g (8.7 mmol) of **1a** in 500 mL of 1 N methanolic hydrochloric acid was boiled under reflux for 128 h. The reaction mixture was refrigerated and filtered, yield 2.84 g. A second crop of 0.5 g was obtained from the filtrate. These fractions were combined and recrystallized from CH_3OH to give 2.45 g, mp 248–250 °C, and a second crop of 0.74 g, mp 245–249 °C, yield 87%. Two further recrystallizations from CH_3OH gave orange prisms: mp 250–251.5 °C; R_f 0.31 (SiO_2; CH_2Cl_2–CH_3OH, 95:5); UV (EtOH) λ_{max} 213 nm (ϵ 26 300), 236 (ϵ 28 180), 257 sh (ϵ 20 420), 279 (ϵ 20 430), 439 (ϵ 14 130); IR (Nujol) 3500, 3070, 1710, 1675, 1625, 1600, 1560, 1315, 1250, 1200, 1160, 1105,

Table I. ^{13}C NMR Chemical Shifts[a]

Position	1a Me_2SO-d_6	1b Me_2SO-d_6	1c Me_2SO-d_6	2a Me_2SO-d_6	2b DMF-d_7	2c Me_2SO-d_6	3a Me_2SO-d_6	4a $CDCl_3$	4e $CDCl_3$
C-10	198.5	198.4	200.0	199.3	199.6	199.4	72.9 (69.2)		
C-5	189.1	189.5	181.4	189.6	191.3	181.5	190.2		
C-12	179.3	180.0	179.7	180.0	181.2	179.4	180.9		
C-2	166.5	166.6	163.8	166.5	168.1	163.6	166.2		
C-4	164.6	164.7	161.4	164.6	166.4	161.4	164.5		
C-6	161.3	161.2	160.2	161.3	161.5	160.2	159.9		
C-10a	135.4	135.3	138.4	136.1	137.6	142.0	149.1		
C-11a	134.1	134.6	135.4	135.4	136.7	135.3	134.9		
C-12a	133.3	133.1	135.2	134.6	136.0	133.9	133.3		
C-6a	132.4	132.9	133.7	132.2	132.2	133.6	131.2		
C-5a	117.9	118.4	129.9	117.9	118.1	130.1	113.6		
C-11	115.2	115.3	118.6	115.3	117.0	119.1	118.0		
C-4a	109.5	110.0	117.0	109.9	111.0	116.9	109.9		
C-1	108.0	108.1	104.7	107.9	109.2	104.6	107.7		
C-3	106.1	106.6	104.0	106.4	107.2	102.5	106.4		
C-7	70.6	70.2	72.0	62.8	26.9	63.5	69.2 (72.9)		
C-8	85.5	85.9	86.1	87.5	84.5	87.6	87.6		
C-9	76.2	76.1	76.1	76.3	78.0	76.3	75.2		
CH_3O (C-2)	56.3	56.4	56.3	56.3	57.2	56.2	56.4		
CH_3O (C-8)	59.7	59.7	59.8	59.5	58.8	59.6	60.4		
CH_3O (C-4)			55.8			55.7			
CH_3O (C-6)			62.6			63.1			
CH_3 (C-9)	23.3	23.3	23.4	23.6	22.2	23.8	21.7		
C-1′	100.9	100.7	101.0					97.7	97.5
C-2′	80.5	80.9	80.9					80.5	80.5
C-3′	71.1	71.6	72.2					71.6	71.3
C-4′	72.2	82.3	72.3					73.5	83.8
C-5′	70.3	68.7	70.3					68.0	67.2
CH_3 (C-5′)	17.8	17.8	17.8					17.6	17.9
CH_3O (C-2′)	58.6	59.9	58.7					58.9	58.9
CH_3O (C-4′)		58.5							60.7
CH_3O (C-1′)								54.0	54.7

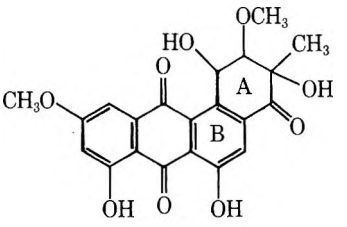
[a] Assignments were made on the basis of comparisons with other anthracycline antibiotics and compounds derived from them, internal comparisons, values derived from similar compounds in the literature, off-resonance decoupling, and theoretical considerations. Values given are in parts per million downfield from Me_4Si.

it must have the aliphatic methoxyl group as a substituent.[17] In the high-resolution mass spectrum of **2a**, a strong ion (29.4%) is found at 340.05633, indicating a loss of $C_3H_6O_2$. Such a loss can occur only if the aliphatic methoxyl is adjacent to the benzylic carbon, thus making possible loss of the fragment $HOCHCHOCH_3$. These results establish that the second hydroxyl group is attached to a quaternary carbon atom substituted by CH_3, and the resonance in the ^{13}C NMR spectrum of **2a** at δ 76.3 must arise from such a carbon atom. The mass spectrum of **2a** has a base peak at 326 (M − 88) and a very strong peak at 298 (M − 116). These transitions have metastable ions occurring at 257.0 and 214.5; and this information, combined with high-resolution mass measurements on the 326 and 298 ions, establishes that these fragments arise, respectively, by loss of $C_4H_8O_2$ and $C_5H_8O_3$ fragments from the molecular ion. The four-carbon fragment can only be $CH_3OCHC(OH)CH_3$, and the five-carbon fragment then is this plus the ketonic carbonyl as indicated in **7**, which shows the structure of ring A necessitated by these data.



7

Such a part structure as **7** can be attached to the anthraquinone portion of **2a** in four ways. Both linear attachment as in **2a** and angular attachment as in **8** are possible. Furthermore, each type of attachment can have the orientation of the ketonic carbonyl either as in **2a** or as in **8**. It has already been suggested that the aromatic proton which is on ring B is α to a quinone carbonyl because of its chemical shift (about δ 8) in the ^1H NMR spectra of various compounds discussed. Naphthoquinone was cited as an example supporting this view. Several anthracycline antibiotics have protons α and β to ketonic carbonyls which exhibit similar patterns of chemical shifts in their ^1H NMR spectra. Examples of these are ϵ_1-pyrromycinone, in which an α proton resonates at δ 7.68 while β protons have chemical shifts of δ 7.29,[15c] and α_2-rhodomycinone, which has chemical shifts of δ 8.28 and 7.29 arising from α and β protons, respectively.[15d] However, it might be possible that a proton ortho to a carbonyl as in **8** might resonate at about δ 8, since this is the case with acetophenone. Such considerations would leave as the three possible structures the two orientations of the linear structure and **8**. Reduction of **2a** with a limited amount of sodium borohydride forms steffimycinol (**3a**) by reduction of the ketonic carbonyl group, as would be expected. Spectral evidence (particularly ^{13}C NMR) shows quite clearly that no other change has occurred. In the resultant product (**3a**) there is a



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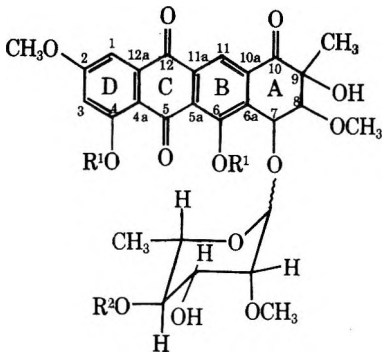
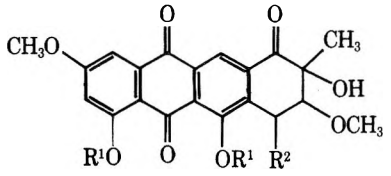
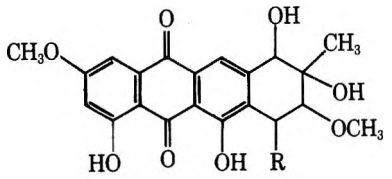


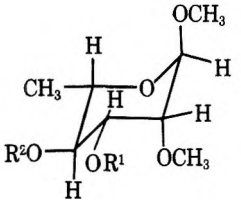
1a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = CH_3$
c, $R^1 = CH_3$; $R^2 = H$



2a, $R^1 = H$; $R^2 = OH$
b, $R^1 = R^2 = H$
c, $R^1 = CH_3$; $R^2 = OH$



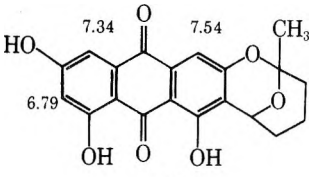
3a, R = OH
b, R = H



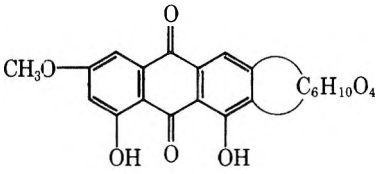
4a, $R^1 = R^2 = H$
b, $R^1 = R^2 = CH_3CO$
c, $R^1 = p\text{-}NO_2C_6H_4CO$; $R^2 = H$
d, $R^1 = R^2 = p\text{-}NO_2C_6H_4CO$
e, $R^1 = H$; $R^2 = CH_3$

similar to **2a** in both its ultraviolet and infrared spectra, and thus must contain the chromophore. Analytical data and high-resolution mass spectrometry establish that the molecular formula is $C_{21}H_{18}O_8$. The ^{13}C and ^1H NMR spectra were very similar to those of **2a** in that three aromatic carbon atoms attached to protons, two CH_3O and a CH_3C group, are indicated. However, the doublet in the proton spectrum with a chemical shift of δ 5.24 has disappeared and a new resonance at δ 3.22, arising from 2 H, has appeared. The corresponding change in the ^{13}C NMR spectrum was from δ 62.8 to 26.9. The above data indicate that **2b** (7-deoxysteffimycinone) results from a reductive carbon–oxygen cleavage to remove a sugar moiety attached at a benzylic position.[13d] Methylation of **1a** using dimethyl sulfate and base formed **1c**. The ^1H and ^{13}C NMR spectra of **1c** quite clearly indicated that two new methyl groups attached to oxygen had been introduced. The analysis and mass spectrum were also consistent with formation of a dimethyl ether of **1a**. Similar treatment of **2a** also gave a dimethyl ether (**2c**), as shown by the same sort of evidence. The ^{13}C NMR spectral data derived from **2c** establish that methylation occurred at two phenolic hydroxyl groups.

The ^1H NMR spectra of **1a**, **2a**, and **2b** all indicate the presence of three aromatic protons. Two of these are coupled (J = 2.5 Hz), suggesting that they are 1,3 to each other. The other is a singlet with chemical shifts of δ 7.97–8.02. In addition to the 1,8-dihydroxyanthraquinone system, a methoxyl group attached to an aromatic ring and a $C_6H_{10}O_4$ moiety are present in **2a**. There are then three positions in the anthraquinone which are not substituted and three which are substituted by a combination of CH_3O and OH. This leaves two positions unaccounted for, so the $C_6H_{10}O_4$ moiety must be attached at these positions. The two protons meta to each other can only be in a ring bearing a hydroxyl group meta to a methoxyl group. The other aromatic proton must be α to a carbonyl, as its chemical shift in its ^1H NMR spectrum is too far downfield for that of a β proton.[13d,15] For example, naphthoquinone has chemical shifts of δ 8.07 and 7.77 for α and β protons, respectively. The pattern of aromatic proton resonance is very similar to the similarly substituted averufin[16] (**5**), although



5



6

differing in absolute values. The partial structure **6** would be a reasonable one for steffimycinone on the basis of these data, although an alternative angular attachment of the six-carbon moiety was possible.

In view of both the ^{13}C and ^1H NMR spectra of **1a** and its degradation products, there must be present in the six-carbon moiety a methoxyl group and a CH_3C on a fully substituted carbon atom. The 1710-cm^{-1} band in the infrared spectrum of **1a** suggests a ketone. This suggestion is confirmed by a chemical shift of δ 198.5 in the ^{13}C NMR spectra of **1a** and one at δ 199.3 in the spectrum of **2a**. The ^{13}C NMR spectra of **2a** and **2c** have three resonances in the range of δ 62.8–87.6. These must arise from aliphatic carbon atoms singly bonded to oxygen, of which one must be that of a CH_3O. The infrared spectrum of **2c** has bands at 3580 and 3420 cm^{-1}, establishing the presence of two hydroxyl groups. The ready conversion of **1a** to **2b** by catalytic hydrogenation indicates an oxygen in a benzylic position, which must be the site of attachment of the sugar. In the formation of **2a**, the sugar is lost, so the substituent at the benzylic position in **2a** must be one of the hydroxyl groups. The ^1H NMR spectrum of **2a** has a resonance appearing as a doublet at δ 5.24, which would be a suitable signal for a proton on a benzylic carbon substituted by oxygen. This proton has a coupling constant of 3 Hz, as does a proton, also appearing as a doublet, at δ 3.62. Consequently, these protons must be on adjacent carbon atoms. In the ^{13}C NMR spectrum of **2a** a carbon bearing a proton resonates at δ 62.8. This must be the benzylic carbon, since it shifts to δ 70.6 in the ^{13}C NMR spectrum of **1a**, in which it is attached in an ether linkage to the sugar moiety. In addition, there is a carbon atom giving a signal in the ^{13}C NMR spectrum of **2a** at δ 87.5. This carbon, as shown by off-resonance decoupling, also has a proton attached. Therefore, it must be the carbon adjacent to the benzylic carbon. Also, because of its resonance at δ 87.5,

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Structures of Steffimycin and Steffimycin B[1]

Robert C. Kelly,* Ilse Schletter, James M. Koert, Forrest A. MacKellar, and Paul F. Wiley*[2]

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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A combination of chemical degradation and spectral studies has established that the structures of steffimycin and steffimycin B are those indicated by structures **1a** and **1b**, respectively.

The discovery of the antibiotic steffimycin (**1a**), produced by *Streptomyces steffisburgensis* and having activity against gram-positive organisms, was reported by Bergy and Reusser[3] some years ago. Subsequently, a description of the isolation of an antibiotic, steffimycin B (**1b**), having very similar physical, chemical, and biological properties, was published.[4] Brodasky and Reusser,[4] on the basis of private communications from Dr. R. C. Kelly, proposed a gross structure for steffimycin. Physical data of various kinds indicated that steffimycin and steffimycin B differed only by the presence of a methyl group in the latter which was absent in the former, and a structure was proposed for steffimycin B. However, the identity of the sugars present in these antibiotics was not published and very limited data were presented. The present paper proposes complete structures (**1a** and **1b**) for these antibiotics, except for stereochemistry in ring A of the linear tetracyclic system, and discusses the data on which these structures are based.

The original publication[3] on steffimycin established that it has a moleclar formula of $C_{28}H_{30}O_{13}$. The ultraviolet spectrum has maxima at 214, 236, 378, and 439 nm with the latter moving to 528 nm in base, which suggests that **1a** has a hydroxyanthraquinone chromophore[5-8] and is related to the anthracycline antibiotics.[9-11] It has been shown[5,6] that such a spectral pattern is present only in hydroxyanthraquinones having two hydroxyl groups α to the quinone carbonyl groups, and that these must be either 1,5 or 1,8. The infrared spectrum has bands at 1672 and 1620 cm^{-1}, which would be those expected for the hydrogen-bonded (1620 cm^{-1}) and nonbonded carbonyls of a 1,8-dihydroxyanthraquinone system.[12] Furthermore, the ^{13}C NMR spectrum of **1a** (Table I) has resonances at δ 179.3 and 189.1 which would arise from such an anthraquinone.[13] Conversion of the phenolic hydroxyls to methoxyls as in **1c** (see below) causes the downfield carbonyl resonance to shift to δ 181.4. In addition, an infrared band at 1710 cm^{-1} indicates a third carbonyl. The ^1H NMR (Me_2SO-d_6) spectrum of **1a** has chemical shifts of δ 6.75, 7.08, and 7.97 arising from aromatic protons present. Signals at δ 1.27 (d, 3 H) and 1.41 (s, 3 H) indicate two CH_3C groups with one being attached to a carbon bearing a proton. Singlets at δ 3.42, 3.44, and 3.90 can be assigned to CH_3O groups. Steffimycin B (**1b**) was found to have a molecular formula of $C_{29}H_{32}O_{13}$ and very similar spectra, except that one more CH_3O was present.[4] The data derived from **1a** and **1b** are so similar to those reported for aranciamycin[14] that it is clear that the three antibiotics are very closely related.

Acidic methanolysis of steffimycin gave rise to two products. One of these was a high-melting orange-red solid designated steffimycinone (**2a**), and the other was a colorless syrup (**4a**) characterized as a diacetate (**4b**), a mono-*p*-nitrobenzoate (**4c**), and a di-*p*-nitrobenzoate (**4d**). Methanolysis of steffimycin B also gave two products. One of these was shown to be **2a** by comparison of physical properties. The second was a second colorless syrup (**4e**), which differed from **4a**. Compound **2a** was shown by analysis and mass spectrometry to have a molecular formula of $C_{21}H_{18}O_9$. Its ultraviolet and infrared spectra were very similar to those of **1a** and were consistent with the assignment of a 1,8-dihydroxyanthraquinone structure to which was attached an aliphatic moiety containing a carbonyl group. The ^{13}C and ^1H NMR spectra indicated that three aromatic protons as well as one of the CH_3C groups and two of the methoxyl groups were present, one of which was attached to an aromatic ring (s, 3 H, δ 3.90) and one to an aliphatic system (s, 3 H, δ 3.48). The resonance arising from the CH_3C was a singlet, indicating the absence of a proton adjacent to the methyl protons. Doublets at δ 3.62 and 5.24 with coupling constants at 3.0 Hz represented 2 H which must be on adjacent carbon atoms. The molecular formula of **2a** accounts for all but a $C_7H_{12}O_4$ moiety of **1a**, which would suggest that **2a** is formed by methanolysis of **1a** to form an aglycone (**2a**) and a sugar (**4a**), which would have a molecular formula of $C_7H_{14}O_5$.

Catalytic reduction of **1a** under low pressure resulted in isolation of a new compound, **2b**. This material was very

1653 cm^{-1} (C=N). The 1-benzyl-3,4-dihydroisoquinoline hydrochloride (17) (7.6 g) was dissolved in a mixture of 200 mL of methanol and 25 mL of water, and the solution cooled in ice water. Sodium borohydride (8 g) was added in small portions while stirring. After the addition was complete, the reaction mixture was stirred at room temperature for 10 min, then refluxed for 1 h. Removal of the solvent left a residue which was treated with water and extracted with chloroform. The combined chloroform extracts were washed with water and dried (Na_2SO_4) to give a pale yellow oil (4.2 g), which was converted to the hydrochloride (18a) and crystallized from methanol: mp 210–213 °C (lit. 207–210,[25] 206–208 °C[26]).

(±)-*O,O*-Dibenzyl-*N*-norprotosinomenine hydrochloride (18a) (1.9 g) was dissolved in 50 mL of ethanol and 70 mL of 25% hydrochloric acid and the solution heated under reflux for 1.5 h in a stream of nitrogen. Evaporation of the solvent left a residue which was dissolved in absolute ethanol and evaporated to dryness. This treatment with ethanol was repeated twice, and the residue was crystallized from methanol to give (±)-norprotosinomenine hydrochloride (18b): mp 236–242 °C (lit.[27] 241–242 °C). The IR (KBr) spectrum was identical with that of authentic (±)-norprotosinomenine.[28]

Mannich Reaction of (±)-Norprotosinomenine. (±)-Norprotosinomenine hydrochloride (18b) (0.5 g) was dissolved in 20 mL of methanol and 60 mL of water and the solution adjusted to pH 6.4 with 5% sodium bicarbonate solution. Formaldehyde solution (16 mL, 37%) was added and pH again adjusted to 6.4. After the reaction mixture had been kept at room temperature for 48 h, methanol was evaporated, water was added, and the solution was basified with sodium bicarbonate and extracted with chloroform. Evaporation of the solvent left a residue which was chromatographed on a column of neutral alumina[29] with chloroform to give 196 mg of (±)-3,9-dihydroxy-2,10-dimethoxytetrahydroprotoberberine (3). Crystallization from methanol afforded colorless prisms; mp 208–212 °C dec, after vacuum drying mp 218–221 °C dec; ir ν_{max}(KBr) 3350 (br), 2800–2700 (*trans*-quinolizidine); NMR δ ($CDCl_3$) 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe) 6.69 (2 H, s, ArH), 6.72 (2 H, s, ArH); MS (EI) *m/e* (rel intensities) 327 (72) (M^+), 326 (48), 178 (100), 176 (42), 150 (58), 135 (32). The abundance of the $(M - OCH_3)^+$ fragment was 2% of the molecular ion peak, indicative of the absence of a methoxyl group in position 9.[8] Gibb's reaction[30] was positive, showing an unsubstituted position para to the phenolic hydroxyl group. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.30. Found: C, 69.68; H, 6.42; N, 4.30. Methylation with diazomethane gave (±)-tetrahydropalmatine (1), which crystallized from ether; mp 149–151 °C (lit.[31] 151–151.5 °C). IR spectrum was superimposable on that obtained with an authentic sample of (−)-tetrahydropalmatine.[32]

Elution of the column was continued with a mixture of chloroform and methanol (95:5) to yield (±)-3,11-dihydroxy-2,10-dimethoxytetrahydropseudoberberine (5) (119 mg). Crystallization from methanol afforded colorless prisms: mp 237–244 °C dec, after vacuum drying 251–255 °C dec (lit.[25] 232–235 °C); IR ν_{max}(KBr) 3500–3400 (br), 2800–2700 cm^{-1} (*trans*-quinolizidine); NMR δ ($CDCl_3$) 3.86 (3 H, s, OMe), 3.91 (3 H, s, OMe), 6.56 (1 H, s, ArH), 6.68 (1 H, s, ArH), 6.72 (2 H, s, ArH); MS (EI) *m/e* (rel intensities) 327 (69) (M^+), 326 (24), 178 (100), 176 (41), 150 (96), 135 (24). The $(M - OCH_3)^+$ fragment was 2% of the molecular ion peak and Gibb's reaction was negative. Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.30. Found: C, 69.43; H, 6.68; N, 4.18. Methylation of 5 (30 mg) with diazomethane gave (±)-xylopinine (10), which crystallized from ether as colorless needles: mp 145–147 °C (lit.[25] 146–148 °C); IR (KBr) spectrum was superimposable on that obtained with an authentic sample of (−)-xylopinine.[33]

(+)-Kikemanine [= (±)-corydalmine]. (±)-Stepholidine (7) (50 mg) was dissolved in 10 mL of methanol and treated with a solution of diazomethane in ether (prepared from 2 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide). After 45 min at room temperature the solution was evaporated to dryness. TLC of the residue on silica gel with chloroform–methanol (96:4) gave four spots, three of which were identified as unreacted stepholidine, isocorypalmine (15), and tetrahydropalmatine (1) by comparison with authentic substances. The fourth component of the mixture was isolated by preparative TLC on silica gel with chloroform–methanol (96:4) (double development) and crystallized from methanol; 11 mg; mp 166–168 °C dec (lit.[19] 187.5–188.5 °C corr); NMR δ ($CDCl_3$) 3.82 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe), 6.62 (1 H, s, ArH), 6.73 (1 H, s, ArH), 6.82 (2 H, s, ArH); MS (EI) *m/e* (rel intensities) 341 (66) (M^+), 340 (43), 310 (10), 192 (100), 190 (30), 150 (27), 135 (29). The $(M - OCH_3)^+$ was 15% of the molecular ion, indicative of a 9-methoxy substituent. The base peak *m/e* 192 (22) showed two methoxy groups in ring A. The isolated compound must, therefore, have structure 8.

Aequaline. An authentic sample of aequaline exhibited proton resonances in $CDCl_3$ at δ 3.82 (3 H, s, OMe), 3.90 (3 H, s, OMe), 6.68 (1 H, s, ArH), 6.70 (1 H, s, ArH), 6.82 (2 H, s, ArH), identical with the NMR spectrum of (±)-discretamine,[15] but different from that of compound 3. The MS (EI) of aequaline showed major peaks at *m/e* (rel intensities) 327 (52) (M^+), 326 (30), 296 (8.2), 178 (100), 176 (27), 150 (30), 135 (28). The $(M - OCH_3)^+$ fragment was 16% of the molecular ion peak, indicative of a 9-methoxy group[8] and in good agreement with that observed for natural[12] and synthetic[15] discretamine. R_f values (TLC) of aequaline were identical with those of (±)-discretamine, but different from those of compound 3 and stepholidine (7) on silica gel with (a) benzene–ethanol (92:8); (b) chloroform–methanol (96:4); and (c) ethyl acetate–methanol (96:4). The IR spectrum of aequaline was superimposable on that obtained with (±)-discretamine.

Schefferine. An authentic sample exhibited NMR peaks ($CDCl_3$) at δ 3.82 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.89 (3 H, s, OMe), 6.62 (1 H, s, ArH), 6.73 (1 H, s, ArH), and 6.82 (2 H, s, ArH), identical with those observed with (±)-kikemanine; MS (EI) *m/e* (rel intensities) 341 (66), 340 (43), 310 (10), 192 (100), 190 (29), 150 (26), 135 (25). The abundance of the $(M - OCH_3)^+$ fragment was 15% of the molecular ion peak, in good agreement with that observed for (±)-kikemanine. The R_f values of schefferine were identical with those of (±)-kikemanine on silica gel with (a) benzene–ethanol (92:8); (b) chloroform–methanol (96:4); and (c) ethyl acetate–methanol (96:4). The IR spectrum (KBr) of schefferine was superimposable on that of (±)-kikemanine.

Coramine. An authentic sample of coramine exhibited proton resonances ($CDCl_3$) at δ 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.54 (1 H, s, ArH), 6.58 (1 H, s, ArH), 6.69 (1 H, s, ArH), 6.81 (1 H, s, ArH); MS (EI) *m/e* (rel intensities) 327 (59) (M^+), 178 (100), 176 (28), 150 (81), 135 (17). The IR spectrum of coramine was different from that of compound 5, but superimposable on the spectrum of (−)-coreximine.

Discretinine. MS (EI) of discretinine gave a molecular ion *m/e* (rel intensities) at 341 (64) and major fragments at 310 (12), 178 (8.2), 176 (22), 164 (100), 149 (59). The $(M - OCH_3)^+$ fragment was 18% of the molecular ion peak. NMR resonances of discretinine ($CDCl_3$) appeared at δ 3.85 (6 H, s, OMe), 3.89 (3 H, s, OMe), 6.68 (1 H, s, ArH), 6.70 (1 H, s, ArH), 6.81 (1 H, s, ArH), 6.84 (1 H, s, ArH), identical with those of authentic (±)-corypalmine. (−)-Isocorypalmine[34] showed the following proton resonances: δ 3.84 (6 H, s, OMe), 3.87 (3 H, s, OMe), 6.59 (1 H, s, ArH), 6.81 (2 H, s, ArH), 6.83 (1 H, s, ArH). The IR spectrum of discretinine was superimposable on that obtained with (±)-corypalmine.

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Registry No.—(±)-1, 2934-97-6; (±)-3, 62057-90-3; (±)-5, 214162-23-9; (±)-6, 55934-50-4; 6, 1356-73-6; (±)-7, 16562-14-4; (±)-8, 32886-80-9; 8, 30413-84-4; 10, 13407-95-9; (±)-13, 6719-48-8; 13, 483-45-4; (±)-14, 27313-86-6; 14, 6018-40-2; 15, 483-34-1; 16, 21411-26-7; 17, 37911-04-9; 17 free base, 21411-27-8; 18a, 63511-81-9; 18b, 19625-07-1; 3-benzyloxy-4-methoxyphenethylamide, 36455-21-7; 3-benzyloxy-4-methoxyphenylacetic acid, 5487-33-2.

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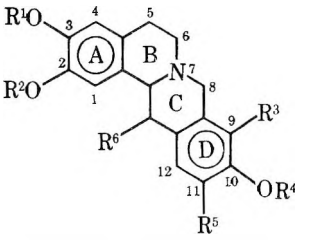
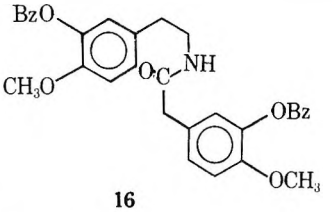


1, $R^1 = R^2 = R^4 = Me$; $R^3 = OMe$; $R^5 = R^6 = H$
2, $R^1 = R^4 = Me$; $R^3 = OH$; $R^2 = R^5 = R^6 = H$
3, $R^1 = R^5 = R^6 = H$; $R^3 = OH$; $R^2 = R^4 = Me$
4, $R^1 = R^2 = R^4 = Me$; $R^3 = OH$; $R^5 = R^6 = H$
5, $R^1 = R^3 = R^6 = H$; $R^2 = R^4 = Me$; $R^5 = OH$
6, $R^1 = R^4 = R^5 = R^6 = H$; $R^2 = Me$; $R^3 = OMe$
7, $R^1 = Me$; $R^2 = R^4 = R^5 = R^6 = H$; $R^3 = OMe$
8, $R^1 = R^2 = Me$; $R^3 = OMe$; $R^4 = R^5 = R^6 = H$
9, $R^1 = R^5 = H$; $R^2 = R^4 = R^6 = Me$; $R^3 = OMe$
10, $R^1 = R^2 = R^4 = Me$; $R^3 = R^6 = H$; $R^5 = OMe$
11, $R^1 = Me$; $R^2 = R^3 = R^4 = R^6 = H$; $R^5 = OMe$
12, $R^1 = R^3 = R^4 = R^6 = H$; $R^2 = Me$; $R^5 = OMe$
13, $R^1 = R^4 = Me$; $R^2 = R^3 = R^6 = H$; $R^5 = OH$
14, $R^1 = R^5 = R^6 = H$; $R^2 = R^4 = Me$; $R^3 = OMe$
15, $R^1 = R^4 = Me$; $R^2 = R^5 = R^6 = H$; $R^3 = OMe$



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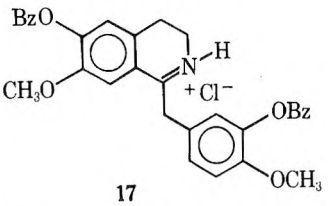

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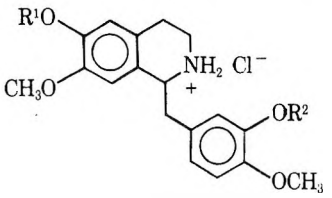
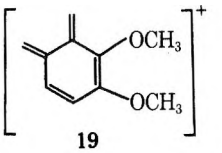


18a, $R^1 = R^2 = Bz$
b, $R^1 = R^2 = H$

as indicated by preliminary mass spectroscopy,[10] giving it structure 8. This compound was isolated by Cava et al.[13] from *Stephania glabra* as (−)-corydalmine and from *Corydalis pallida* by Kametani et al.,[16] who named it kikemanine. In 1962, Imaseki and Taguchi[17] isolated what they believed to be (+)-corydalmine from *Corydalis* species, but this compound was later shown to be identical with (±)-corybulbine[18] (9). (±)-Corydalmine [= (±)-kikemanine] has been synthesized.[19,20] Comparison (IR, NMR, MS, TLC) of schefferine with (±)-kikemanine showed that they have the same structure (8).

A protoberberine alkaloid believed to represent a new structure was isolated from *Corydalis pseudoadunca* by Yunosov et al.[21] and named coramine. Elemental analysis showed a $C_{19}H_{21}NO_4$ composition and methylation with diazomethane gave (−)-xylopinine (10), thus establishing a 2,3,10,11-tetraoxygenated substitution pattern. Based on degradative evidence structure 5 was proposed.[22] However, comparison of a sample of coramine with compound 5 obtained by synthesis (ir, NMR, mass spectrometry) showed that the two compounds were different. Coramine was also not identical with 11 and 12 produced by synthesis.[15] This left only (−)-coreximine (13) to be considered. Identity of coramine with coreximine was borne out by comparison of their respective IR, NMR, and mass spectra.

A tetrahydroprotoberberine alkaloid was isolated by Schmutz[11] in 1959 from *Xylopia discreta*. Elemental analysis showed a $C_{20}H_{23}NO_4$ composition and methylation with diazomethane gave (−)-tetrahydropalmatine. The alkaloid, which was named discretinine, was described as an isomer of corypalmine (14) and isocorypalmine (15), but no attempt was made to establish the position of the phenolic hydroxyl group. Mass spectrometry gave a molecular ion *m/e* 341, and the abundance of the $(M - OCH_3)^+$ fragment was 18% of the molecular ion peak, indicating the presence of a 9-methoxy substituent.[8] Fragment 19, formed by retro-Diels–Alder cleavage of ring C, was the base peak at *m/e* 164. The second most abundant fragment had a mass *m/e* 149 (19 − CH_3), while fragments 20 (*m/e* 178) and 21 (*m/e* 176) were consid-



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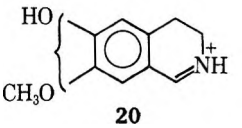

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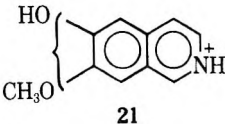

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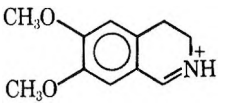

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erably less prominent. This contrasts with tetrahydroprotoberberines containing a hydroxyl group in ring D (e.g., 2–8), where the base peak is derived from the A/B moiety (fragments 20 and 22). Having established a 9,10-dimethoxy substitution of ring D, there are only two alternative structures available for discretinine. It must be either corypalmine (14) or isocorypalmine (15). Spectroscopic comparison (IR, NMR) showed discretinine to be identical with corypalmine.

Experimental Section

General. Melting points (mp) were determined with a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were obtained in potassium bromide, unless otherwise indicated, on a Perkin-Elmer 337 spectrometer. ^1H NMR spectra were obtained in deuteriochloroform with tetramethylsilane as an internal reference on a Varian XL-100 spectrometer equipped with a Nicolet Technology Corp. Fourier transform accessory. Electron impact (EI) mass spectra were taken on a AEI MS-12 mass spectrometer interfaced to a PDP 8/I computer using the DS-30 software.

(±)-Norprotosinomenine (18b). 3-Benzyloxy-4-methoxyphenethylamine[23] (3 g) and 3.2 g of 3-benzyloxy-4-methoxyphenylacetic[24] acid were mixed and fused at 160–170 °C for 4.5 h under reduced pressure. After cooling, the mixture was dissolved in 60 mL of chloroform and washed with 10% sodium bicarbonate solution, then with water, 10% hydrochloric acid, and, finally, with water again, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a yellowish brown, oily substance (16), which crystallized from absolute ethanol (5.1 g): mp 114–115 °C (lit.[25] 113.5–115 °C); IR ν_{max}(Nujol) 3290 (NH), 1630 cm^{-1} (C=O). A mixture of 1 g of the amide (16), 1.1 mL of freshly distilled phosphorus oxychloride, and 15 mL of dry toluene was heated in an oil bath at 105–110 °C for 1.5 h in a nitrogen atmosphere. The reaction mixture was evaporated to dryness under reduced pressure. The residue was washed repeatedly with anhydrous benzene and dried to afford a brown, oily substance which crystallized from aqueous ethanol as light yellow needles (17): mp 145–148 °C (lit.[25] 145–148 °C); IR ν_{max}(Nujol) 2450 (br), 1850–1925 (immonium band), 1640 cm^{-1} (C=$^+$NH). The free base of 17 showed a band at

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Registry No.—**2a,** 601-95-6; **2b,** 63533-72-2; **2c,** 63533-73-3; **2d,** 61543-88-2; **2e,** 63533-74-4; **2f,** 63533-75-5; **3c** isomer 1, 63533-76-6; **3c** isomer 2, 63533-77-7; **4a,** 61543-93-9; **4b,** 63533-78-8; **4c,** 63533-79-9; **4d,** 63533-80-2; **4e,** 63533-81-3; **4f,** 63533-82-4; **4g,** 63533-83-5; **5a,** 63533-84-6; **5b,** 63533-85-7; **5c,** 63533-86-8; **6,** 63533-87-9; **7a,** 63533-88-0; **7b,** 63533-89-1; **7c,** 62251-60-9; **7d,** 63547-45-5; **7e,** 63533-90-4; **7f,** 63533-91-5; **8a,** 63533-92-6; **8c,** 63533-93-7; **8d,** 63533-94-8; **9a,** 63533-95-9; **9b,** 63533-96-0; **9c,** 63533-97-1; **10b,** 63533-98-2; **10c,** 63533-99-3.

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Protoberberine Alkaloids. Structures of Aequaline, Coramine, Discretinine, and Schefferine

Einar Brochmann-Hanssen* and Hsüch-Ching Chiang

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, California, 94143, and School of Pharmacy, National Taiwan University, Taipei, Taiwan, Republic of China.

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The structures assigned to the protoberberine alkaloids aequaline and coramine were found to be incorrect. Instead, aequaline was shown to be identical with discretamine (**6**), and coramine was identical with coreximine (**13**). Schefferine was found to have the same structure as kikemanine [(−)-corydalmine] (**8**), and discretinine was shown to be corypalmine (**14**) by comparison with authentic samples.

The protoberberine alkaloids are widely distributed in many plant families, mainly as the tetrahydroprotoberberines and the quaternary protoberberine salts.[1-4] They are biosynthesized from benzyltetrahydroisoquinolines[5-7] and, in turn, serve as biosynthetic intermediates for many other alkaloid groups.

The assignment of the substitution pattern of protoberberines isolated from natural sources has often presented considerable problems, especially when insufficient material has been available for chemical degradations. Spectroscopic data can give valuable information,[8] but the final proof of structure comes from chemical synthesis. Several protoberberine alkaloids have been isolated whose structures are still not known in all detail, and there are others which have been assigned incorrect structures.

In 1972 two tetrahydroprotoberberine alkaloids were isolated from the bark of *Schefferomitra subaequalis* and named aequaline and schefferine.[9] Both alkaloids were levorotatory and gave (−)-tetrahydropalmatine (**1**) on methylation with diazomethane, thereby establishing a 2,3,9,10-tetraoxygenated substitution pattern. Elemental analysis of aequaline gave the molecular formula $C_{19}H_{21}NO_4$. The NMR spectrum established the presence of two methoxyl and two hydroxyl groups, and mass spectroscopy showed that both rings A and D each had one hydroxyl and one methoxyl group. A 9-hydroxy-10-methoxy substitution was suggested based on the relative abundances of the fragments. Since aequaline was shown by direct comparison to be different from scoulerine (**2**), the structure of aequaline was proposed to be (−)-3,9-dihydroxy-2,10-dimethoxytetrahydroprotoberberine (**3**).

Microanalysis of the second alkaloid, schefferine, gave a molecular formula $C_{20}H_{23}NO_4$ and a molecular ion peak *m/e* 341 in its mass spectrum indicating the presence of one hydroxyl and three methoxyl groups. Based on the fragmentation pattern, two methoxyl groups could be assigned to ring A. Since monomethylation of aequaline with diazomethane gave schefferine as one of the products, structure **4** was assigned to schefferine.

Recently, mass spectrometric criteria were developed for detecting a methoxyl group in position 9 of protoberberine alkaloids based on the abundance of the $(M - OCH_3)^+$ fragment compared to that of the molecular ion.[8] Compounds with a 9-methoxy substituent give a $(M - OCH_3)^+$ fragment ranging from 12 to 19% of the molecular ion. If the compounds are either unsubstituted in position 9 or have a 9-hydroxy substituent, the relative abundance of the $(M - OCH_3)^+$ fragment is <3% of the molecular ion peak. Preliminary mass spectroscopic studies[10] have indicated that both aequaline and schefferine contain a 9-methoxy substituent. In order to clarify this discrepancy and to establish unequivocally the correct structure of aequaline, compound **3** was synthesized by intramolecular Mannich condensation of (±)-norprotosinomenine (**18b**) with formaldehyde at pH 6.4 and room temperature. Cyclization occurred ortho and para to the phenolic hydroxyl group to give a mixture of (±)-3,9-dihydroxy-2,10-dimethoxytetrahydroprotoberberine (**3**) and (±)-3,11-dihydroxy-2,10-dimethoxytetrahydropseudoberberine (**5**). Spectroscopic comparison (IR, NMR, MS) of aequaline with compound **3** showed that aequaline did not have the structure assigned to it. Two diphenolic 2,3,9,10-substituted isomers of compounds **2** and **3** have been isolated from natural sources and are named discretamine (**6**)[11,12] and stepholidine (**7**).[13,14] Both compounds have recently been synthesized.[15] A comparison of aequaline with discretamine and stepholidine (IR, NMR, mass spectrometry, TLC) showed clearly that aequaline is identical with discretamine. It, therefore, also follows that schefferine must be 9-methoxy-10-hydroxy-substituted,

* Address correspondence to this author at University of California.

405 (47, M − CH_3CO − CH_3OH), 387 (15, 405 − H_2O), 360 (33, M − 2HOAc), 345 (28, 360 − CH_3), 328 (38, M − 2HOAc − CH_3OH), 301 (52, M − 2HOAc − CO_2CH_3), 300 (48, 328 − CO), 285 (40, 300 − CH_3), and 241 (100).

Anal. Calcd for $C_{25}H_{36}O_9$: C, 62.49; H, 7.55. Found: C, 62.35; H, 7.57.

3α-Nitroxy-12α-acetoxy-13α-carbomethoxy-16-oxo-17-oxa-13,17-seco-7α,17-cyclo-5β-androstane (7f). A mixture of nitrate **4c** (1.0 g), CH_3OH (50 mL), H_2O (10 mL), and KOH (2 g) was heated at reflux for 12 h. The mixture was concentrated on a rotating evaporator to remove most of the CH_3OH. The aqueous residue was acidified with concentrated HCl, warmed for 0.5 h, and then cooled and extracted with EtOAc. EtOAc was evaporated off, and the residue **7d** was dissolved in CH_2Cl_2 and treated with diazomethane to yield δ-lactone **7e**. Lactone **7e** was acetylated and recrystallized from benzene–chloroform to afford δ-lactone **7f** (0.3 g): mp 224–226 °C; $\bar{\nu}_{max}$ 1740 (br) and 1620, 1280, and 880 cm^{-1} (NO_3); ^1H NMR δ 5.13 (peak, 1 H, 12β-H), 4.9 (hump, 1 H, 3β-H), 4.4 (hump, 1 H, 7β-H), 2.4 (m, 2 H, C-15), 2.03 (s, 3 H, 12α-OAc), 1.28 (s, 3 H, C-18), and 0.89 (s, 3 H, C-19); *m/e* (%) 453 (3, M^+), 422 (4, M − CH_3O), 411 (100, M − CH_2CO), 393 (4, M − HOAc), 383 (25), 352 (10), 348 (11), 347 (12), 330 (13), 329 (14), 315 (19), 287 (40), and 271 (95, M − HOAc − HNO_3 − CO_2CH_3).

Anal. Calcd for $C_{22}H_{31}O_9N$: C, 58.27; H, 6.89; N, 3.09. Found: C, 58.20; H, 6.91; N, 3.01.

3α-Nitroxy-12,16-dioxo-13β-carbomethoxy-17-oxa-13,17-seco-7α,17-cyclo-5β-androstane (8a). δ-Lactone **7e** obtained from 1.0 g of nitrate **4c** was oxidized with Jones reagent to a mixture of the following four compounds isolated by preparative TLC.

The higher R_f component was recrystallized from hexane–EtOAc giving diketone **5a** (0.2 g): mp 177–179 °C; $\bar{\nu}_{max}$ 1740, 1710 and 1620, 1280 and 880 cm^{-1} (NO_3); ^1H NMR δ 4.8 (hump, 1 H, 3β-H), 3.73 (s, 3 H, 13α-CO_2CH_3), 3.58 (s, 3 H, C-16, OCH_3), 1.30 (s, 3 H, C-18), and 1.26 (s, 3 H, C-19); *m/e* (%) 439 (19, M^+), 421 (9, M − H_2O), 408 (55, M − CH_3O), 380 (55, M − CO_2CH_3), 362 (65, M − H_2O − CO_2CH_3), 345 (40), 343 (40), 330 (100), 301 (40), and 283 (85).

Anal. Calcd for $C_{21}H_{29}NO_9$: C, 57.40; H, 6.65. Found: C, 57.40; H, 6.82.

The second most mobile component was recrystallized from hexane–benzene to afford the desired δ-lactone **8a** (0.2 (0.2 g): mp 199–201 °C; $\bar{\nu}_{max}$ 1740, 1710 and1625, 1280, and 860 cm^{-1} (NO_3); ^1H NMR δ 4.9 (hump, 1 H, 3β-H), 4.5 (hump, 1 H, 7β-H), 3.76 (s, 3 H, OCH_3), 1.36 (s, 3 H, C-18), and 0.93 (s, 3 H, C-19); *m/e* (%) 409 (3, M^+), 378 (3, M − CH_3O), 363 (13, M − NO_2), 350 (9, M − CO_2CH_3), 346 (20, M − HNO_3), 287 (25, M − HNO_3 − CO_2CH_3), and 285 (18).

Anal. Calcd for $C_{20}H_{27}O_8N$: C, 58.67; H, 6.65; N, 3.42. Found: C, 59.07; H, 6.92; N, 3.18.

The third most mobile component (30 mg) was triketone **5c**: $\bar{\nu}_{max}$ 1740 and 1715 cm^{-1}; ^1H NMR δ 3.70 (s, 3 H, 13α-CO_2CH_3), 3.59 (s, 3 H, C-16, OCH_3), 1.33 (s, 3 H, C-18), and 1.28 (s, 3 H, C-19); *m/e* (%) 392 (5, M^+), 374 (7, M − H_2O), 360 (10, M − CH_3OH), 333 (9, M − CO_2CH_3), 315 (8, M − CO_2CH_3 − H_2O), 301 (23), 287 (26), and 283 (45).

The most polar component (35 mg) was δ-lactone **8d**.

Methyl 3α-Acetoxy-12,16-dioxo-13β-carbomethoxy-17-oxa-16,17-seco-7α,17-cyclo-5β-androstane (8c). Nitroxy δ-lactone **8a** (0.10 g) was reduced with Zn and acetylated to afford acetoxy δ-lactone **8c** (80 mg) after recrystallization from hexane–benzene: mp 210–212 °C; $\bar{\nu}_{max}$ 1740 and 1710 cm^{-1}; ^1H NMR δ 4.7 (hump, 1 H, 3β-H), 4.5 (hump, 1 H, 7β-H), 3.75 (s, 3 H, OCH_3), 1.36 (s, 3 H, C-18), and 0.90 (s, 3 H, C-19); *m/e* (%) 406 (25, M^+), 346 (92, M − HOAc), 331 (15), 328 (19), 318 (30), 314 (28), 287 (98, M − HOAc − CO_2CH_3), and 259 (100).

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.06; H, 7.30.

Methyl 3α,12α-Diacetoxy-7α-hydroxy-16,17-seco-5β-androstane-16,17-dioate (4e). A solution of δ-lactone **7c** (0.10 g) was reacted for 1 h with CH_3OH containing AcCl at room temperature. Dilution of the reaction mixture with H_2O and subsequent workup yielded diol **4d** which could be acetylated with Ac_2O–pyridine (1:2) at room temperature for 12 h to give diester **4e** (80 mg): mp 158–160 °C; $\bar{\nu}_{max}$ 2450 (OH), 1740, 1715, and 1250 cm^{-1}; ^1H NMR δ 5.14 (peak, 1 H, 12β-H), 4.5 (hump, 1 H, 3β-H), 4.23 (peak, 1 H, 7β-H), 3.74 (s, 3 H, 13α-CO_2CH_3), 3.63 (s, 3 H, C-16, OCH_3), 2.08 and 2.04 (s, 3 H each, 3α,12α-OAc's), 1.19 (s, 3 H, C-18), and 0.98 (s, 3 H, C-19); *m/e* (%) 482 (5, M^+), 464 (4, M − H_2O), 430 (6, M − CH_3OH), 422 (22, M − HOAc), 404 (10, M − H_2O − HOAc), 390 (23, M − CH_3OH − HOAc), 372 (11, 390 − H_2O), 362 (32, M − 2HOAc), 344 (14, 362 − H_2O), 330 (45, 362 − CH_3OH), 312 (20), 302 (27), 285 (70, 344 − CO_2CH_3) and 271 (65).

Anal. Calcd for $C_{25}H_{38}O_9$: C, 62.22; H, 7.94. Found: C, 61.99; H, 8.08.

3α,12α-Diacetoxy-7-oxo-16,17-seco-5β-androstane-13,17-dioate (4g). Hydroxy diacetate **4e** was oxidized with Jones reagent to give ketone **4g** in nearly quantitative yields: mp 154–155 °C; ^1H NMR δ 5.12 (peak, 1 H, 12β-H), 4.5 (hump, 1 H, 3β-H), 3.68 and 365 (s, 3 H each, OCH_3), 2.05 and 2.02 (s, 3 H each, 3α,12α-OAc's), 1.22 (s, 3 H, C-18), and 1.20 (s, 3 H, C-19); *m/e* (%) 480 (11, M^+), 449 (9, M − CH_3O), 448 (10, M − CH_3OH), 420 (18, M − HOAc), 389 (13, M − CH_3O − HOAc), 388 (13, M − CH_3OH − HOAc), 360 (48, M − 2HOAc), 329 (20, 360 − CH_3O), 328 (54, 360 − CH_3OH), 313 (14), 301 (20), 300 (36), 287 (25), 285 (18), and 269 (100).

Anal. Calcd for $C_{25}H_{36}O_9$: C, 62.49; H, 7.55. Found: C, 62.31; H, 7.68.

3,16-Dioxo-12α-acetoxy-13α-carbomethoxy-17-oxa-13,17-seco-7α,17-cyclo-5β-androstane (9b). Ketone **4f** (0.40 g) was saponified and subsequently treated with warm HCl solution to yield δ-lactone **9a**. Treatment of crude δ-lactone **9a** with diazomethane and then Ac_2O–pyridine yielded a product which was purified by TLC. The polar material thus isolated was recrystallized from hexane–benzene to afford δ-lactone **9b** (0.10 g): mp 211–212 °C; $\bar{\nu}_{max}$ 1750, 1730, and 1710 cm^{-1}; ^1H NMR δ 5.17 (peak, 1 H, 12β-H), 4.5 (hump, 1 H, 7β-H), 3.65 (s, 3 H, OCH_3), 2.3 (m, 6 H, C-2, C-4, and C-15), 2.03 (s, 3 H, 12α-OAc), 1.25 (s, 3 H, C-18), and 0.95 (s, 3 H, C-19); *m/e* (%) 406 (8, M^+), 375 (6, M − CH_3O), 364 (55, M − CH_2CO), 346 (10, M − HOAc), 336 (7, M − CH_2CO − CO), 328 (8, M − HOAc − H_2O), 318 (15), 314 (13, M − CH_2CO − HOAc), 305 (10), 304 (11), 300 (11), 287 (31, M − HOAc − CO_2CH_3), and 241 (75).

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.17; H, 7.51.

3,16-Dioxo-12α-nitroxy-13α-carbomethoxy-17-oxa-13,17-seco-7α,17-cyclo-5β-androstane (9c). δ-Lactone **9a** made from ketone **4f** (0.50 g) was nitrated and purified by TLC to yield δ-lactone **9c** (0.10 g) as a glassy solid: $\bar{\nu}_{max}$ 1740 (br) and 1640, 1280, 860, and 760 cm^{-1} (NO_3); ^1H NMR δ 5.22 (peak, 1 H, 12 β-H), 4.6 (hump, 1 H, 7β-H), 3.70 (s, 3 H, OCH_3), 2.4 (m, 6 H), 1.33 (s, 3 H, C-18), and 0.97 (s, 3 H, C-19); *m/e* (%) 409 (8, M^+), 394 (6, M − CH_3), 376 (9, M − CH_3 − H_2O), 334 (8, 376 − CH_2CO), 302 (60), and 287 (45, 302 − CH_3).

Methyl 3α-Acetoxy-7,12-dioxo-16,17-seco-5β-androstane-16,17-dioate (5b). Zn dust reduction of nitrate **5a** (0.20 g) followed by acetylation yielded acetate **5b** (0.19 g): mp 143–144 °C; $\bar{\nu}_{max}$ 1740, 1720, and 1710 cm^{-1}; ^1H NMR δ 4.7 (hump, 1 H, 3β-H), 3.74 and 3.61 (s, 3 H each, OCH_3), 1.99 (s, 3 H, 3α-OAc), 1.32 (s, 3 H, C-18), and 1.24 (s, 3 H, C-19); *m/e* (%) 436 (8, M^+), 418 (8, M − H_2O), 404 (11, M − CH_3OH), 386 (9, M − H_2O − CH_3OH), 377 (25, M − CO_2CH_3), 376 (28, M − HOAc), 359 (34, 377 − H_2O), 345 (63, M − CH_3OH − CO_2CH_3), 327 (30), 316 (26), 299 (39), and 285 (100, M − CH_3OH − HOAc − CO_2CH_3).

Anal. Calcd for $C_{23}H_{32}O_8$: C, 63.29; H, 7.39. Found: C, 63.54; H, 7.46.

Methyl 3α-Acetoxy-7,12-dioxo-13,17-seco-17-nor-5β,13α-androstan-16-oate (6). Acetate **5b** (0.15 g) was heated at reflux in HOAc (2 mL) containing concentrated HCl (0.5 mL) for 4 h. Workup and TLC yielded acetate **6** (0.10 g) as a glassy solid: $\bar{\nu}_{max}$ 1730 and 1710 cm^{-1}; ^1H NMR δ 4.7 (hump, 1 H, 3β-H), 3.62 (s, 3 H, OCH_3), 1.97 (s, 3 H, 3α-OAc), 1.27 (s, 3 H, C-19), and 1.07 (d, J = 6 Hz, 3 H, C-18); *m/e* (%) 378 (12, M^+), 318 (25, M − HOAc), 305 (22, M − $CH_2CO_2CH_3$), 300 (21, M − HOAc − H_2O), 287 (39, 305 − H_2O), 258 (28), and 245 (84, M − HOAc − $CH_2CO_2CH_3$).

3,12,16-Trioxo-17-oxa-13,17-seco-7α,17-cyclo-5β,13α-androstane (10b). A solution of δ-lactone **8d** (50 mg) in glacial HOAc (2 mL) containing concentrated HCl (0.5 mL) was heated at reflux for 4 h. Workup and recrystallization from hexane–benzene afforded δ-lactone **10b** (30 mg): mp 171–173 °C; $\bar{\nu}_{max}$ 1740, 1720, and 1700 cm^{-1}; ^1H NMR δ 4.8 (hump, 1 H, 7β-H), 1.12 (d, J = 6 Hz, 3 H, C-18), and 1.03 (s, 3 H, C-19); *m/e* (%) 304 (65, M^+), 289 (6, M − CH_3), 286 (12, M − H_2O), 277 (20), 278 (17, M − CO), and 260 (17, M − CO_2).

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.03; H, 7.83.

3α-Acetoxy-12,16-dioxo-17-oxa-13,17-seco-7α,17-cyclo-5β,13α-androstane (10c). δ-Lactone **7d** obtained from **4c** (0.8 g) was oxidized with Jones reagent, then treated with Zn dust/HOAc, and finally acetylated to yield acetoxy δ-lactone **10c** (0.2 g): mp 185–187 °C; $\bar{\nu}_{max}$ 1755, 1720, and 1695 cm^{-1}; ^1H NMR δ 4.7 (hump, 1 H, 3β-H), 4.5 (hump, 1 H, 7β-H), 2.00 (s, 3 H, 3α-OAc), 1.06 (d, J = 6 Hz, 3 H, C-18), and 0.90 (s, 3 H, C-19); *m/e* (%) 348 (11, M^+), 288 (100, M − HOAc), 273 (27, M − HOAc − CH_3), 270 (10, M − HOAc − H_2O), 260 (11), 245 (18), 229 (48), 228 (45), and 216 (72).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.95; H, 8.23.

in refluxing glacial HOAc containing concentrated HCl without difficulty, methyl esters **8a** and **8c** under these conditions led to product mixtures consisting, presumably, of elimination and chloride-substituted products which was avoided by decarboxylating acid **8b** requiring no prior transesterification and therefore a shorter reaction period. As expected, the NMR spectra of **10b** and **10c** exhibited a doublet (J = 6 Hz) for the C-18 methyl group which was assigned the more stable α orientation.

Experimental Section

General. All melting points were determined with a Fisher-Johns apparatus and are corrected. Infrared data ($\bar{\nu}_{max}$) were obtained in $CHCl_3$ solution against a blank; ^1H NMR data, reported in ppm (δ) form Me_4Si, were determined in $CDCl_3$ with a Varian A-60 or T-60 NMR; mass spectra were obtained at an ionization voltage of 70 eV with a Nuclide 12-90-G single-focusing instrument having a resolution capability of 10 000. C, H, N microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Column chromatography was performed using silica gel (MCB Grade 62), and TLC was performed on silica gel HF_{254} (E. Merck) using hexane–EtOAc as the mobile phase. Visualization of the TLC was effected by spraying with 2% ceric sulfate in 2 N H_2SO_4 followed by brief heating.

3α,7α-Diacetoxy-12α-hydroxy-5β-pregnan-20-one (2b). A solution of triol **2a** (1.0 g) in benzene (50 mL) was reacted with Ac_2O (2 mL) and pyridine (2 mL) at 20 °C for 24 h.[6] Diacetate **2b** (0.8 g) was obtained after workup and crystallization from hexane–acetone: mp 217–219 °C; $\bar{\nu}_{max}$ 3500 (OH), 1740, and 1715 cm^{-1}; ^1H NMR δ 4.90 (peak, 1 H, 7β-H), 4.6 (hump, 1 H, 3β-H), 4.02 (peak, 1 H, 12β-H), 3.2 (t, 1 H, C-17), 2.13 (s, 3 H, C-20), 2.06 and 2.02 (s, 3 H each, 3α,7α-OAc's), 0.93 (s, 3 H, c-19), and 0.65 (s, 3 H, C-18); *m/e* (%) 434 (3, M^+), 374 (100, M − HOAc), 314 (42, M − 2HOAc), 253 (48), and 229 (90).

3α,7α-Diacetoxy-12α-nitroxy-5β-pregnan-20-one (2c). Fuming HNO_3 (1 mL) was added to Ac_2O (3 mL) at −5 °C.[7] To this mixture, a solution of **2b** (0.3 g) in $CHCl_3$ (5 mL) was added dropwise and stirred for 0.5 h. Workup and column chromatography afforded **2c** (0.22 g): $\bar{\nu}_{max}$ 1740 and 1250 (OAc), 1715, and 1630, 1280, 860, and 760 cm^{-1} (NO_3); ^1H NMR δ 5.37 (peak, 1 H, 12β-H), 4.85 (peak, 1 H, 7β-H), 4.5 (hump, 1 H, 3β-H), 2.9 (t, 1 H, C-17), 2.08 (s, 3 H, C-20), 2.06 and 2.02 (s, 3 H each, 3α,7α-OAc's), 0.97 (s, 3 H, C-19), and 0.83 (s, 3 H, C-18); *m/e* (%) 479 (2, M^+), 436 (7, M − CH_3CO), 419 (7, M − HOAc), 373 (3, M − CH_3CO − HNO_3), 359 (63, M − 2HOAc), 313 (33, 359 − NO_2), 295 (57, 359 − HNO_3), 281 (39), 271 (46, 313 − CH_2CO), and 253 (87).

3α-Hydroxy-7α,12α-diacetoxy-5β-pregnan-20-one (2e). A solution of triacetate **2d** (2.0 g) in absolute CH_3OH (20 mL) was reacted with AcCl (1 mL) and allowed to stand at room temperature for 1 h. The organic solid obtained by H_2O precipitation was recrystallized from hexane–ether to yield diacetate **2e** (1.7 g): mp 186–187 °C; $\bar{\nu}_{max}$ 3550 (OH), 1720 (br), and 1250 cm^{-1} (OAc); ^1H NMR δ 5.17 (peak, 1 H, 12β-H), 4.95 (peak, 1 H, 7β-H), 3.5 (hump, 1 H, 3β-H), 2.9 (t, 1 H, C-17), 2.20 (s, 3 H, C-20), 2.10 and 2.03 (s, 3 H each, 7α,12α-OAc's), 0.93 (s, 3 H, C-19), and 0.72 (s, 3 H, C-18); *m/e* (%) 434 (2, M^+), 419 (3, M − CH_3), 392 (38, M − CH_2CO), 374 (7, M − HOAc), 332 (11, M − CH_2CO − HOAc), 314 (100, M − 2HOAc), 299 (40). 296 (84, M − 2HOAc − H_2O), 281 (80), and 253 (80, 296 − CH_3CO).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.07; H, 8.77.

3α-Nitroxy-7α,12α-diacetoxy-5β-pregnan-20-one (2f). Diester **2e** (1.0 g) was nitrated to yield **2f** (0.8 g): $\bar{\nu}_{max}$ 1740 and 1250 (OAc), and 1630, 1280, 870, and 760 cm^{-1} (NO_3); ^1H NMR δ 5.17 (peak, 1 H, 12β-H), 4.97 (peak, 1 H, 7β-H), 4.8 (hump, 1 H, 3β-H), 3.0 (t, 1 H, C-17), 2.20 (s, 3 H, C-20), 2.09 and 2.03 (s, 3 H each 7α,12α-OAc's), 0.98 (s, 3 H, C-19), and 0.73 (s, 3 H, C-18); *m/e* (%) 479 (2, M^+), 436 (14, M − CH_3CO), 419 (5, M − HOAc), 376 (7, M − CH_3CO − HOAc), 359 (31, M − 2HOAc), 313 (35 359 − NO_2), 295 (55, 313 − H_2O), 253 (56), and 213 (100).

Bromination and Dehydrobromination of 2f. To a solution of nitrate **2f** (1.0 g) in HOAc (30 mL) containing 40% HBr (2 dp) was added Br_2/HOAc (2.1 mL of 1.0 M). After stirring for 15 min, the acetic acid mixture was poured into ice-water. This was then extracted with ether, and the ether layer was washed with H_2O, aqueous $NaHCO_3$, and then H_2O again. The residue obtained from evaporation of the ether was dissolved in HMPT (30 mL) and heated at 100 °C for 1.5 h under a N_2 atmosphere. The cooled reaction mixture was diluted with H_2O which was extracted with EtOAc. Chromatography yielded two bromoenone products (**3c**). The minor and lower R_f component gave the following spectra: $\bar{\nu}_{max}$ 1730 and 1250 (OAc), 1665 and 1600 (C=C–C=O), and 755 cm^{-1} (C–Br); ^1H NMR δ 6.63 (peak, 1 H, C-16), 5.50 (peak, 1 H, 12β-H), 5.02 (peak, 1 H, 7β-H), 4.72 (peak, 1 H, 3α-H), 2.24 (s, 3 H, C-20), 2.07 and 1.97 (s, 3 H each, 7α,12α-OAc's), 1.03 (s, 3 H, C-19), and 0.95 (s, 3 H, C-18); *m/e* (%) 496 and 494 (1 and 1, M^+), 481 and 479 (1 and 1), 453 and 451 (96 and 96, M − CH_3CO), 436 and 434 (11 and 11, M − HOAc), 421 and 419 (2 and 2, M − HOAc − CH_3), 376 and 374 (89 and 89, M − 2HOAc), 361 and 359 (100 and 100, M − 2HOAc − CH_3), and 333 and 331 (21 and 21, M − 2HOAc − CH_3CO). The major component of higher R_f gave the following spectra: $\bar{\nu}_{max}$ 1730 and 1250 (OAc), 1660 and 1600 (C=C–C=O), and 750 cm^{-1} (C–Br); ^1H NMR δ 6.62 (peak, 1 H, C-16), 5.45 (peak, 1 H, 12β-H), 5.00 (peak, 1 H, 7β-H), 3.8 (hump, 1 H, 3β-H), 2.24 (s, 3 H, C-20), 2.10 and 2.00 (s, 3 H each, 7α,12α-OAc's), and 0.96 (s, 6 H, C-18 and C-19); *m/e* 496 and 494 (1 and 1, M^+).

3α,12α-Diacetoxy-13α-carbomethoxy-16-oxo-17-oxa-13,17-seco-7α,17-cyclo-5β-androstane (7c). Diester **4a** (0.5 g) was heated at reflux with 5% KOH/CH_3OH (30 mL) for 12 h, cooled, diluted with H_2O, and concentrated in vacuo to remove most of the CH_3OH. The aqueous mixture was acidified with concentrated HCl and extracted with EtOAc. The residue **7a** left after removal of the EtOAc was dissolved in CH_2Cl_2 and sequentially reacted with diazomethane (**7b**) and Ac_2O and pyridine. The solid obtained after dilution with H_2O was recrystallized from benzene–hexane: mp 233–235 °C; $\bar{\nu}_{max}$ 1740 and 1250 cm^{-1} (OAc); ^1H NMR δ 5.13 (peak, 1 H, 12β-H), 4.6 (hump, 1 H, 3β-H), 4.3 (hump, 1 H, 7β-H), 3.63 (s, 3 H, OCH_3), 2.02 (s, 6 H, 3α, 12α-OAc's), 1.27 (s, 3 H, C-18), and 0.83 (s, 3 H, C-19); *m/e* (%) 450 (3, M^+), 419 (5, M − CH_3O), 408 (42, M − CH_2CO), 390 (7, M − HOAc), 348 (42, M − CH_2CO − HOAc), 330 (48, M − 2HOAc), 298 (29, M − CH_2CO − 2HOAc), 271 (100, M − 2HOAc − CO_2CH_3), and 270 (57).

Anal. CALCD FOR $C_{24}H_{34}O_8$: C, 63.98; H, 7.61. Found: C, 64.36; H, 7.60.

3,12,16-Trioxo-13α-carbomethoxy-17-oxa-13,17-seco-7α,17-cyclo-5β-androstane (8d). δ-Lactone **7b** (0.30 g) obtained as above was dissolved in acetone (20 mL), and Jones reagent was added dropwise while stirring on an ice bath until a brown color was obtained. The reaction was terminated by adding 2-propanol and the Grignard precipitate removed by filtration. The acetone was evaporated off and the residue taken up in EtOAc. This organic layer was washed with H_2O several times and evaporated to dryness. Recrystallization of the residue thus obtained with hexane–benzene gave diketone **8d** (0.07 g): mp 213–215 °C; $\bar{\nu}_{max}$ 1740 and 1720 cm^{-1}; ^1H NMR δ 4.7 (hump, 1 H, 7β-H), 3.80 (s, 3 H, OCH_3), 1.39 (s, 3 H, C-18), and 1.01 (s, 3 H, C-19); *m/e* (%) 362 (100, M^+), 347 (11, M − CH_3), 344 (25, M − H_2O), 331 (18, M − OCH_3), 318 (21, M − CO_2), 305 (63), 290 (28), 277(60), and 259 (48).

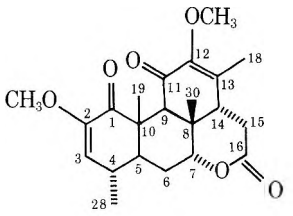
Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.32; H, 7.37.

Methyl 3α-Hydroxy-7α,12α-diacetoxy-16,17-seco-5β-androstane-16,17-dioate (4b). Triacetate **4a** (1.0 g) was reacted for 0.5 h in CH_3OH (10 mL) containing AcCl (0.5 mL). Diacetate **4b** (0.9 g) was obtained: mp 196–197 °C; $\bar{\nu}_{max}$ 3650 (OH), 1740 and 1250 (OAc), and 1720 cm^{-1} (CO_2CH_3); ^1H NMR δ 5.20 (peak, 1 H, 12β-H), 4.90 (peak, 1 H, 7β-H), 3.66 (s, 6 H, OCH_3), 3.6 (hump, 1 p, 3β-H), 2.62 (m, 2 H, C-15), 2.13 and 2.10 (s, 3 H each, 7α,12α-OAc's), 1.18 (s, 3 H, C-18), and 0.93 (s, 3 H, C-19); *m/e* (%) 482 (6, M^+), 451 (5, M − OCH_3), 439 (14, M − CH_3CO), 422 (13, M − HOAc), 407 (82, M − CH_3CO − CH_3OH), 389 (30, 407 − H_2O), 362 (22, M − 2HOAc), 347 (21, 362 − CH_3), 344 (16, M − 2HOAc − H_2O), 330 (53, 362 − CH_3OH), 312 (31, 344 − CH_3OH), and 285 (100, 344 − CO_2CH_3).

Anal. Calcd for $C_{25}H_{38}O_9$: C, 62.22; H, 7.94. Found: C, 62.39; H, 8.05.

Methyl 3α-Nitroxy-7α,12α-diacetoxy-16,17-seco-5β-androstan-16,17-dioate (4c). Diacetate **4b** (1.0 g) was nitrated to give **4c** (0.9 g) as a glassy solid: $\bar{\nu}_{max}$ 1740 and 1250 (OAc), 1630, 1280, 860, and 760 cm^{-1} (NO_3); ^1H NMR δ 5.13 (peak, 1 H, 12β-H), 4.87 (peak, 1 H, 7β-H), 4.8 (hump, 1 H, 3β-H), 3.61 and 3.58 (s, 3 H each, OCH_3's), 2.08 and 2.07 (s, 3H each, 7α,12α-OAc's), 1.17 (s, 3 H, C-18), and 0.97 (s, 3 H, C-19); *m/e* (%) 527 (2, M^+), 484 (6, M − CH_3CO), 467 (12, M − HOAc), 452 (50, M − HOAc − CH_3), 407 (42, M − 2HOAc), and 375 (27).

Methyl 3-Oxo-7α,12α-diacetoxy-16,17-seco-5β-androstane-16,17-dioate (4f). Diacetate **4b** (0.50 g) was oxidized by Jones reagent to give ketone **4f** (0.42 g): mp 218–220 °C; $\bar{\nu}_{max}$ 1740, 1715, and 1250 cm^{-1}; ^1H NMR δ 5.15 (peak, 1 H, 12β-H), 4.92 (peak, 1 H, 7β-H), 3.62 (s, 6 H, OCH_3's), 2.3 (m, 2 H, C-15), 2.08 and 2.05 (s, 3 H each, 7α,12α-OAc's), 1.20 (s, 3 H, C-18), and 1.03 (s, 3 p, C-19); *m/e* 480 (8, M^+), 449 (4, M − OCH_3), 437 (3, M − CH_3CO), 420 (28, M − HOAc),



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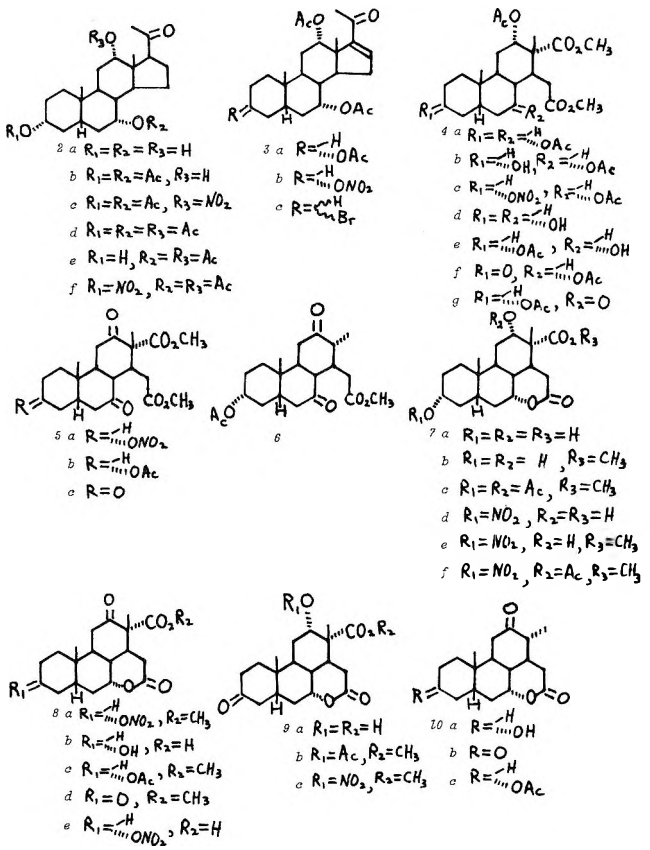
ification in 5% methanolic KOH, and selective acetylation[4] gave the diacetate **2b** which was transformed to **2c** with fuming nitric acid in Ac_2O. Selective hydrolysis of **2d** with methanolic HCl[1] gave diacetate **2e** which was also nitrated with fuming HNO_3 to give **2f**. Nitrate **2f** was treated with Br_2/HOAc and the isolated bromide was heated in HMPT, but did not yield the anticipated **3b**; the product of this conversion turned out to be a mixture of bromides **3c**. A similar bromination and HMPT reaction sequence for **2c** gave a complex mixture that we presume to be C-ring bromide products and was not further investigated.

The lactones were made from the various seco esters by a reaction sequence starting with saponification and subsequent lactone closure with acid treatment. Diester **4a**, formed from enone **3a** by ozonolysis and subsequent esterification, was saponified with methanolic KOH and treated with acid to yield lactone **7a** which yielded lactone **7b** upon esterification with diazomethane and lactone **7c** upon acetylation with acetic anhydride and pyridine; some recovered diester **4a** was also obtained from this sequence of reactions. Jones oxidation



of lactone **7b** gave lactone **8d** and a trace of **5c**. Alternatively, diester **4a** was selectively deacetylated with methanolic HCl to give hydroxy diester **4b** which was nitrated to yield nitroxy diester **4c** or oxidized to yield keto diester **4f**. Controlled saponification of **4c** followed by acid treatment (**7d**) and esterification with diazomethane afforded lactone **7e**. Acetylation or Jones oxidation of **7e** gave either **7f** or nitroxy δ-lactone **8a**, respectively; variable amounts of **5a** and **5c** were coproducts with the latter. Reduction of **8a** with Zn dust in HOAc (**8b**) followed by acetylation provided acetoxy δ-lactone **8c**. Attempts to selectively remove the 3α-acetate group in lactone **7c** with methanolic HCl resulted in concurrent lactone ring opening to yield dihydroxy diester **4d** which could be selectively acetylated with Ac_2O and pyridine to give hydroxy diester **4e**; oxidation of **4e** gave keto diester **4g**. Saponification of **4f** followed by acid treatment gave **9a**. Lactone **9a** was esterified with diazomethane and appropriately transformed to either **9b** or **9c**.

Introduction of the 12-oxo group led to decarboxylation at position 13 under acidic conditions. Diketo diester **5b** and diketo lactone **8d** were decarboxylated in refluxing glacial HOAc containing concentrated HCl to afford diketo ester **6** and δ-lactone **10b**, respectively. Jones oxidation of **7d** followed by Zn dust reduction of the nitroxy group in glacial HOAc gave a product (**8b**) that underwent decarboxylation upon removal of the acetic acid solvent to afford **10a**; acetylation of **10a** gave **10c** containing some precursor acid to ester **6**. Similar decarboxylation of **8a** in glacial HOAc containing concentrated HCl was attended by decomposition of the nitroxy group giving a complex mixture presumed to contain A-ring elimination and chloride products.

Discussion

Since nitrate esters are more resistant to hydrolysis than acetate esters under both acidic and basic conditions but are easily removed through reduction with Zn dust and glacial HOAc, we sought to selectively introduce the nitroxy group at positions 3 or 12 either before or after D-ring cleavage of 16-en-20-one cholic acid derivatives. Introduction before provided nitrate **2f** and **2c** which were subjected to bromination with Br_2/HOAc, but treatment of the corresponding 17α-bromo derivatives with hot HMPT led to **3c**.[5] Selective introduction of the nitroxy group at positions 3 or 12 after D-ring cleavage was easily accomplished on the seco esters **4**.

Conversion of the seco esters **4** to δ-lactones **7** was achieved by saponification of the esters and acid treatment to close the lactone ring. This conversion was never totally complete, for, invariably, starting material or products thereof were also recovered. Treatment of δ-lactone **7c** with methanolic HCl opened the lactone ring faster than hydrolysis of the 3α-acetoxy group, since a brief reaction period (0.5 h) gave both **4d** and **4e** and pure **4d** only after a longer reaction period (>1 h). A distinctive feature in the NMR spectra of the δ-lactones **7** is the wide separation of the angular methyl resonance signals (~18 Hz) as compared with the corresponding diesters (~10 Hz); a major contribution for this wider separation has come from increased shielding of the C-19 methyl group in the δ-lactone. Additionally, the 7β-H NMR signal appears as a hump (δ ~4.6) in the spectra of the δ-lactones but is a downfield peak (δ ~4.9) in the spectra of the precursor diesters, indicating that this proton is in an axial-like orientation in the δ-lactones. These facts may be explained by assuming chair conformations for rings A and C and strained boat conformations for ring B and the lactone ring. The mass spectral loss of ketene from the molecular ion of the 12α-acetoxy- and, to a lesser extent, 12α-nitroxy δ-lactones (**7c, 7f, 9b,** and **9c**) is characteristic of these lactones.

Although it is possible to selectively acetylate the 3α- and 7α-hydroxy groups in **2a**, a similar attempt to selectively acetylate only the 3α-hydroxy group in δ-lactone **7b** was without success, as only **7c** was obtained. However, it was possible to selectively deacetylate the 3α-acetate group in diester **4a** to give **4b**, which was transformed to an intermediate having the 12-oxo group (acid **8b**) permitting easy decarboxylation (to **10a**). Unlike methyl esters **8d** and **5b** which underwent transesterification followed by decarboxylation

−11° (c 0.227, $CHCl_3$); UV (MeOH) 220, 263 nm (ε 15 900, 6600); IR (KBr) 3530, 1795, 1750, 1720, 1640 cm^{-1}.

Anal. Calcd for $C_{30}H_{42}O_7$: C, 70.01; H, 8.23. Found: C, 69.71; H, 8.25.

The acetate **4b** could, however, be obtained as the major component of a mixture in the following manner.

A solution of chromium trioxide (0.260 g) in acetic acid (20 mL) was added slowly (144 h) to a solution of neriifolin 4′-acetate (**2c**, 0.500 g). The reaction mixture was worked up in the manner described above for neriifolin to give a crude product (0.380 g), which was mainly the acetate **4b** (see Table I for NMR spectrum) contaminated with a small amount of digitoxigenin formate **2g**. The mixture was subjected to column chromatography on neutral alumina (80 g, Fluka, activity I). The enone **6** (0.350 g, 78%) was eluted with hexane–ethyl acetate (9:1 and 17:3).

Digitoxigenin (2e). (A) Hydrolysis of Digitoxigenin Formate (2g). A solution of the formate (2.28 g, 0.00564 mol) in methanol (250 mL) and 0.1 N sulfuric acid (125 mL) was boiled under reflux for 1 h. The solution was neutralized by the addition of dilute sodium bicarbonate solution, the solvent was then removed in vacuo, and the residue was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated in vacuo, giving a residue which after crystallization from aqueous methanol and then ethyl acetate–ether gave digitoxigenin (1.56 g): mp 237–238 °C; $[\alpha]_D$ +18° (c 0.348, $CHCl_3$); UV (MeOH) 218 nm (ε 14 500) [lit.[25] mp 249–255 °C; $[\alpha]_D$ +14.6 ± 2° (MeOH)]. Chromatography of the mother liquor on silica gel (50 g) gave digitoxigenin formate [0.326 g, 14% recovery, eluted with hexane–ethyl acetate (2:1)] and a small amount (0.194 g) of digitoxigenin (total yield 1.75 g, 83%).

(B) Hydrolysis of the Enone 5. A solution of the enone (1.2 g, 0.00233 mol) in methanol (60 mL) and 0.1 N sulfuric acid (30 mL) was left at room temperature for 18 h. The reaction was worked up as described above to provide a solid, which was crystallized from ethyl acetate–ether to give digitoxigenin (0.61 g), mp 242–245 °C. The residue obtained on evaporation of the mother liquor was separated by TLC on silica gel using hexane–ethyl acetate as the developing solvent. In this way a further quantity (0.17 g, total yield 89%) of digitoxigenin was isolated as well as the nonpolar methyl glycoside **7** and the γ-pyrone **8**. After crystallization from dichloromethane–ether compound **7**, obtained in 8% yield, had: mp 97–98 °C; $[\alpha]_D$ −64° (c 0.45, $CHCl_3$); UV (MeOH) 255.5 nm (ε 5410); IR (KBr) 1710, 1645 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (d, 3 H, J = 6.8 Hz), 3.48 (s, 3 H), 3.62 (s, 3 H), 4.61 (q, 1 H, J = 6.8 Hz), 5.24 (d, 1 H, J = 4.2 Hz), 5.74 (d, 1 H, J = 4.2 Hz).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 56.06; H, 7.06.

The γ-pyrone **8**, obtained in 23% yield, had mp 155–157 °C [lit.[26] mp 160–162 °C] after crystallization from dichloromethane–ether: $[\alpha]_D$ 0° (c 0.252, $CHCl_3$); UV (MeOH) 277 nm (ε 11 000); IR (KBr) 3265, 1655, 1620, 1563 cm^{-1}.

Anal. Calcd for $C_6H_5O_3$: C, 57.14; H, 4.80. Found: C, 57.16; H, 4.69.

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Registry No.—7, 63493-69-6; 8, 118-71-8.

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Studies Directed toward Synthesis of Quassinoids. 5.[1] Conversion of D-Ring Seco Derivatives of Cholic Acid to δ-Lactones

Jerry Ray Dias* and R. Ramachandra[2]

Department of Chemistry, University of Missouri, Kansas City, Missouri 64110

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Various δ-lactones, 5,14-*epi*-28,30-dinorquassinoids, were synthesized from D-ring seco derivatives of cholic acid. Chemical and spectral evidence suggests that the δ-lactone ring in these compounds exists in a strained boat conformation.

In pursuit of our goal to convert cholic acid into analogues of quassin (**1**), we had the opportunity to synthesize a number of unique δ-lactones that may be regarded as 5,14-*epi*-28,30-dinorquassinoids. Herein, we describe our results in the lactonization of D-ring seco derivatives of cholic acid.[3]

Results

Conversion of the various ketones **2a** to **2f** to 16-en-20-ones for subsequent ozonolysis to give D-ring seco derivatives was explored. The ester ketone **2d** was converted to **2a** by sapon-

dium sulfate and evaporated in vacuo, giving a residue which on crystallization from ethyl acetate gave neriifolin (20 g) with mp 216–218 °C. The mother liquor from the crystallization was subjected to column chromatography on neutral alumina (800 g, Fluka, Activity III). Elution with hexane–ethyl acetate (60:40) gave a mixture of monoacetates which could be transesterified in the manner described above to give more neriifolin. Elution with hexane–ethyl acetate (1:1) gave a further quantity (6 g) of neriifolin (total of 26 g or 94% based on diacetate taken).

The transesterification could also be effected with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in methanol at room temperature (23 h). The reaction was worked up as described above to give a mixture which was separated by column chromatography on alumina. Neriifolin was isolated in 64% yield together with neriifolin 4′-monoacetate (**2c**, 30%). If the transesterification was allowed to proceed for 6 h the principal product was **2c** (see below).

Neriifolin 4′-Monoacetate (2c). A solution of neriifolin diacetate (6.0 g, 0.0097 mol) in dry methanol (250 mL) containing DBN (15 drops) was left at room temperature for 6 h. The solution was diluted with water, the product was extracted into ethyl acetate, and the extract was washed with water and dried over sodium sulfate. Evaporation of the solvent gave a residue which was chromatographed on neutral alumina (1.1 kg, Fluka, activity III). Elution with hexane–ethyl acetate (65:35) gave the starting diacetate (0.61 g, 10%). Neriifolin 4′-monoacetate (3.6 g, 64%) was eluted with hexane–ethyl acetate (3:2) and after crystallization from ether–pentane it had: mp 221–222 °C; $[\alpha]_D$ −55° (c 0.34, $CHCl_3$); UV (MeOH) 220.5 nm (ε 13 200); IR ($CHCl_3$) 3590, 3560, 1785, 1745, 1625 cm^{-1}.

Anal. Calcd for $C_{32}H_{48}O_9$: C, 66.64; H, 8.39. Found: C, 66.44; H, 8.41.

Finally, elution with hexane–ethyl acetate (9:11) gave neriifolin (1.2 g, 23%, mp 212–215 °C).

Oxidation of Neriifolin. (A) Chromium Trioxide in Acetic Acid. A solution of chromium trioxide in acetic acid (10 mg CrO_3/mL) was added, in a dropwise manner at room temperature, to a stirred solution of neriifolin (1.30 g, 0.00243 mol) in acetic acid (10 mL). The consumption of the starting material was followed by TLC, and the addition of the oxidant was continued until the starting material had almost disappeared. A total of 89 mL of the chromium trioxide solution was added during 28 h. The mixture was poured into ice–water and the resultant was exhaustively extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution, then with water, and finally, it was dried over sodium sulfate. The solvent was removed in vacuo and the residue was chromatographed on silica gel (100 g) to give the following products in succession.

1. Digitoxigen 3-formate (**2g**, 0.061 g; 6%) eluted with hexane–ethyl acetate (7:3). After crystallization from chloroform–ether it had: mp 191–193 °C; $[\alpha]_D$ +18° (c 0.276, $CHCl_3$); UV (MeOH) 218.5 nm (ε 17 000) [lit.[23] mp 198–201 °C; $[\alpha]_D$ +18 ± 3° ($CHCl_3$)].

2. Digitoxigenone (**2f**, 0.137 g, 15% eluted with hexane–ethyl acetate (3:2). After crystallization from acetone–ether it had: mp 194–197 °C; $[\alpha]_D$ +25° (c 0.313, $CHCl_3$); UV (MeOH) 217 nm (ε 16 200) [lit.[7b] mp 204–205 °C; $[\alpha]_D$ +32.3 ± 2° ($CHCl_3$)]. This was identical with an authentic specimen prepared by the oxidation of digitoxigenin.

3. Neriifolin-2′-one (**4a**, 0.087 g, 7%) eluted with hexane–ethyl acetate (3:2). The physical constants of this substance are recorded below.

4. Neriifolin-4′-one (**3a**, 0.234 g, 18%) eluted with hexane–ethyl acetate (3:2 and 1:1). The physical constants for this substance are recorded below.

5. Neriifolin (0.038 g, 3%) eluted with ethyl acetate.

6. A polar acidic material (0.415 g) eluted with methanol. After dissolution in aqueous sodium bicarbonate solution and reprecipitation with dilute hydrochloric acid, it had: mp 250–260 °C dec; $[\alpha]_D$ 0° (MeOH); UV (MeOH) 219 nm (ε 6600); IR (KBr) 3450, 1745, 1625 cm^{-1}.

Repetition of the above oxidation on a larger scale, using neriifolin (4.2 g) and chromium trioxide (6.0 g) in acetic acid (total volume of 185 mL) over a 48-h period, gave a crude product which was subjected to acidic hydrolysis. This was effected by heating a solution of the above mixture in methanol (160 mL) and 0.1 N sulfuric acid (120 mL) for 0.5 h at reflux temperature. The solvent was removed in vacuo and the residue was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and then evaporated in vacuo. The residue was subjected to thin-layer chromatography on silica gel using hexane–ethyl acetate (7:3) as the developing solvent. From this mixture was isolated digitoxigenone (0.50 g, 17%, mp 194–197 °C after crystallization from acetone–ether) and digitoxigenin (0.50 g, 17%). This latter substance had mp 233–236 °C after crystallization from acetone–ether: $[\alpha]_D$ +22° (c 0.382, $CHCl_3$); UV (MeOH) 217 nm (ε 15 500) [lit.[24] mp 243–246 °C; $[\alpha]_D$ +23° ($CHCl_3$); UV (MeOH) 217 nm (ε 16 200)].

(B) Collins Oxidation. To a vigorously stirred suspension of dry Celite (60 g) and pyridinium chromate (60 g) in dry dichloromethane (800 mL) at 0 °C was added a solution of neriifolin (10 g, 0.0187 mol) in anhydrous dichloromethane (100 mL). The mixture was stirred at 0 °C for 2.5 h and then at room temperature for 2 h. Sodium bisulfate monohydrate (100 g) was then added and agitation was continued for an additional 0.5 h. The mixture was filtered, the filter cake was exhaustively extracted with dichloromethane (total of 12 L), and the combined dichloromethane filtrate and extracts were washed with water and then dried over sodium sulfate. Evaporation of the solvent in vacuo gave a residue which was chromatographed on neutral alumina (1 kg, Fluka, activity III). Elution with hexane–ethyl acetate (65:35) removed a small amount of nonpolar material, which was followed by neriifolin-2′-one (1.0 g, 10%). This substance had mp 145–148 °C after crystallization from aqueous methanol: $[\alpha]_D$ 0° (c 0.108, $CHCl_3$); UV (MeOH) 217 nm (ε 11 750); IR (KBr) 3400, 1780, 1740 cm^{-1}.

Anal. Calcd for $C_{30}H_{44}O_8 \cdot 2H_2O$: C, 63.36; H, 8.51. Found: C, 63.66; H, 8.21.

Elution with hexane–ethyl acetate (60:40) gave neriifolin-4′-one (5.80 g, 58%), which after crystallization from aqueous methanol had: mp 163–166 °C; $[\alpha]_D$ −84° (c 0.274, MeOH); UV (MeOH) 216 nm (ε 13 500); IR (KBr) 3400, 1780, 1740, 1620 cm^{-1}.

Anal. Calcd for $C_{30}H_{44}O_8$: C, 67.64; H, 8.33. Found: C, 66.86; H, 8.42.

(C) Brown Oxidation.[18] A solution of neriifolin (5.14 g, 0.096 mol) in dichloromethane (500 mL) was vigorously stirred at room temperature with a chromic acid solution prepared from sodium dichromate dihydrate (7.63 g), water (48 mL), and concentrated sulfuric acid (4 mL). The reaction was followed by TLC on silica gel using a hexane–ethyl acetate (3:1) solvent system. After 48 h the chromic acid solution was replaced by an equivalent amount of fresh reagent and agitation was continued for 128 h. The organic phase was separated and combined with a dichloromethane extract of the aqueous phase. The dichloromethane solution was washed with water, dried over sodium sulfate, and evaporated in vacuo. The complex mixture thus obtained was resolved by column chromatography on silica gel (500 g). Elution with hexane–ethyl acetate (3:2) gave, in succession, digitoxigenin 3-formate (0.43 g, 11%), the enone **6** (0.072 g, 1.5%; the physical constants of this substance are recorded below), and the enone **5** (0.025 g, 0.5%; the physical constants of this substance are given below). Elution with hexane–ethyl acetate (9:1) gave digitoxigenone (0.13 g, 4%), followed by neriifolin-2′-one (**4a**, 0.74 g, 14%). Elution with ethyl acetate–hexane (1:1, 3:2, and 3:1) gave neriifolin-4′-one (**3a**, 2.62 g, 51%). Finally, neriifolin (0.94 g, 18%) was removed from the column by elution with ethyl acetate and then with methanol.

Acetylation of Neriifolin-4′-one (3a). A solution of **3a** (0.887 g, 0.00167 mol) in pyridine (25 mL), containing acetic anhydride (5 mL), was left at room temperature for 1 h. The solution was evaporated to dryness in vacuo and the residue (0.884 g) was crystallized from dichloromethane–ether to give **3b**: mp 193–194 °C; $[\alpha]_D$ −114° (c 0.302, $CHCl_3$); UV (MeOH) 218 nm (ε 11 500); IR (KBr) 3560, 1790, 1745, 1635 cm^{-1}.

Anal. Calcd for $C_{32}H_{46}O_9$: C, 66.87; H, 8.07. Found: C, 66.88; H, 8.17.

The acetate **3b**, synthesized in this way, was identical with a sample prepared by the Collins oxidation of neriifolin monoacetate (**2b**).

Synthesis of the Enone 5. A solution of the acetate **3b** (5.00 g, 0.0087 mol) in pyridine (100 mL) was heated at 80 °C for 48 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel (500 g). The solvents used for the development of the column contained a small amount of pyridine to minimize the acid hydrolysis of the enone to digitoxigenin. Elution with ethyl acetate–hexane (35:65) removed a small amount of a less polar impurity. The enone **5** [3.16 g, 71%; UV (MeOH) 221, 257 nm (ε 14 000, 5720)] was obtained as an amorphous solid, which after crystallization from methanol–water had mp 119–123 °C. Several recrystallizations from the same solvent system gave material: mp 175–178 °C; UV (identical with above); IR (KBr) 3500, 1790, 1755, 1715, 1650 cm^{-1}.

Anal. Calcd for $C_{30}H_{42}O_7 \cdot 0.5\ H_2O$: C, 68.88; H, 8.28. Found: C, 69.01; H, 8.10.

Elution with ethyl acetate–hexane (3:2) gave digitoxigenin (0.89 g, 27%), which was spectroscopically indistinguishable from that prepared in the manner described below.

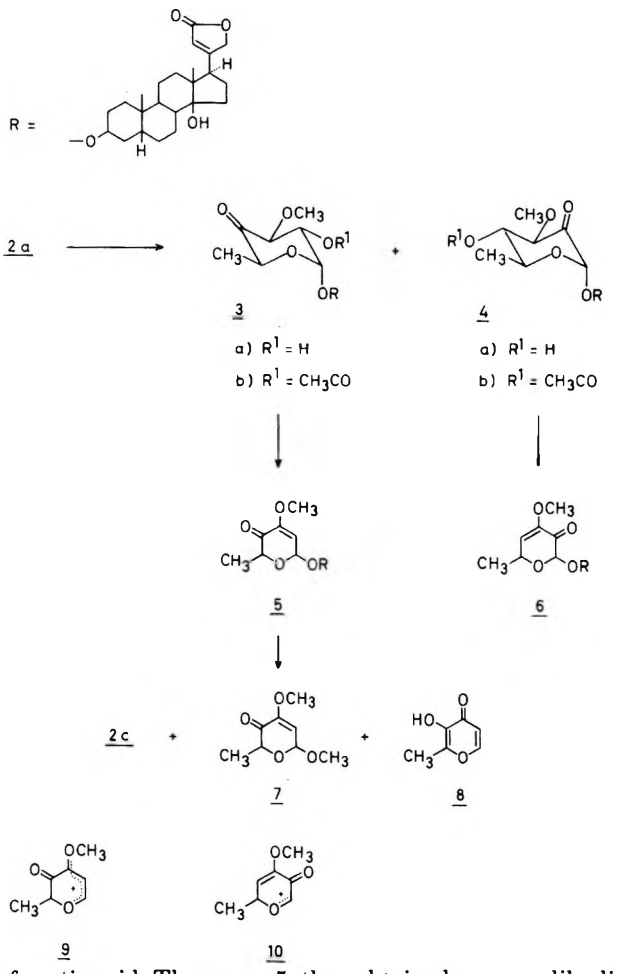
Synthesis of Acetate 4b and Enone 6. Acetylation of **4a** in the manner described above for **3a** gave the enone **6** directly in high yield. After crystallization from acetone–ether it had: mp 217–221 °C; $[\alpha]_D$

Table I. NMR Data[a] for Neriifolin and Related Compounds

Compd	Registry no.	1′-H	2′-H	3′-H	3′-OCH_3	4′-H	5′-H	5′-CH_3	3α-H	17α-H	18-CH_3	19-CH_3	H-21	H-21′	H-22
2a[b]	466-07-9	4.63 d J = 3.3			3.49	2.81 t J = 8.6		1.06 d J = 6.2	3.79 m	2.73 m	0.76	0.88	4.93	4.93	5.90
2b	25633-34-5	5.04 d J = 3.7	4.61 q J = 3.7 J = 10		3.55	3.16 t J = 9		1.24 d[c] J = 6	3.84 m	2.74 m	0.86	0.94	4.77 q[d,e]	5.02 q	5.85 t
2c	25633-33-4	4.91 d J = 3.7		3.36 t J = 9.1	3.50	4.65 t J = 9.1	3.79 m J = 6 J = 9.1	1.09 d[f] J = 6		2.73 m	0.87	0.96	4.74 q	4.97 q	5.82 t
2d	1065-34-5	5.06 d J = 3.4	4.65 q J = 3.4 J = 9.5	3.65 t J = 9.7	3.42	4.70 t J = 9.1	3.87 m J = 6 J = 9.1	1.10 d[g] J = 6	3.86 m	2.73 m	0.87	0.95	4.76 q	5.01 q	5.84 t
2e	143-62-4								4.11 m	2.76 m	0.87	0.97	4.75 q	5.01 q	5.86 t
2f	1102-88-1									2.75 m	0.90	1.01	4.75 q	5.00 q	5.85 t
2g	1250-96-0								5.22 m[h]	2.78 m	0.87	0.96	4.76 q	5.02 q	5.84 t
3a	58924-92-8	5.06 d J = 4.0		4.00 d J = 10	3.60		4.29 q J = 6.5	1.24 d J = 6.5	4.05 m	2.74 m	0.87	0.97	4.75 q	5.00 q	5.85 t
3b	63493-66-3	5.29 d J = 4.0	4.93 q J = 4.0 J = 10.7	4.20 d J = 10.7	3.58		4.36 q J = 6.5	1.28 d[i] J = 6.5	4.00 m	2.76 m	0.87	0.97	4.78 q	5.03 q	5.90 t
4a	63511-68-2	4.77		4.11 d J = 9	3.67			1.32 d J = 6.2	4.03 m	2.78 m	0.88	0.94	4.73 q	5.01 q	5.86 t
4b	63493-67-4	4.80		4.21 d J = 10.4	3.49	4.93 t J = 9.7		1.20 d[j] J = 6.2	4.03 m	2.74 m	0.87	0.94	4.76 q	4.94 q	5.87 t
5	63527-41-3	5.41 d J = 4.4	5.68 d J = 4.4		3.63		4.63 q J = 7	1.37 d J = 7	4.03 m	2.76 m	0.88	0.94	4.74 q	5.00 q	5.88 t
6	63493-68-5	4.95			3.62	5.71 d J = 1.5	4.84 m J = 1.5 J = 7	1.37 d J = 7	4.04 m	2.77 m	0.86	0.90	4.80 q	5.02 q	5.84 t

[a] Unless indicated otherwise, the spectra were recorded in $CDCl_3$. [b] Measured in Me_2SO-d_6. [c] Acetate methyl at δ 2.04. [d] H-21 and H-21′ assigned arbitrarily. [e] $J_{21,21'}$ = 18.0 ± 0.5 Hz, $J_{21,22}$ = 1.5 ± 0.2 Hz = $J_{21',22}$ for this and all subsequent compounds. [f] Acetate methyl at δ 2.08. [g] Acetate methyls at δ 2.03, 2.07. [h] Formyl hydrogen at δ 8.03. [i] Acetate methyl at δ 2.08. [j] Acetate methyl at δ 2.10.

Scheme I



of acetic acid. The enone **5,** thus obtained, was readily differentiated from **6** by means of its NMR spectrum. In particular, for **5,** the anomeric hydrogen and the adjacent olefinic proton appeared as a pair of doublets (J = 4.4 Hz) at δ 5.41 and 5.68, while for **6,** H-1′ and H-4′ showed singlet and doublet resonances at δ 4.95 and 5.71 (J = 1.5 Hz), respectively. In addition to the NMR spectral differences, the enones possessed markedly dissimilar stabilities toward 0.05 N sulfuric acid in 50% aqueous methanol. Whereas **5** was rapidly hydrolyzed to an easily separable mixture of digitoxigenin (45% yield from neriifolin), the methyl glycoside **7,** and 2-methyl-3-hydroxy-4-pyrone (**8**), even at room temperature, **6** was largely recovered from the hydrolytic medium after 1 h at reflux temperature. The ease of hydrolysis of **5** is presumably a reflection of the enhanced stability of the carbonium ion **9,** while the resistance to cleavage of **6** must derive from the destabilized nature of the α-oxocarbonium ion **10,** which would be generated if the hydrolysis of **6** was to occur.

The formation of the ketol **4a** was obviously deleterious to the yield of digitoxigenin, and therefore, various oxidative methods were investigated in order to reduce the amount of this substance in the mixture, or to eliminate it entirely. None of the methods studied was, however, as effective as the Collins oxidation, since a lower ratio of **3a/4a** was produced in every case.[16]

As mentioned previously, neriifolin monoacetate represents a considerable portion of the glycosidic material obtainable from *Thevetia* species, and consequently the conversion of this substance into digitoxigenin is also of importance. Oxidation of this acetate by the Collins method gave the ketoacetate **3b** in high yield, the degradation of which to digitoxigenin has already been described.

The formation of **3b** from neriifolin monoacetate conclusively establishes the structure of this substance as **2b.** Furthermore, it unambiguously demonstrates that, in both thevetin (**1a**) and thevetin monoacetate (**1b**), the gentobiose residue is attached to the C-4 oxygen of the thevetose moiety. This corrects a previous,[6] admittedly[21] uncertain, assignment of this structural point.

Neriifolin isolated from Mexican sources, as mentioned previously, contains neriifolin monoacetate and a glycoside (as well as the monoacetate thereof), the structure of the aglycone portion of which is not yet known.[22] The separation of these substances could be achieved by a combination of crystallization and column chromatography on silica gel. A more convenient procedure was to acetylate the glycosidic mixture and then separate the diacetates by column chromatography on silica gel. Neriifolin diacetate (**2d**) was then converted back into neriifolin by the zinc acetate or 1,5-diazabicyclo[4.3.0]non-5-ene promoted transesterification in methanol.

The experiments described above show that neriifolin is an attractive alternative source of digitoxigenin, especially in those parts of the world where *Thevetia* species are abundant.

Experimental Section

The melting points were determined in a Mel-Temp melting point apparatus and are not corrected. The infrared spectra were measured with a Perkin-Elmer Model 237 grating infrared spectrophotometer. The ultraviolet spectra were recorded on a Perkin-Elmer Model 402 ultraviolet visible spectrophotometer. The NMR spectra were measured with a Varian HA-100 spectrometer and are expressed as parts per million (δ) from internal tetramethylsilane.

Isolation of Neriifolin and Monoacetylneriifolin from *Thevetia thevetoides* Schum. The defatted (hexane), powdered meal (1.06 kg) from the seeds was incubated in water in the manner described by Helfenberger and Reichstein (see ref 7a, p 1479). The crude methanol extract (52 g) obtained therefrom crystallized spontaneously. Crystallization of this material from methanol–water gave crude neriifolin (25 g): mp 198–206 °C; $[\alpha]_D$ −46° (MeOH); UV (MeOH) 218 nm (ϵ 15 800). After recrystallization from the same solvent system, material with mp 209–214 °C was obtained: $[\alpha]_D$ −49° (c 0.39, MeOH); UV (MeOH) 218 nm (ϵ 17 300) [lit.[7a] mp 218–225 °C; $[\alpha]_D$ −50.2 ± 2° (MeOH); UV (EtOH) 217 nm (ϵ 12 500)]. Chromatography of the mother liquors on a column of silica gel gave monoacetylneriifolin (9 g, eluted with ethyl acetate–hexane, 2:3), which after crystallization from methanol had: mp 203–205 °C; $[\alpha]_D$ −88° (MeOH); UV (MeOH) 218 nm (ϵ 14 700). Recrystallization from aqueous methanol gave material with: mp 218–220 °C; $[\alpha]_D$ −91° ($CHCl_3$); UV (MeOH) 218 nm (ϵ 23 000) [lit.[7a] mp 240 °C; $[\alpha]_D$ −72.5° ($CHCl_3$)].

There was also obtained from the above chromatographic separation a mixture of glycosides (3.5 g) of unknown[22] structures.

Isolation of Neriifolin via Neriifolin Diacetate. The crude mixture of glycosides (100 g), from which some of the neriifolin had been removed (see above), pyridine (300 mL), and acetic anhydride (100 mL) were left to react at room temperature for 18 h. The solution was diluted with water and the products were extracted into ethyl acetate. The extract was washed successively with dilute hydrochloric acid, dilute sodium bicarbonate solution, and water, and then dried over sodium sulfate. Removal of the solvent in vacuo gave a residue (113 g) which was subjected to chromatography on neutral alumina (7 kg, Fluka, activity III). The column was eluted with hexane and then hexane–ethyl acetate mixtures, the hexane content of which was decreased gradually from 80 to 65%. Neriifolin diacetate (57.1 g, 95% pure by TLC), of a purity sufficient to be used in the transesterification reaction, was removed from the column with the 65:35 hexane–ethyl acetate mixture. One crystallization of this material from hexane–dichloromethane gave material: mp 126–128 °C; $[\alpha]_D$ −83° (c 0.41, $CHCl_3$); UV (MeOH) 219 nm (ϵ 13 800) [lit.[7a] mp 136–138 °C; $[\alpha]_D$ −79 ± 2° ($CHCl_3$)].

Elution of the column with pure ethyl acetate gave a mixture (28 g) of more polar acetates.

A solution of neriifolin diacetate (32 g, 0.052 mol) and zinc acetate (64 g, 0.42 mol) in anhydrous methanol (400 mL) was boiled under reflux for 48 h. Most of the methanol was removed in vacuo and water was added to the residue. The mixture was extracted with a large volume of ethyl acetate, and the extract was washed with dilute hydrochloric acid and then with water. The extract was dried over so-

Seeds of *Thevetia* Species as an Alternative Source of Digitoxigenin[1,2]

Alicia Cruz, Irene García, José Iriarte, Joseph M. Muchowski,* and Ignacio Regla

Research Laboratories, Syntex, S. A., Apartado Postal 10-820, Mexico 10, D. F.

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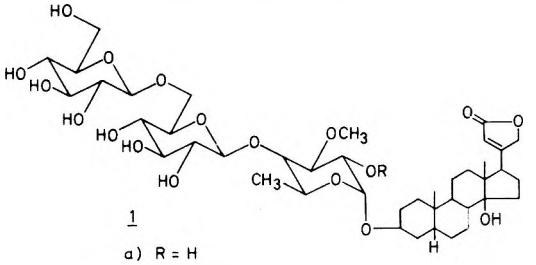
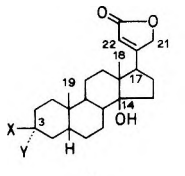
The Collins oxidation of neriifolin (**2a**) resulted in the selective formation of the β-ketol **3a**. This substance, after acetylation and pyridine-induced elimination of the elements of acetic acid, gave the enone **5**, which underwent hydrolysis to digitoxigenin (**2e**) under very mild acidic conditions.

Several species of *Thevetia* (Apocinacae), for example, *Th. thevetoides* Schum., and *Th. neriifolia*, Juss., grow wild in Mexico,[3] and the latter species in particular is also found in many other areas of the world.[4] The seeds of these plants have a high content of cardenolide triglycosides, mainly thevetin (**1a**) and acetylated or oxidized derivatives thereof.[5,6] Hydrolytic cleavage of the triglycosides by the endogenous enzyme(s) of the plant is known to give[5-7] a mixture of monoglycosides which consists mainly of neriifolin (**2a**), as well as

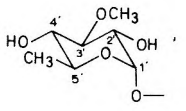


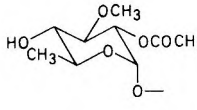
1

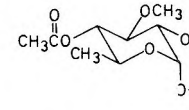
a) R = H
b) R = CH_3CO

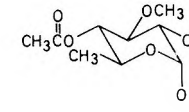


2

a) X =  Y = H

b) X =  Y = H

c) X =  Y = H

d) X =  Y = H

e) X = OH, Y = H

f) X, Y = O

g) X = OCHO, Y = H

lesser amounts of neriifolin monoacetate (**2b**) and other minor components. In principle, neriifolin and neriifolin monoacetate might serve as practical sources of digitoxigenin (**2e**), but the cleavage of the glycosidic linkages of these α-L-thevetosides[8] has to date not been accomplished in satisfactory yield either by chemical[7] or enzymatic[11] methods. Digitoxigenin is of importance in that it can serve as a useful point of embarcation for the synthesis of modified cardenolides.[12]

This paper describes a method whereby neriifolin and neriifolin monoacetate can be chemically degraded, under mild conditions and in practical yield, to digitoxigenin.

In connection with the determination of the structure of neriifolin, Helfenberger and Reichstein[7a] showed that acidic hydrolysis (0.35 N hydrochloric acid in acetone at room temperature) of this substance could not be effected without prior (or concomitant) elimination of the hydroxyl group at C-14 of the steroidal residue. These authors[7b] did, however, demonstrate that the glycosidic linkage could be cleaved, without loss of the 14-hydroxyl group, by the combined oxidative–hydrolytic process shown in eq 1 and 2. Digitoxigenin must have been liberated during the second phase of the process, at least, because oxidation (step 3) of the crude hydrolysate gave digitoxigenone (**2f**) in about 20% overall yield.

$$\text{Neriifolin} \xrightarrow[\text{2. 0.05 N } H_2SO_4]{\text{1. } CrO_3/CH_3COOH/\text{R.T.}} \text{Digitoxigenin?} \quad (1)$$

$$\text{Digitoxigenin} \xrightarrow[CH_3OH\text{–}H_2O/\text{reflux}]{\text{3. } CrO_3/CH_3COOH/\text{R.T.}} \text{Digitoxigenone} \quad (2)$$

Repetition of the first two steps of the above process gave a mixture in which the presence of digitoxigenin was confirmed (17% isolated yield), but this substance was accompanied by an equal amount of digitoxigenone. Indeed, careful examination of the oxidation mixture before acidic hydrolysis showed that digitoxigenone[13] was already present at this stage. Two glycosidic α-ketols (**3a** and **4a**, see below), digitoxigenin formate (**2g**), and an acid-soluble degradation product still containing the butenolide moiety were also isolated from this mixture. Digitoxigenin formate was rapidly converted into digitoxigenin under the conditions of step 2.

The early formation of digitoxigenone in the above process suggested that perhaps a part of the degradation of neriifolin was occurring via a glycosidic intermediate which fragmented to digitoxigenin under the acidic oxidation conditions. The synthesis of such an acid-labile intermediate, the hypothetical structure of which was based on speculation concerning the mechanistic nature of the oxidative degradation, was therefore investigated.

Collins oxidation[15] of neriifolin gave a 5.2–6.0:1 mixture of two β-ketols, **3a** and **4a** (Scheme I), which were easily distinguished by means of the multiplicity of the NMR absorptions (see Table I) of the anomeric hydrogens. The anomeric proton of the major product **3a** appeared as a doublet at δ 5.06 ($J_{1',2'}$ = 4 Hz), whereas this proton resonated as a singlet at δ 4.77 for the less abundant ketone. Both ketols were stable to the hydrolysis conditions shown in eq 1, but, as expected, chromic acid oxidation of either ketol gave digitoxigenin formate and digitoxigenone in a 1:2 ratio. The 4′-ketone **4a** was, however, oxidized at least five times as rapidly as **3a**. Acetylation of **3a** and **4a** with acetic anhydride in pyridine solution gave the acetate **3b** and the enone **6**, respectively. The acetate **4b**, obviously, had lost the elements of acetic acid under the acetylation conditions. This substance was preparable, albeit in an impure state, by the chromic acid oxidation of neriifolin 4′-acetate (**2c**, see below), but attempted purification of this substance by chromatography on alumina or silica gel resulted in the formation of the enone **6**. The acetate **3b** required heating in pyridine solution at 80 °C to effect the elimination

(8) C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.* **75,** 3505 (1953).
(9) M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29,** 1120 (1964).
(10) R. R. Muccino and C. Djerassi, *J. Am. Chem. Soc.*, **96,** 556 (1974), and earlier references therein.
(11) The 7-dehydrocholesterol benzoate was purchased from Dawe's Laboratories, Inc. It can be synthesized from cholesterol benzoate through a bromination–dehydrobromination sequence. See (a) R. Ikan, A. Markus, and E. D. Bergman, *Isr. J. Chem.*, **8,** 819 (1970); (b) F. Hunziker and F. X. Mullner, *Helv. Chim. Acta*, **41,** 70 (1958).
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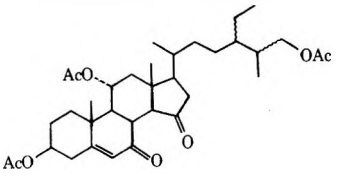
(16) Also, hydroboration of **7b** using B_2D_6 followed by oxidation with alkaline peroxide gave **8**-*14α-d*. Subsequent reactions produced cholest-7-ene-*14α-d* which has the physical and spectral properties characteristic of the unlabeled compound. This confirms the 14α configuration obtained from the hydroboration reaction. See, L. Partridge, Ph.D. Thesis, Stanford University, 1977; L. Partridge, I. Midgley, and C. Djerassi, *J. Am. Chem. Soc.*, submitted for publication.
(17) J. Romo, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73,** 5489 (1951).
(18) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry", Holden-Day, San Francisco, Calif., 1965.
(19) Compound **14** was prepared by hydrogenation of a sample of pregn-8(9)-ene-3β,11α,20β-triol-7-one (**22a**).[35] See ref 8.
(20) D. N. Kirk and W. Klyne, *J. Chem. Soc., Perkin Trans. 1*, 1076 (1974), and references therein.
(21) (a) H. Eggert and C. Djerassi, *J. Org. Chem.*, **38,** 3788 (1973); (b) H. Eggert, C. L. VanAntwerp, N. S. Bhacca, and C. Djerassi, *ibid.*, **41,** 71 (1976).
(22) The base peak in the mass spectrum of **13** at *m/e* 403 results from loss of the side chain from the molecular ion. This cleavage is readily rationalized for a C-15 ketone, but it would not be expected for a ketone at C-11.



This cleavage is analogous to the intense loss of methyl from 16-keto steroids. See, H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. II, Holden-Day, San Francisco, Calif., 1964, p 84. The loss of the side chain (plus acetic acid) is also a major mass spectral fragmentation for the 15-keto compound below obtained from oogoniol (see ref 6).
(23) (a) D. R. James and C. W. Shoppee, *J. Chem. Soc.*, 1064 (1956); (b) T. Barr, I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *ibid.*, 334 (1938).
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(25) See ref 15, pp 63–66.
(26) A. Dinner and K. Z. Farid, *Lloydia*, **39,** 144 (1976).
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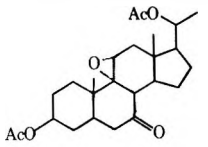
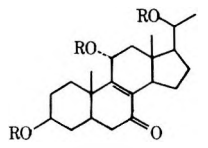
(28) B. N. Lutsky, J. A. Martin, and G. J. Schroepfer, Jr., *J. Biol. Chem.*, **246,** 6737 (1971).
(29) J. S. Dixon, I. Midgley, and C. Djerassi, *J. Am. Chem. Soc.*, **99,** 3432 (1977).
(30) The CD curve of a similar epoxy ketone, 9α, 11α-epoxypregnane-3β,20β-diol-7-one diacetate (**21**),[31] also displays a negative Cotton effect,



21

$[\theta]_{295}$ −2780. The magnitude of this Cotton effect is considerably more negative than that of epoxy ketone **10,** which may be due to a positive front octant contribution[20] of the 15α-acetate of **10.**
(31) A sample of this compound (see ref 8) was provided by Dr. L. Throop of Syntex Research, Palo Alto, Calif.
(32) The chemical shift value for the effect of the conjugated 8(9)-en-7-one chromophore was obtained from the observed chemical shifts of the angular methyl groups of cholest-8(9)-en-7-one. See I. Midgley and C. Djerassi, *J. Chem. Soc. Perkin Trans. 1*, 2771 (1972).
(33) The shape of the CD curve of **11a** $[\theta]_{245}$ −22 200, $[\theta]_{372}$ +1090 is similar to that of the related compound **22a**[31] (obtained by base treatment of epoxy



22a, R = H
22b, R = Ac

ketone **21**), but several differences are apparent. The major change is that the magnitude of the Cotton effect for **11a** in the $\pi \rightarrow \pi^*$ transition region $[\theta]_{288}$ −4440 is considerably less negative than that of **22a,** $[\theta]_{245}$ −22 000, and occurs at shorter wavelength. The differences may be due to the strong hydrogen-bonding interaction between the C-7 ketone and the 15α-alcohol of **11a.**
(34) There is a dramatic change in the shape of the CD curve upon acetylation of **11a** to yield the triacetate **11b.** The Cotton effect for **11b** in the $\pi \rightarrow \pi^*$ transition region has a large positive value $[\theta]_{248}$ +47 600, whereas **11a** shows a small negative value $[\theta]_{238}$ −4440. There must be a large conformational change around the unsaturated ketone upon acetylation of the alcohols which essentially results in a reversal of the chirality of this chromophore. See ref 18 and A. W. Burgstahler and R. C. Barkhurst, *J. Am. Chem. Soc.*, **92,** 7601 (1970). This conformational change is probably due mostly to the interaction of the 15α-acetate with the C-7 ketone; however, acetylation at C-11 may also have some effect, as seen from the CD curve of the triacetate **22b**[35], $[\theta]_{255}$ −6950, $[\theta]_{375}$ +2360, compared with that of the triolone **22a.**
(35) Compound **22b** was prepared by acetylation of a sample of **22a.**[31] See ref 8.
(36) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(37) The CD curve of this compound is similar to that of 7-ketocholesterol acetate, $[\theta]_{214}$ −45 900, $[\theta]_{335}$ +3600.

with saturated sodium thiosulfate, saturated $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Evaporation of the ether solution yielded 294 mg of yellow oil which was chromatographed on 25 g of silica eluting with 10% acetone–hexane to give a small amount (30 mg) of a yellow oil which was probably triacetylated material, then 235 mg of a crude mixture of the epimeric 6-bromo-7-ketones **15** as a yellow oil: NMR δ 4.21 [small signal, d, J = 2 Hz, 6α-H (6β-Br)], 4.68 [<1 H, d (superimposed on 3α-H signal at 4.61), J = 12 Hz, 6β-H(6α-Br)].

The α-bromo ketone **15** was directly dehydrobrominated with 120 mg of calcium carbonate in 4 mL of dry dimethylacetamide. The mixture was heated at the boiling point for 1 min and then poured into water. After neutralizing with dilute HCl, the mixture was extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to yield 240 mg of pale yellow oil which contained the enone **16a** plus some of the 3,5-dien-7-one (λ_{max} 283 nm). Chromatography on 20 g of silica eluting with 10% acetone–hexane afforded 176 mg (71%) of white crystals of the enone **16a:** mp 149–151 °C (acetone–hexane), $[\alpha]^{20}D$ −84.5° (c 1.14); IR 3440 (O–H), 1724, 1660 cm^{-1} (C=O); NMR δ 0.79 (s, 3 H, 18-CH_3; calcd[15] 0.78), 1.35 (s, 3 H, 19-CH_3; calcd[15] 1.28), 2.02, 2.04 (2× s, 6 H, -OAc), 3.94 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.32 (s, 1 H, 11β-H, $w_{1/2}$ ca. 14 Hz), 5.64 (s, 1 H, O–H), 5.87 (s, 1 H, 6-H); UV λ_{max} 239 (log ϵ = 4.05); CD[37] $[\theta]_{218}$ −46 700, $[\theta]_{321}$ +5230; mass spectrum m/e 516 (7%, M$^+$), 456 (100, M − AcOH), 396 (41, M − AcOH), 381 (16, M − 2AcOH + CH_3), 378 (24, M − 2AcOH + H_2O), 363 (11, M − 2AcOH + H_2O + CH_3), 325 (11, M − AcOH + H_2O + side chain), 283 (33, M − 2AcOH + side chain), 265 (24, M − 2AcOH + H_2O + side chain), 261 (14), 249 (11), 227 (26, M − 2AcOH + side chain + ring D − 1 H), 213 (48, M − 2AcOH + CH_3 + side chain + ring D), 209 (20, $C_{14}H_{25}O$).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.06; H, 9.50.

Cholest-5-ene-3β,11α,15α-triol-7-one (16b). A solution of the diacetate **16a** (20 mg) in 5 mL of methanol and 0.5 mL of H_2O was treated with 50 mg of K_2CO_3 at room temperature overnight. The solution was diluted with H_2O, neutralized with dilute HCl, and extracted well with ether. The combined ether extracts were dried over anhydrous Na_2SO_4 and evaporated to yield 18 mg of white semicrystalline material which contained the triolenone **16b** plus some 3,5-dien-7-one (UV 283 nm). Purification by preparative TLC on silica and developing with 1:1 acetone–hexane afforded 13 mg (78%) of white crystals of the triolenone **16b:** mp 102–104 °C (EtOAc–hexane); $[\alpha]^{20}D$ −65° (c 0.136); IR 3610, 3400 (O–H), 1653 cm^{-1} (C=O); NMR δ 0.75 (s, 3 H, 18-CH_3; calcd[15] 0.74), 1.36 (s, 3 H, 19-CH_3; calcd[15] 1.30); 3.5–4.3 [3× m (overlapping), 3 H, 3α-H, 11β-H, 15β-H], 5.81 (s, 1 H, O–H), 5.84 (s, 1 H, 6-H); UV λ_{max} 240 nm (log ϵ = 4.00); CD[37] $[\theta]_{224}$ −41 500, $[\theta]_{320}$ +6220; mass spectrum m/e 432.3255 (18%, M$^+$; calcd for $C_{27}H_{44}O_4$: 432.3239), 414.3128 (95, M − H_2O; calcd for $C_{27}H_{42}O_3$: 414.3134), 399 (11, M − H_2O + CH_3), 396 (18, M − 2H_2O), 381 (12, M − 2H_2O + CH_3), 301 (22, M − H_2O + side chain), 283 (40, M − 2H_2O + side chain), 265 (12, M − 3H_2O + side chain), 245 (11, M − H_2O + ring D + side chain − 1 H), 227 (16, M − 2H_2O + ring D + side chain − 1 H), 161 (100, $C_{11}H_{13}O$ (rings A + B − H_2O from C-3 + 1 H)).

Cholest-5-ene-3β,11α-diol-7,15-dione Diacetate (18). A solution of cholest-5-ene-3β,11α-15α-triol-7-one 3β,11α-diacetate (**16a**) (90 mg) in 10 mL of acetone was treated with excess Jones reagent[36] (ca. 0.1 mL) and stirred at room temperature for 20 min. The mixture was diluted with water and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to yield 89 mg of pale yellow semicrystalline material. Recrystallization from acetone–hexane afforded 80 mg (90%) of the diketone **18:** mp 173–176 °C; $[\alpha]^{20}D$ −101° (c 0.133); IR 1740, 1725, 1684 (C=O); NMR δ 0.80 (s, 3 H, 18-CH_3; calcd[15] 0.82), 1.34 (s, 3 H, 19-CH_3; calcd[15] 1.28), 2.04, 2.06 (2× s, 6 H, -OAc), 4.68 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.32 (m, 1 H, 11β-H, $w_{1/2}$ ca. 18 Hz), 5.90 (s, 1 H, 6-H); UV λ_{max} 235 (log ϵ = 4.10); CD $[\theta]_{233}$ −35 000, $[\theta]_{300}$ +12 600, $[\theta]_{330}$ +10 000; mass spectrum m/e 514 (1%, M$^+$), 454 (23, M − AcOH), 439 (95, M − AcOH + CH_3), 394 (42, M − 2AcOH), 379 (98, M − 2AcOH + CH_3), 341 (72, M − AcOH + side chain), 313 (14, M − AcOH + $C_{10}H_{21}$), 287 (12, M − AcOH + side chain + ring D), 281 (15, M − 2AcOH + side chain), 263 (M − 2AcOH + H_2O + side chain), 134 (100, $C_9H_{10}O$).

Anal. Calcd for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.06; H, 9.14.

Cholest-5-ene-3β,11α,15β-triol-7-one 3β,11α-Diacetate (20). A solution of the diketone 18 (70 mg) in 2 mL of dry THF was added to a stirred solution of LiAlH (O-t-Bu)$_3$[27] (140 mg) in 2 mL of dry THF and stirred overnight at room temperature. The excess hydride was decomposed by the addition of 15 mL of 5% AcOH and the solution was extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, and evaporated to yield 67 mg of the alcohol mixture **19** as a colorless oil: IR 3370 (O–H), 1730 cm^{-1} (C=O); mass spectrum 518 (M$^+$).

The crude alcohol mixture **19** was oxidized directly with MnO_2 (670 mg) in 10 mL of $CHCl_3$ by stirring overnight at room temperature. The MnO_2 was filtered and the precipitate was washed well with chloroform. The filtrate and washings were evaporated to yield 65 mg of pale yellow oil which contained predominantly the desired cholest-5-ene-3β,11α,15β-triol-7-one 3β,11α-diacetate (**20**). Preparative TLC on silica eluting with 30% acetone–hexane afforded 52 mg of colorless oil which was recrystallized from acetone–hexane to give 40 mg (57%) of white crystals of **20**, which contained some of the 15α-alcohol **16a** by NMR. A second recrystallization yielded 23 mg of **20** which still contained ca. 20–25% of the 15α epimer **16a:** mp 115–119 °C; $[\alpha]^{20}D$ −101° (c 1.35); IR 3480 (O–H), 1720, 1655 (C=O); NMR δ 1.02 (s, 3 H, 18-CH_3; calcd[15] 1.01), 1.32 (s, 3 H, 19-CH_3; calcd[15] 1.31), 2.02, 2.06 (2× s, 6 H, -OAc), 4.69 (2× m, 2 H, 3α-H and 15α-H), 5.32 (m, 1 H, 11β-H, $w_{1/2}$ ca. 18 Hz), 5.84 (s, 1 H, 6-H), plus small signals at 0.79 (18-CH_3), 3.96 (15β-H), and 5.64 (O–H) for the 15α-alcohol **16a;** UV λ_{max} 235 nm (log ϵ = 4.05); CD[37] $[\theta]_{215}$ −43 400, $[\theta]_{330}$ + 6950; mass spectrum m/e 516 (11%, M$^+$), 456 (100, M − AcOH), 396 (36, M − 2AcOH), 381 (19, M − 2AcOH + CH_3), 378 (24, M − 2AcOH + H_2O), 363 (11, M − 2 AcOH + H_2O + CH_3), 283 (30, M − 2AcOH + side chain), 265 (24, M − 2AcOH + H_2O + side chain), 261 (15), 227 (11, M − 2AcOH + side chain + ring D − 1H), 213 (32, M − 2AcOH + CH_3 + side chain + ring D), 211 (13) 209 (17).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 71.96, H, 9.42.

Cholest-5-ene-3β,11α,15β-triol-7-one (4). The diacetate **20** (which contained ca. 20–25% **16a**) (20 mg) was dissolved in 5 mL of methanol and 0.5 mL of H_2O and treated with 50 mg of K_2CO_3 overnight at room temperature. Standard workup yielded 19 mg of colorless oil which contained some 3,5-dien-7-one (UV 283 nm). Preparative TLC yielded 12 mg (70%) of white semicrystalline material which was predominantly the desired triolenone **4** plus some (ca. 20–25%) of the 15α-alcohol epimer **16b** (by NMR) and could not be recrystallized: $[\alpha]^{20}D$ −73° (c 0.15); IR 3610, 3440 (O–H), 1655 (C=O); NMR δ 0.99 (s, 3 H, 18-CH_3; calcd[15] 0.98), 1.36 (s, 3 H, 19-CH_3; calcd[15] 1.33), 3.72 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 4.15 (m, 1 H, 11β-H, $w_{1/2}$ ca. 18 Hz), 4.70 (m, 1 H, 15α-H, $w_{1/2}$ ca. 16 Hz), 5.83 (s, 1 H, 6-H), plus small signals at 0.75 (18-CH_3), 3.90 (15β-H), and 5.96 (O–H) for the 15α-alcohol **16b;** UV λ_{max} 238 nm (log ϵ = 4.0); CD[37] $[\theta]_{214}$ −53 000, $[\theta]_{327}$ +5250; mass spectrum m/e 432.3242 (24%, M$^+$; calcd for $C_{27}H_{44}O_4$: 432.3239), 414 (86, M − H_2O), 399 (15, M − H_2O + CH_3), 396 (17, M − 2H_2O), 381 (11, M − 2H_2O + CH_3), 301 (31, M − H_2O + side chain), 283 (32, M −2H_2O + side chain), 245 (14, M − H_2O + ring D + side chain − 1 H), 227 (14, M − 2H_2O + ring D + side chain − 1 H), 161 (100, $C_{11}H_{13}O$, rings A + B − H_2O from C − 3 + 1 H).

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Registry No.—**7a,** 20748-22-5; **7b,** 27751-96-8; **8,** 63358-19-0; **9a,** 63358-81-6; **9b,** 63324-87-8; **10,** 63324-88-9; **11a,** 63324-89-0; **11b,** 63324-90-3; **13,** 63324-91-4; **6α-15,** 63324-92-5; **6β-15,** 63358-83-8; **19,** 63324-93-6.

References and Notes

(1) This work was taken from the Ph.D. Thesis of E. J. Taylor, Stanford University, 1977.
(2) For reviews see: (a) L. Machlis in "The Fungi", Vol. II, G. C. Ainsworth and A. S. Sussman, Ed., Academic Press, New York, N.Y., 1966, p 415; (b) A. W. Barksdale, *Science*, **166,** 831 (1969); (c) L. Machlis, *Mycologia*, **64,** 235 (1972); (d) G. W. Gooday, *Annu. Rev. Biochem.*, **43,** 35 (1974).
(3) T. C. McMorris and A. W. Barksdale, *Nature (London)*, **215,** 320 (1967).
(4) G. P. Arsenault, K. Biemann, A. W. Barksdale, and T. C. McMorris, *J. Am. Chem. Soc.*, **90,** 5635 (1968); for proof of the C-22, C-23 configurations in the side chain, see ref 5d.
(5) (a) J. A. Edwards, J. S. Mills, J. Sundeen, and J. H. Fried, *J. Am. Chem. Soc.*, **91,** 1248 (1969); (b) T. C. McMorris, *J. Org. Chem.*, **35,** 458 (1970); (c) T. C. McMorris, R. Seshadri, and T. Arunachalam, *ibid.*, **39,** 669 (1974); (d) J. A. Edwards, J. Sundeen, W. Salmond, T. Iwadare, and J. H. Fried, *Tetrahedron Lett.*, 791 (1972).
(6) T. C. McMorris, R. Seshadri, G. R. Weihe, G. P. Arsenault, and A. W. Barksdale, *J. Am. Chem. Soc.*, **97,** 2544 (1975).
(7) R. F. N. Hutchins, M. J. Thompson, and J. A. Svoboda, *Steroids*, **15,** 113 (1970); see also G. D. Anderson, T. J. Powers, C. Djerassi, J. Fayos, and J. Clardy, *J. Am. Chem. Soc.*, **97,** 388 (1975).

peroxide and stirred at room temperature for 2 h.[8] (All the steroid had dissolved after 15 min.) The solution was poured into 1 L of ice–water, and the precipitate was filtered and dissolved in ether. The ether solution was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to give 8.10 g of pale yellow oil. This oil consisted of a complex mixture of products by TLC. The major product was the crystalline epoxyketone **10** which was isolated by column chromatography on silica (350 g) eluting with 2:1 hexane–ether. Recrystallization from methanol afforded 2.34 g (30%) of pure epoxy ketone **10** as white needles: mp 195–197 °C; $[\alpha]^{20}_D$ −46.0° (c 1.02); IR 1720 cm^{-1} (C=O); NMR δ 0.79 (s, 3 H, 18-CH_3; calcd[15] 0.73) 1.38 (s, 3 H, 19-CH_3; calcd[15] 1.30), 2.02, 2.04 (2 × s, 6 H, -OAc), 3.17 (d, 1 H, 11β-H, J = 5 Hz), 3.23 (d, 1 H, 8β-H, J = 11 Hz), 4.62 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.04 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz); $CD^{30}[\theta]_{295}$ −1140; mass spectrum *m/e* 516 (8%, M^+), 474 (42, M − C_2H_2O), 473 (13, M − C_2H_3O), 456 (97, M − AcOH), 455 (13), 428.3280 (16, M − AcOH + CO; calcd for $C_{28}H_{44}O_3$: 428.3290), 413.3047 (48, M − AcOH + CO + CH_3; calcd for $C_{27}H_{41}O_3$: 413.3056), 412.2978 (53, M − AcOH + C_2H_4O; calcd for $C_{27}H_{40}O_3$: 412.2977), 368 (12, M − 2AcOH + CO), 343 (57, M − AcOH + side chain), 316.1673 (100, M − AcOH + $C_{10}H_{20}$; calcd for $C_{19}H_{24}O_4$: 316.1675), 299.1651 (33, M − AcOH + C_2H_4O + side chain; calcd for $C_{19}H_{23}O_3$: 299.1647), 288 (12), 283 (13, M − 2AcOH + side chain), 261.2218 (34, M − AcOH + $C_{11}H_{15}O_3$; calcd for $C_{18}H_{29}O$: 261.2218), 260.2218 (13, M − AcOH + $C_{11}H_{16}O_3$; calcd for $C_{18}H_{28}O$: 260.2135), 260.1412 (10, calcd for $C_{16}H_{20}O_3$: 260.1412), 247.1333 (18, calcd for $C_{15}H_{19}O_3$: 247.1334).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.15; H, 9.56.

Cholest-8(9)-ene-3β,11α,15α-triol-7-one (11a). A solution of the epoxy ketone **10** (2.34 g) in 100 mL of 1% methanolic potassium hydroxide was allowed to stand overnight at room temperature. The solution was diluted with water, neutralized with dilute HCl, and extracted with ether, and the ether extracts were dried (Na_2SO_4) and evaporated to yield 2.13 g of pale yellow semicrystalline material. Chromatography on silica (60 g) eluting with 1:2 acetone–hexane gave 1.95 g (99%) of the triolenone **11a** as white crystals: mp 116–119 °C (EtOAc–hexane); $[\alpha]^{20}_D$ +112° (c 1.39); IR 3610, 3460 (O–H), 1655 (C=O), 1600 cm^{-1} (C=C); NMR δ 0.59 (s, 3 H, 18-CH_3; calcd[15,32] 0.65), 1.18 (s, 3 H, 19-CH_3; calcd[15,32] 1.30), 3.69 (m, 1 H, 3α-H, $w_{1/2}$ ca. 16 Hz), 4.21 (m, 1 H, 15β-H, $w_{1/2}$ ca. 15 Hz), 4.48 (m, 1 H, 11β-H, $w_{1/2}$ ca. Hz); UV λ_{max} 254 (log ε = 3.90); $CD^{33}[\theta]_{215}$ +2850, $[\theta]_{238}$ −4,440, $[\theta]_{267}$ +524, $[\theta]_{287}$ −207, $[\theta]_{347}$ +1490; mass spectrum *m/e* 432.3242 (2%, M^+, calcd for $C_{27}H_{44}O_4$: 432.3239), 414.3128 (100, M − H_2O; calcd for $C_{27}H_{42}O_3$: 414.3134), 399 (19, M − H_2O + CH_3), 301 (36, M − H_2O + side chain), 288 (10, M − H_2O + C_9H_{18}), 283 (26, M − $2H_2O$ + side chain), 245.1548 (M − H_2O + side chain + ring D − 1 H; calcd for $C_{16}H_{21}O_2$: 245.1542), 157.0656 (43, calcd. for $C_{11}H_9O$: 157.0633).

Cholest-8(9)-ene-3β,11α,15α-triol-7-one Triacetate (11b). Acetylation of the triolenone (**11a**) (50 mg) with excess acetic anhydride (0.5 mL) in pyridine (1 mL) at room temperature overnight yielded 62 mg of pale yellow crystals of the triacetate derivative **11b:** mp 160–162 °C (MeOH); $[\alpha]^{20}_D$ +140° (c 1.08); IR 1725, 1672 cm^{-1} (C=O); NMR δ 0.62 (s 3 H, 18-CH_3; calcd[15,32] 0.72), 1.14 (s, 3 H, 19-CH_3; calcd[15,32] 1.29), 2.05, 2.08, 2.10 (3 × s, 9 H, -OAc), 2.80 (d, 1 H, 14α-H, J = 10 Hz), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.72 (2 × m, 2 H, 11β-H and 15β-H); UV λ_{max} 249 (log ε = 4.00); CD^{34} $[\theta]_{218}$ −21 200, $[\theta]_{248}$ +47 600, $[\theta]_{285}$ −452, $[\theta]_{362}$ +2770; mass spectrum *m/e* 498 (7%, M − AcOH), 457.3311 (16, M − $C_4H_5O_3$; calcd for $C_{29}H_{45}O_4$: 457.3318), 456.3236 (26, M − $C_4H_6O_4$; calcd for $C_{29}H_{44}O_4$: 456.3239), 455.3165 (28, M − AcOH + C_2H_3O; calcd for $C_{29}H_{43}O_4$: 455.3161), 440.3287 (46, M − $C_4H_6O_4$; calcd for $C_{29}H_{44}O_3$: 440.3290), 438 (21, M − 2AcOH), 423 (12, M − 2AcOH + CH_3), 353 (11), 351.1967 (25; calcd for $C_{23}H_{27}O_3$: 351.1960), 338 (12), 327 (41, M − $C_4H_6O_4$ + side chain), 325 (32, M − 2AcOH + side chain), 311.1651 (63, M − 2AcOH + C_9H_{19}; calcd for $C_{20}H_{23}O_3$: 311.1647), 298.1574 (100, M − 2AcOH + $C_{10}H_{20}$; calcd for $C_{19}H_{22}O_3$: 298.1569), 287 (12), 284 (13).

Anal. Calcd. for $C_{33}H_{50}O_7$: C, 70.94; H, 9.02. Found: C, 71.05; H, 9.09.

Cholestane-3β,11α,15α-triol-7-one (12a). The catalytic hydrogenation of the triolenone **11a** (1.00 g) with 500 mg of 10% Pd on C in 50 mL of ethanol plus a couple of drops of pyridine at 20 °C and 1 atm was complete after 2 h. The catalyst was removed by filtration and the solution was concentrated to give 1.02 g of pale yellow oil which showed two spots on TLC. The oil was dissolved in 50 mL of 5% methanolic potassium hydroxide and heated under reflux for 3 h. TLC analysis of the reaction showed that the mixture had equilibrated to one product having the same R_f as the higher R_f compound (minor product) prior to base treatment. Chromatography of the resulting pale yellow crystalline material (1.03 g) on silica (30 g) eluting with 1:2 acetone–hexane afforded 905 mg (90%) of white crystals of the triolone **12a:** mp 117–120 °C (ether); $[\alpha]^{20}_D$ +4.7° (c 1.11); IR 3610, 3450 (O–H), 1695 cm^{-1} (C=O); ^1H NMR δ 0.72 (s, 3 H, 18-CH_3; calcd[15] 0.72), 1.21 (s, 3 H, 19-CH_3; calcd[15] 1.21), 3.60, 3.80, 4.00 (3× m (overlapping), 3 H, 3α-H, 15β-H, and 11β-H); ^{13}C NMR, see Table I; CD $[\theta]_{290}$ +1770 (dioxane), $[\theta]_{288}$ +922 (methanol), $[\theta]_{288}$ +931 (room temp EPA), $[\theta]_{289}$ +922 (low temp EPA); mass spectrum *m/e* 434.3394 (14%, M^+; calcd for $C_{27}H_{46}O_4$: 434.3396), 416 (9, M − H_2O), 398 (15, M − $2H_2O$), 303 (21, M − H_2O + side chain), 285 (8, M − $2H_2O$ + side chain), 209.1911 (60, calcd for $C_{14}H_{25}O$: 209.1905), 208.1456 (36, calcd for $C_{13}H_{20}O_2$: 208.1463), 207.1380 (100, calcd for $C_{13}H_{19}O_2$: 207.1385); metastable defocusing, parent ions of 209; 434.49 (M^-, ca. 30%), 253.39 (M − $C_{11}H_{17}O_2$ (rings A and B + 1 H), ca. 60%), also 417.01, 398.57, 380.77, 322.28, 266.98, 223.70 (all <2%): 208; 434.94 (M^+, ca. 75%), 417.23 (M − OH, ca. 23%), also 304.61, 251.55, 222.68 (all <1%): 207; 434.42 (M^+, ca. 56%), 416.48 (M − H_2O, ca. 37%), 303.14 (M − side chain + H_2O, ca. 5%), also 399.48, 265.68, 249.72, 236.29 (all <1%).

Cholestane-3β,11α,15α-triol-7-one 3β,11α-Diacetate (12b). The triolone **12a** (900 mg) was acetylated in pyridine (20 mL) by treatment with acetic anhydride (10 mL) at room temperature for 2.5 h. The pale yellow oil (1.09 g) obtained after standard workup was chromatographed on silica (70 g) eluting with 10% acetone–hexane to give first a colorless oil (36 mg) which was identified as the triacetylated derivative **12c** and then 989 mg (92%) of white crystals of the 3β,11α-diacetate **12b:** mp 126–127.5 °C (acetone–hexane); $[\alpha]^{20}_D$ −7.0° (c 1.51); IR 3455 (O–H), 1720 and 1700 cm^{-1} (C=O); ^1H NMR δ 0.76 (s, 3 H, 18-CH_3; calcd[15] 0.75), 1.22 (s, 3 H, 19-CH_3; calcd[15] 1.20), 2.00, 2.04 (2× s, 6 H, -OAc), 3.80 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz), 4.64 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.07 (s, 1 H, OH), 5.25 (m, 1 H, 11β-H, $w_{1/2}$ ca. 16 Hz); ^{13}C NMR, see Table I; CD $[\theta]_{290}$ +2510; mass spectrum *m/e* 518 (8%, M^+), 503 (7, M − CH_3), 458 (25, M − AcOH), 443 (12, M − AcOH + CH_3), 440 (52, M − AcOH + H_2O), 425 (8, M − AcOH + H_2O + CH_3), 405 (30, M − side chain), 380 (12, M − 2AcOH + H_2O), 365 (15, M − 2AcOH + H_2O + CH_3), 345 (33, M − AcOH + side chain), 327 (33, M − AcOH + H_2O + side chain), 267 (14, M − 2AcOH + H_2O + side chain), 250 (61, $C_{15}H_{22}O_3$), 249 (100, $C_{15}H_{21}O_3$), 211 (21), 209 (70, $C_{14}H_{25}O$).

Anal. Calcd for $C_{31}H_{50}O_6$: C, 71.78; H, 9.72. Found: C, 71.92; H, 9.84.

Cholestane-3β,11α,15α-triol-7-one Triacetate (12c). When the acetylation of the triolone **12a** was allowed to run for a longer period of time, i.e., overnight, larger amounts of the triacetate **12c** were obtained. Column chromatography separated this triacetate from the diacetate **12b,** but as a colorless oil which could not be crystallized: $[\alpha]^{20}_D$ −32.3° (c 1.16); IR 1720 cm^{-1} (C=O); ^1H NMR δ 0.81 (s, 3 H, 18-CH_3; calcd[15] 0.78), 1.23 (s, 3 H, 19-CH_3; calcd[15] 1.19), 1.97, 2.00 (3× s, 9 H, -OAc), 4.36–5.46 (3 m (overlapping), 3 H, 3α-H, 11β-H, and 15β-H); ^{13}C NMR, see Table I; CD $[\theta]_{295}$ +2070; mass spectrum *m/e* 517 [100%, M − 43 (C_2H_3O)], 457 (19, M − AcOH + 43), 440 (83, M − 2AcOH), 425 (10, M − 2AcOH + CH_3), 397 (9, M − 2AcOH + 43), 327 (42, M − 2AcOH + side chain).

Anal. Calcd for $C_{33}H_{52}O_7$: C, 70.68; H, 9.35. Found: C, 70.53; H, 9.29.

Cholestane-3β,11α-diol-7,15-dione Diacetate (13). A solution of cholestane-3β,11α,15α-triol-7-one 3β,11α-diacetate (**12b**) (50 mg) in 5 mL of acetone was treated with excess Jones reagent[36] (ca. 0.05 mL) and stirred 30 min at room temperature. The reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to yield a colorless oil (49 mg, 98%) which crystallized on standing. Recrystallization from acetone–hexane gave fine white needles of the diketone (**13**): mp 179–181 °C; $[\alpha]^{20}_D$ −2.1° (c 0.52); IR 1740, 1720 cm^{-1} (C=O); NMR δ 0.76 (s, 3 H, 18-CH_3; calcd[15] 0.79), 1.22 (s, 3 H, 19-CH_3; calcd[15] 1.20), 2.01, 2.03 (2× s, 6 H, -OAc), 4.62 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.21 (m, 1 H, 11β-H, $w_{1/2}$ ca. 17 Hz); CD $[\theta]_{295}$ +9680; mass spectrum *m/e* 516 (5%, M^+), 501 (25, M − CH_3), 457 (51), 456 (78, M − AcOH), 441 (71, M − AcOH + CH_3), 403 (100, M − side chain), 343 (34, M − AcOH + side chain), 288 (17, M − AcOH + side chain + ring D), 283 (23, M − 2AcOH + side chain), 273 (11, M − AcOH + side chain + ring D + CH_3), 228 (46, M − 2AcOH + side chain + ring D), 211 (28), 209 (13).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.07; H, 9.48.

Cholest-5-ene-3β,11α,15α-triol-7-one 3β,11α-Diacetate (16a). A solution of cholestane-3β,11α,15α-triol-7-one 3β,11α-diacetate (**12b**) (250 mg, 0.483 mmol) in 5 mL of acetic acid was warmed to 70 °C. Pyridinium hydrobromide perbromide[24] (162 mg, 0.507 mmol) was added portionwise over 10 min and the solution was stirred an additional 20 min at 70–75 °C. The solution was poured into saturated $NaHCO_3$ and extracted with ether. The ether extracts were washed

lest-5-ene-3β,11α,15β-triol-7-one 3β,11α-diacetate (**20**). Unfortunately, this reduction was not as stereospecific as had been anticipated and the product contained ca. 20–25% [as judged by the intensity of the C-18 methyl, C-15 proton, and 15α-OH signals in the NMR spectrum (see Table II)] of the 15α-alcohol **16** which could not be separated from the 15β-epimer **20** by TLC. Two recrystallizations of this mixture left the product ratio essentially unchanged.

The spectral properties of cholest-5-ene-3β,11α,15β-triol-7-one 3β,11α-diacetate (**20**) (which contained some **16a**), with the exception of the NMR spectrum, are very similar to those of the 15α epimer **16a**. Both the mass spectrum and the CD curve of **20** are almost identical to those of **16a**. The infrared and UV spectra of **20** show unsaturated carbonyl absorptions at 1655 cm^{-1} and 235 nm (log ε = 4.05) compared to 1660 cm^{-1} and 239 nm (log ε = 4.05) for **16a**. The NMR spectrum of the 15β-alcohol **20**, however, shows two major differences from that of the 15α-epimer **16a** (see Table II). The signal for the C-18 methyl group of **20** appears at δ 1.02 ppm, which is 0.23 ppm further downfield than the C-18 methyl resonance of **16a** at 0.79 ppm. This large downfield shift is expected for the change from a 15α-alcohol to a 15β-alcohol.[14,15] The 15α-H of the 15β-alcohol **20** is also strongly deshielded by the C-7 ketone[25] and appears at 4.69 ppm. This chemical shift is comparable to the 4.73 ppm resonance of the 15α-H of the analogous 15β-alcohol **17** in the oogoniol series[6] (see Table II), whereas the 15β-H of the 15α-alcohol **16a** appears at 3.94 ppm. The other NMR signals for the protons at C-3, C-11, and C-6 have similar chemical shifts to the corresponding protons in both **16a** and **17**.

To complete the synthetic scheme, the diacetate **22** was treated with potassium carbonate in aqueous methanol to yield cholest-5-ene-3β,11α,15β-triol-7-one (**4**), the target molecule of this synthesis. Again, with the exception of the NMR spectrum (see Table II), the spectral properties of the 15β-alcohol **4** (which contains some of the 15α-epimer **16b**) resemble those of the 15α-alcohol **16b**. As is the case for the diacetate precursor **20**, the NMR spectrum of **4** shows a 0.24 ppm downfield shift of the C-18 methyl group at δ 0.99 ppm compared to the C-18 methyl resonance of the 15α epimer **16b** at 0.75 ppm. Furthermore, the 15α-H of the 15β-alcohol **4**, which is deshielded by the C-7 ketone,[25] resonates at 4.70 ppm compared with a chemical shift of 4.68 ppm for the 15α-H of oogoniol (**2d**).[6]

Cholest-5-ene-3β,11α,15β-triol-7-one (**4**) and cholest-5-ene-3β,11α,15α-triol-7-one (**16b**) were submitted to Professor T. C. McMorris (University of California at San Diego) for hormone B bioassay in *Achlya*. Even at the highest doses tested (3.5 μg/mL for the 15α-isomer **16b** and 22.6 μg/mL for the 15β-isomer **4**) no biological activity was observed, whereas the natural oogoniol-1 was fully active at 1.8 μg/mL. Unless the small contaminant of the 15α epimer **16b** present in **4** had a hormone antagonist action, one can conclude that the intact nuclear skeleton is not sufficient for significant sex-hormone activity and that the hydroxylated side chain plays an essential role.

Experimental Section

General Notes. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded for solutions in chloroform on a Perkin-Elmer Model 421 spectrometer. Optical rotations were measured for solutions in chloroform using a Perkin-Elmer Model 141 spectropolarimeter. Ultraviolet (UV) spectra were recorded on a Cary-14 spectrometer for solutions in ethanol. Nuclear magnetic resonance (NMR) spectra were recorded on Varian Model T-60 (^1H NMR) and Varian XLFT-100 (^1H and ^{13}C NMR) spectrometers using deuteriochloroform as solvent and tetramethylsilane as internal reference. The 100 MHz ^1H NMR spectra were determined by Ronald L. Elsenbaumer and Dr. L. J. Durham and the ^{13}C NMR spectra by Craig L. VanAntwerp. Circular dichroism (CD) curves were determined by Mrs.R. Records with a JASCO Model ORD/UV-5 spectrometer modified for CD for solutions in dioxane, unless otherwise specified. Low-resolution mass spectra were determined by Mr. R. G. Ross with an AEI MS-9 spectrometer operating at 70 eV using a direct inlet system. The mass spectra and CD curves are reproduced in the Ph.D. thesis of E. J. Taylor, Stanford University, 1977. High-resolution mass spectra and metastable defocussing were also obtained with the MS-9 instrument. Element analyses were determined by the Microanalytical Laboratory, Stanford University.

Column chromatography was done using E. Merck silica gel 60 (60–230 mesh ASTM). The progress of all reactions and column chromatographies was monitored by thin-layer chromatography on E. Merck silica gel $HF_{254+366}$ plates visualized by spraying with ceric sulfate solution (2% in 1 M sulfuric acid) followed by heating. Preparative thin-layer chromatography was done on 0.75-mm thick $HF_{254+366}$ silica gel plates and the bands were detected either visually or by viewing under ultraviolet light.

Cholesta-7,14-dien-3β-ol (7b). Cholesta-7,14-dien-3β-ol benzoate (**7a**)[10] (11.0 g) was saponified by heating under reflux in 5% methanolic potassium hydroxide (150 mL) for 3 h. The white crystalline material obtained after workup was recrystallized from methanol to yield 8.10 g (92%) of the alcohol **7b** as white needles: mp 103–105 °C (lit.[28] mp 104–105 °C); $[\alpha]^{20}_D$ −185° (*c* 1.41); IR 3610, 3450 (O–H), 1635 cm^{-1} (C=C); NMR δ 0.77 (s, 3 H, 18-CH_3), 0.80 (s, 3 H, 19-CH_3), 3.60 (m, 3α-H, $w_{1/2}$ ca. 16 Hz), 5.48, 5.75 (2 × m, 2 H, 7-H, and 15-H); mass spectrum *m/e* 384 (100%, M^+), 369 (25, M − CH_3), 351 (12, M − CH_3 + H_2O), 271 (94, M − side chain), 257 (29, M − C_9H_{19}), 253 (15, M − side chain + H_2O).

Cholest-7-ene-3β,15α-diol (8). Cholesta-7,14-dien-3β-ol (**7b**) was hydroborated using a modification of Sondheimer's procedure.[9] A stirred solution of dienol **7b** (7.50 g, 19.5 mmol) in 300 mL of anhydrous ether was cooled to 0 °C under nitrogen. To this solution was added 80 mL of a 1 M solution of BH_3 in THF dropwise over 1 h at 0 °C under nitrogen. Stirring was continued an additional hour at room temperature, and then the excess borane was decomposed by careful addition of water. This mixture was oxidized directly with alkaline peroxide by cooling to 0 °C and adding 80 mL of 10% aqueous sodium hydroxide. Then, 60 mL of 30% aqueous hydrogen peroxide was added dropwise and the mixture was stirred at 0 °C for 1 h. The organic layer was separated and washed with 10% sodium sulfite solution and brine. After drying over anhydrous Na_2SO_4, the solution was evaporated to give 7.57 g of white crystalline material. Column chromatography on 300 g of silica eluting with ether yielded 6.15 g (78%) of the enediol 8 as white crystals: mp 184.5–186 °C (acetone); $[\alpha]^{20}_D$ +45.6° (*c* 1.32); IR 3615, 3470 cm^{-1} (O–H); NMR δ 0.57 (s, 3 H, 18-CH_3; calcd[15] 0.57), 0.80 (s, 3 H, 19-CH_3; calcd[15] 0.81), 3.57 (m, 1 H, 3α-H, $w_{1/2}$ ca. 14 Hz), 4.20 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz), 5.44 (m, 1 H, 7-H); mass spectrum *m/e* 402 (47%, M^+), 387 (39, M − CH_3), 384 (100, M − H_2O), 369 (36, M − H_2O + CH_3), 351 (15, M − 2H_2O + CH_3), 317 (11), 290 (20, M − $C_7H_{12}O$ (RDA from Δ^7 double bond)[29]), 289 (10, M − side chain), 271 (84, M − H_2O + side chain), 257 (22, M − H_2O + C_9H_{19}), 253 (13, M − 2H_2O + side chain), 247 (16), 235 (12), 112 (48, $C_7H_{12}O$(RDA)).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.64; H, 11.56.

Cholesta-7,9(11)-dien-3β,15α-diol Diacetate (9b). Mercuric acetate (10.0 g) was added to a solution of 5.00 g of cholest-7-ene-3β,15α-diol in 125 mL of chloroform and 200 mL of acetic acid, and the mixture was stirred vigorously for 18 h at room temperature.[17] The mixture was filtered, and the filtrate was concentrated to a small volume in vacuo, dissolved in ether, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The resulting orange crystalline material (5.78 g) containing the dienediol **9a** was acetylated directly with acetic anhydride in pyridine. The orange oil (6.36 g) obtained after workup was chromatographed on 250 g of silica eluting with 15% ether–hexane. Recrystallization of the product from methanol gave 3.74 g (62%) of the diene diacetate **9b**: mp 126–128 °C; $[\alpha]^{20}_D$ +107° (*c* 1.06); IR 1725 (C=O), 1604 cm^{-1} (C=C); NMR δ 0.57 (s, 3 H, 18-CH_3; calcd[15] 0.57), 0.90 (s, 3 H, 19-CH_3; calcd[15] 0.92), 2.00, 2.03 (2 × s, 6 H, –OAc), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 14 Hz), 5.00 (m, 1 H, 15β-H, $w_{1/2}$ ca. 16 Hz), 5.45 (m, 2 H, 7-H and 11-H); UV λ_{max} 234, 242, 249 (log ε = 4.23, 4.29, 4.12); mass spectrum *m/e* 242 (32%, M − AcOH), 311 (100, M − AcOH + side chain), 251 (14, M − 2AcOH + side chain).

Anal. Calcd for $C_{31}H_{48}O_4$: C, 76.82; H, 9.98. Found: C, 76.64; H, 9.98.

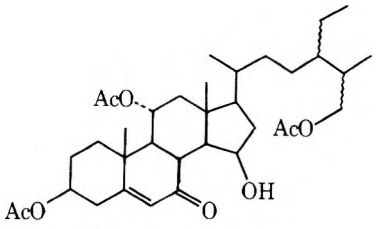
9α,11α-Epoxycholesta-3β,15α-diol-7-one Diacetate (10). A suspension of cholesta-7,9(11)-diene-3β,15α-diol diacetate (**9b**) (7.30 g) in 200 mL of formic acid was treated with 5 mL of 30% hydrogen

Table II. Chemical Shifts of Proton Signals in a Series of Steroids Related to Oogoniol (2d)

Compd	Registry no.	18-CH_3	19-CH_3	3α-H	11β-H	15β-H	15α-H	6-H	15α-OH
12b		0.76	1.22	4.64	5.25	3.80			5.07
16a	63324-83-4	0.79	1.35	4.70	5.32	3.94		5.87	5.64
18	63324-84-5	0.80	1.34	4.68	5.32			5.90	
17	63358-17-8	1.01	1.32	4.73	5.32		4.73	5.84	
20	63324-85-6	1.02	1.32	4.69	5.32		4.69	5.84	
16b	63340-13-6	0.75	1.36	~3.65	~4.15	~3.95		5.84	5.81
4	63324-86-7	0.99	1.36	3.72	4.15		4.70	5.83	
2d	63358-18-9	0.96	1.34	Not given	4.14		4.68	5.80	

forded a 71% yield (from **12b**) of cholest-5-ene-3β,11α,15α-triol-7-one 3β,11α-diacetate (**16a**). The mass spectrum of **16a** shows slight traces of the saturated ketone **12b,** but the spectral properties are in accord with the assigned structure.

The presence of the unsaturated ketone is confirmed by the appropriate carbonyl absorptions in the IR and UV spectra, and the CD curve of **16a** is almost identical to that of cholest-5-en-3β-ol-7-one acetate. The NMR spectrum shows a vinyl proton signal as well as a sharp singlet at δ 5.64 ppm which is assigned to the alcohol proton on the basis of its ability to exchange with D_2O. Compound **12b** shows a similar alcohol proton resonance at 5.07 ppm and the presence of these signals probably is due to the previously demonstrated hydrogen-bonding interaction of the 15α-alcohol and the C-7 ketone. The signals in the NMR spectrum of the enone **16a** for the 3α, 11β, and 15β protons appear at approximately the same chemical shifts as for the saturated ketone **12b** (see Table II). However, the 15α proton of the related 15β alcohol **17**[6] in the oogoniol series resonates at 4.73 ppm, compared to



17

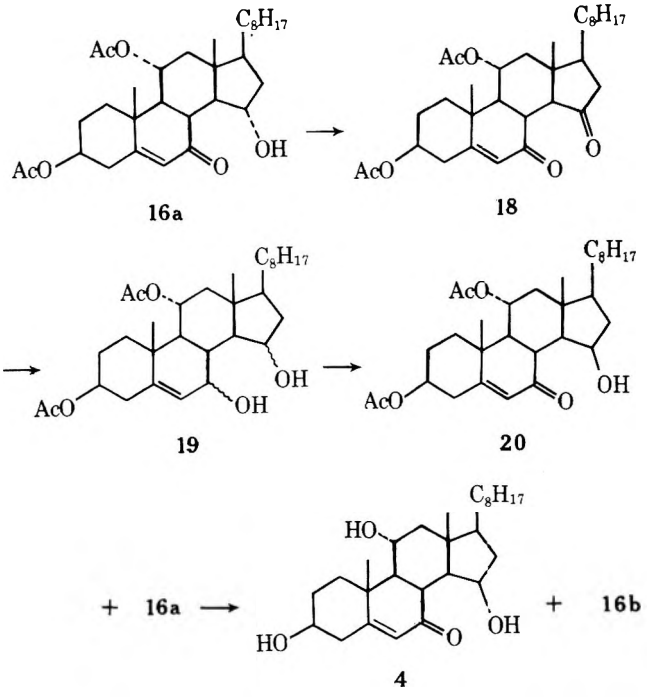
3.94 ppm for the 15β-H of **16a,** which proves that these two compounds have different C-15 alcohol configurations. The 15α-H of **17** is strongly deshielded by the C-7 ketone.[25]

The triolenone **16b,** the C-15 epimer of cholest-5-ene-3β,11α,15β-triol-7-one (**4**), obtained by treatment of the diacetate **16a** with potassium carbonate in aqueous methanol had spectral properties which were completely consistent with the proposed structure. The CD curve is similar to that of the diacetate precursor **16a** and the NMR chemical shifts are listed in Table II for comparison with those of oogoniol (**2d**).[6] Again, these NMR data show the obvious C-15 stereochemical difference between the 15β-H of **16b** at ca. δ 3.95 ppm and the 15α-H of **2d** at 4.68 ppm.

The high-resolution mass spectrum of **16b** establishes a molecular weight of 432.3225 compared with calculated value of 432.3239 for $C_{27}H_{44}O_4$. The *m/e* 414 ion, which corresponds to loss of water, is quite pronounced, but the base peak appears at *m/e* 161. The *m/e* 161 ion is also responsible for the base peak in the mass spectrum of oogoniol (**2d**)[6] and is an intense ion in the mass spectrum of 7-keto-β-sitosterol,[26] another compound containing the 3β-ol-5-en-7-one moiety. Thus, this *m/e* 161 ion probably results from cleavage through ring C and loss of water from C-3 as indicated by the wavy line in structure **16.**

The final stage of the synthesis is the inversion of the C-15 alcohol to generate the required 15β configuration. This conversion was accomplished as depicted in Scheme V. Jones

Scheme V



oxidation of compound **16a** produced a 90% yield of cholest-5-ene-3β,11α-diol-7,15-dione diacetate (**18**) with the expected spectral properties (see Experimental Section and Table II).

A hydride reduction of the C-15 ketone of **18** was expected to produce predominantly the 15β-alcohol. Lithium tri-*tert*-butoxyaluminum hydride[27] was chosen as the reducing agent for two reasons. First, this reagent is generally more stereospecific than sodium borohydride or lithium aluminum hydride and it should therefore yield more of the desired 15β-alcohol.[27b] Second, it has been reported that a saturated ketone can be selectively reduced in the presence of an α,β-unsaturated ketone using lithium tri-*tert*-butoxyaluminum hydride.[27b] Thus, it should be possible to reduce the diketone **18** directly to the 15β-alcohol **20** in which the 5-en-7-one chromophore is still present.

However, an attempt to selectively reduce the C-15 ketone of **18** using this reducing agent was unsuccessful. The 5-en-7-one moiety appeared to be reduced at least as rapidly if not faster than the saturated ketone. This unexpected result is probably due to the sterically hindered nature of the C-15 ketone and the proximity of the two carbonyl groups.

Therefore, the diketone **18** was reduced completely to the diol mixture **19** using an excess of lithium tri-*tert*-butoxyaluminum hydride. The allylic alcohol of **19** was then directly oxidized with manganese dioxide in chloroform to give a 57% yield of a product which was predominantly the desired cho-

Table I. ^{13}C NMR Chemical Shifts (ppm Relative to Me_4Si) for Cholesta-3β,11α,15α-triol-7-one (12a), the 3β,11α-Diacetate (12b), and the Triacetate (12c)

Carbon	12a[a]	12b[a]	12c[a]
1	37.6	36.0	35.8
2	31.5	27.5	27.5
3	70.0	71.9	72.0
4	38.5	34.3	34.3
5	46.1	45.4	45.0
6	46.2	45.7	47.1
7	214.6	212.9	208.1
8	49.6	49.4	48.5
9	61.0	56.4	56.4
10	37.6	37.5	38.2
11	68.0	70.2	69.8
12	50.8	45.4	46.2
13	45.0	44.6	43.4
14	57.8	57.2	52.8
15	72.1	71.9	74.3
16	39.1	39.1	36.5
17	53.7	53.4	50.6
18	14.2	13.9	14.0
19	12.4	12.3	12.5
20	35.1	34.9	35.2
21	18.7	18.7	18.7
22	36.1	36.0	36.0
23	24.0	23.8	23.8
24	39.5	39.5	39.5
25	28.0	28.0	28.0
26	22.5	22.5	22.5
27	22.7	22.7	22.7
CH_3 (acetate)		21.6, 21.1	21.6, 21.4, 21.1
C=O (acetate)		169.9, 169.6	171.5, 169.8, 169.6

[a] Registry no.: **12a**, 63324-80-1; **12b**, 63324-81-2; **12c**, 63324-82-3.

Acetylation of the triolone **12a**, in contrast to the results for the unsaturated precursor **11a**, proved to be selective for the 3β- and 11α-alcohols even using an excess of acetic anhydride in pyridine. Trace amounts of the triacetate **12c** were separated from the diacetate **12b** by careful column chromatography on silica affording a 92% yield of cholestane-3β,11α,15α-triol-7-one 3β,11α-diacetate (**12b**). The location of the free alcohol in **12b** was ascertained by a specific mass spectral fragmentation process (see Experimental Section) as well as by infrared spectral evidence. The latter showed carbonyl absorptions at 1720 and 1700 cm^{-1} for the acetates and the saturated ketone of **12b**, compared with the carbonyl absorption at 1695 cm^{-1} for the triolone **12a**. The triacetate **12c** shows only one carbonyl peak at 1720 cm^{-1}. Thus, it appears that the diacetate **12b** still retains the hydrogen bonding interaction between the 15α-alcohol and the C-7 ketone which lowers the frequency of the carbonyl absorption.

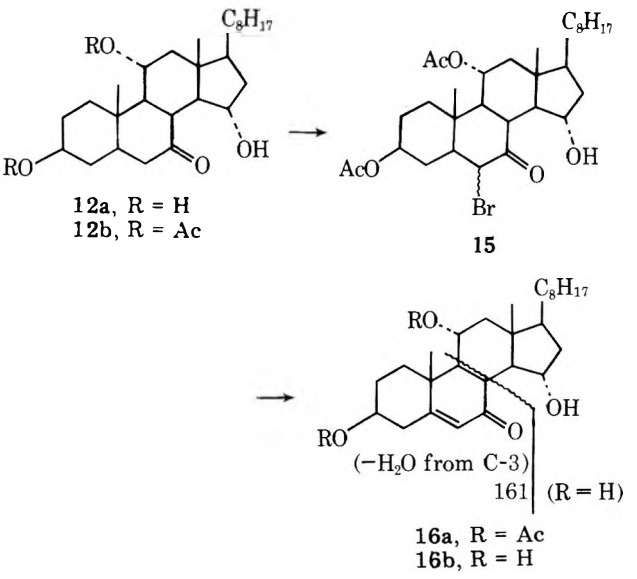
The ^{13}C NMR spectra of compounds **12a**, **12b**, and **12c** provide further supporting evidence for locating the free hydroxyl group of **12b** at C-15 (Table I). The assignments of the chemical-shift values to specific carbon atoms is based on previous work done in this laboratory on the ^{13}C NMR spectra of keto and hydroxy steroids.[21] The data for the diacetate **12b** show that the resonances for C-3 and C-11 have shifted the appropriate 2 ppm downfield upon acetylation, whereas the C-15 signal has not changed. The resonances for the carbon atoms adjacent to the acetoxy carbons, C-2, C-4, C-9, and C-12, also show the characteristic 4–5 ppm upfield shift compared with the triol **12a**.[21a] The chemical shifts for C-14 and C-16 are unchanged in the spectrum of **12b**, but they do shift upfield in the spectrum of the triacetate **12c**. It can be concluded from these data that the 15α-alcohol is not acetylated in the diacetate **12b**.

The CD curves for **12b** and **12c** are very similar to that of **12a** both in shape and in showing a positive Cotton effect. The presence of an acetate at C-15 as opposed to an alcohol does not appear to have much effect on the magnitude of the Cotton effect, $[\theta]_{290}$ +2510 for **12b** and $[\theta]_{295}$ +2070 for **12c**; however, there is a slight shift in wavelength.

Additional proof for locating the free hydroxyl group of **12b** at C-15 was obtained by chemical transformation. Jones oxidation of **12b** produced a quantitative yield of cholestane-3β,11α-diol-7,15-dione diacetate (**13**) with the expected carbonyl absorption at 1740 cm^{-1} characteristic of a five-membered ring ketone, as well as the absorption at 1720 cm^{-1} for the acetates and the C-7 ketone. The CD curve of the diketone **13** displays a very large positive Cotton effect, $[\theta]_{295}$ +9680 (compared to $[\theta]_{290}$ +2510 for **12b**), which would be expected for the contribution of a C-15 ketone.[18] The mass spectral fragmentation of **13** also locates the new ketone at C-15.[22]

The introduction of the Δ^5 double bond is the next step in the synthetic sequence (Scheme IV). Enone **16b** is the C-15

Scheme IV



epimer of **4**, the model compound for the steroid nucleus of oogoniol, and the diacetylated enone **16a** is suitably functionalized to accomplish the inversion of the C-15 alcohol. The most general method for synthesizing α,β-unsaturated ketones is through the dehydrobromination of the α-bromo ketone. It has been reported that cholestan-3β-ol-7-one acetate is not brominated at an appreciable rate in acetic acid at room temperature; however, bromination in chloroform proceeds rapidly to give a mixture of the 6α- and 6β-bromo isomers with no detectable 8-bromo ketone.[23] Dehydrobromination of this mixture should then produce only the desired 5-en-7-one.

However, the attempted bromination in chloroform of either **12a** or **12b** resulted only in recovery of starting material. The bromination of **12b** to give the 6α- and 6β-bromo ketone mixture **15** was eventually achieved by treatment with pyridinium hydrobromide perbromide[24] in acetic acid at 70–75 °C. These reaction conditions also caused a slight amount of acetylation at C-15 of **12b**. Because of the acetylation side reaction of these bromination conditions, the triolenone **16b** could not be synthesized directly from the corresponding triolone **12a**. Compound **16b** was obtained instead by saponification of the diacetate **16a**.

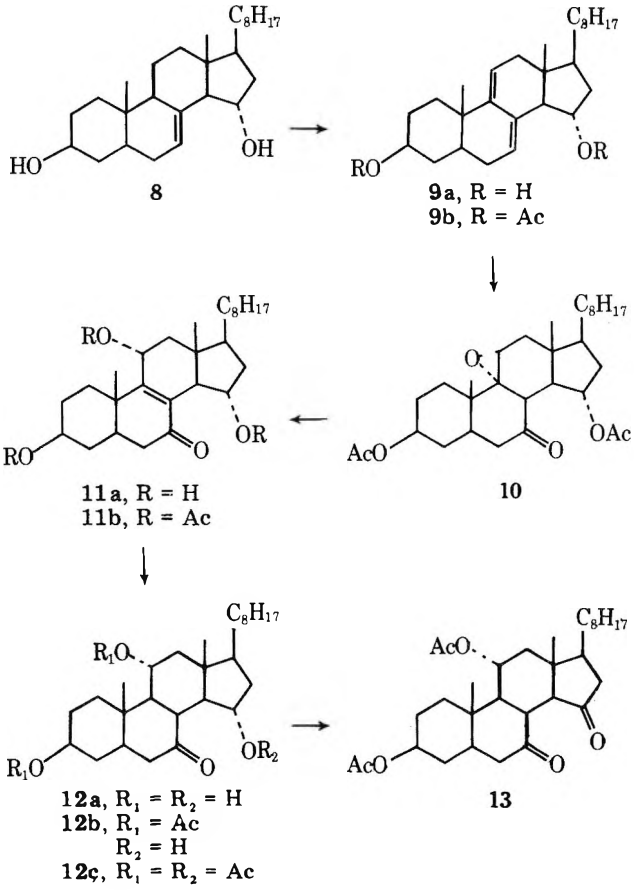
After partial purification by column chromatography, the crude α-bromo ketone mixture **15** was dehydrobrominated by treatment with calcium carbonate in boiling dimethylacetamide to give the enone **16a** plus some 3,5-dien-7-one side product (UV 285 nm). Column chromatography on silica af-

is in accord with the positive $\Delta[M]_D$ contribution expected for a 15α-hydroxyl group, rather than the negative value associated with a 15β-alcohol.[9,14] Further proof of structure **8** is offered by subsequent chemical transformations.[16]

Attempts to oxidize **8** to the corresponding diketone using either Jones or Collins reagent led to mixtures of products presumably due to allylic oxidation of the double bond and also isomerization to the conjugated 8(14)-en-15-one. The desired cholest-7-ene-3,15-dione could not be isolated from this mixture. It had been hoped that the 15β-alcohol configuration could be obtained by hydride reduction of this diketone to cholest-7-ene-3α,15β-diol. In light of these unpromising results, however, it was decided to delay this C-15 configurational inversion until later in the synthesis. This decision to carry through the 15α-alcohol proved to have some interesting consequences as will be discussed later.

The next few steps in the synthesis (Scheme III) are concerned with the formation of the desired 11α-hydroxy-7-one **12a** from the Δ^7 precursor **8,** based on the earlier work of Djerassi and co-workers (see Scheme I).[8] The mercuric acetate dehydrogenation[17] of **8** proceeded smoothly to give the 7,9(11)-diene **9a** which was directly acetylated with acetic anhydride in pyridine. After purification by column chromatography on silica and recrystallization from methanol, a 62% yield of cholesta-7,9(11)-diene-3β,15α-diol diacetate (**9b**) was obtained. This product exhibited spectral properties consistent with the structure **9b.**

Scheme III

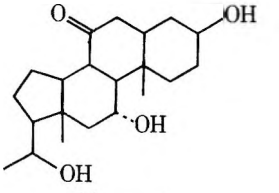


The treatment of the 7,9(11)-diene **9b** with performic acid as described in the literature[8] led to a complex mixture of products from which a 30% yield of pure 9α,11α-epoxycholestane-3β,15α-diol-7-one diacetate (**10**) could be isolated. The physical and spectral properties of this compound outlined in the Experimental Section are completely consistent with the assigned structure. Subsequent rearrangement of **10** in dilute methanolic potassium hydroxide produced a nearly quantitative yield of cholest-8(9)-ene-3β,11α,15α-triol-7-one (**11a**), thus providing independent chemical confirmation of the epoxyketone structure **10.** The spectral properties of **11a,** notably those associated with the presence of an α,β-unsaturated ketone, establish the identity of this compound.

Attempted selective diacetylation of the 3β- and 11α-alcohols of **11a** using 2 equiv of acetic anhydride led to a mixture of products in which the di- and triacetates could not be separated by chromatography. Therefore, the configuration of the C-15 alcohol could not be inverted at this stage of the synthesis. The triacetate **11b** was prepared by acetylation of **11a** with an excess of acetic anhydride in pyridine.

The next step in the synthetic scheme is the reduction of the $\Delta^{8(9)}$ double bond. The catalytic hydrogenation of the triolenone **11a** with palladium on carbon did not produce directly the saturated ketone **12a** with the normal 8β-H,9α-H trans configuration that was expected from the literature report.[8] Instead, two products were observed by TLC. The major product appeared to equilibrate slowly to the minor product on standing in solution or upon chromatography. Complete conversion of the hydrogenation product to the more stable isomer was achieved by heating under reflux in 5% methanolic potassium hydroxide. This afforded a 90% yield of cholestane-3β,11α,15α-triol-7-one (**12a**) as white crystals. If the catalytic hydrogenation of **11a** occurs from the α side of the molecule, the initial product must possess the unstable 8α-H,9α-H cis configuration. Base treatment causes equilibration at C-8 (α to the ketone) to give the normal all trans steroid configuration for the triolone **12a.** The spectral properties of this compound are in agreement with the assigned structure.

However, the CD curve of **12a** is extremely interesting because of the positive Cotton effect, $[\theta]_{290}$ +1770 (dioxane), that it displays. This is in contrast to the negative value expected for a C-7 ketone[18] and shown by the related ketone, pregnane-3β,11α-20β-triol-7-one (**14**),[19] $[\theta]_{298}$ −2250 (dioxane).



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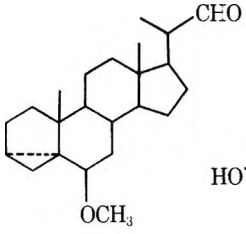
Also, the magnitude of the Cotton effect for **12a** is solvent dependent, showing a considerable decrease in methanol, $[\theta]_{288}$ +922, compared to dioxane, $[\theta]_{290}$ +1770. The results can be explained in terms of a large positive front octant contribution of the 15α-alcohol.

Kirk and Klyne[20] have found that there is a definite front octant effect of ring D in the CD spectra of 5α-androstan-7-one and D-homo-5α-androstan-7-one, which is caused mostly by the interaction of C-15 with the carbonyl group. These authors suggested that this interaction falls off rapidly with distance, which explains the observed large positive contribution to the Cotton effect for the six-membered ring D of the D homocompound compared to the much smaller positive contribution for the normal five-membered ring D in which C-15 is farther from the C-7 ketone. This being the case, the 15α-alcohol of **12a,** which has a strong interaction with the C-7 ketone, would be expected to make a large front octant contribution. Apparently, this front octant effect is large enough to reverse the normal sign of the Cotton effect and give a positive CD curve. The decrease in magnitude of the Cotton effect in methanol solvent as compared to dioxane can be attributed to the ability of methanol to disrupt the internal hydrogen bonding between the alcohol and the ketone and thus increase the distance between these two functionalities.

of the synthesis is the introduction of the correct functionalities into the steroid nucleus. This was the synthetic approach that was decided upon in this laboratory.

Specifically, the aldehyde **3**, which is derived from stigmasterol[7] was chosen as a convenient starting material for the elaboration of the side chain. The main skeleton functionalities of oogoniol can then be introduced by means of the regenerated 5-en-3β-ol moiety. Since both parts of this synthesis were expected to be multistep and to involve selective manipulations of several functionalities, it was decided to devise the route for the introduction of the functional groups into the steroid nucleus using a model system, i.e., starting with a compound containing the cholesterol side chain. The synthesis of this model compound cholest-5-ene-3β,11α,15β-triol-7-one (**4**) is described here. Compound **4** is also of intrinsic interest,



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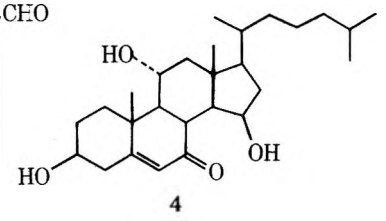


4

since it provides an opportunity to determine the importance of the substituents at C-24 and C-26 of **2** for biological activity.

Discussion

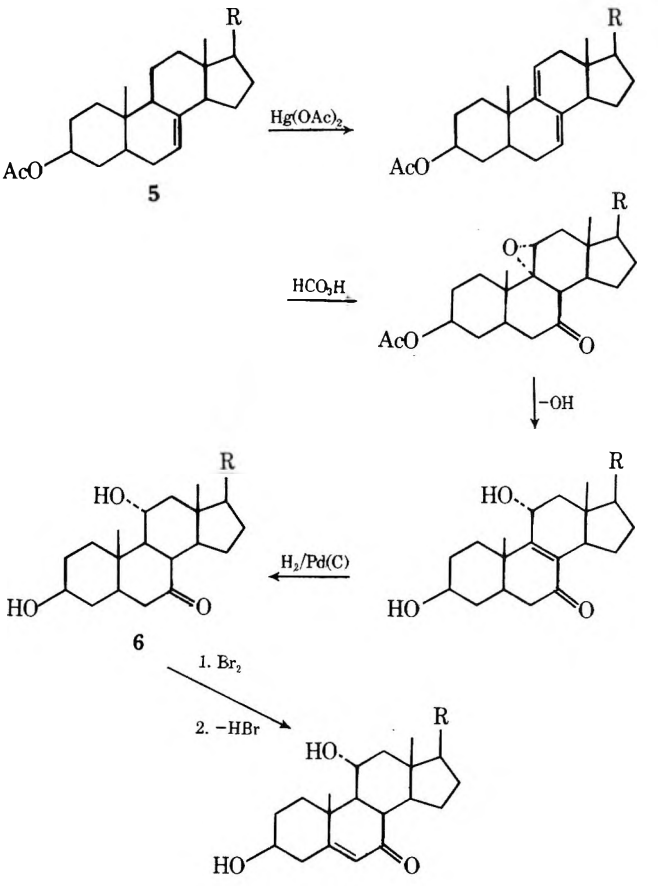
The synthetic scheme proposed above for oogoniol requires that the oxygen functions in rings B, C, and D of **4** be introduced starting from the 5-en-3β-ol group of cholesterol. As part of the work done in the early 1950s to develop methods for synthesizing 11-oxygenated steroids from ring C unsubstituted precursors, it was shown that the 11α-ol-7-one compound **6** can be produced in several steps from the Δ^7-steroid **5**.[8] Bromination at C-6 followed by dehydrobromination to the 5-en-7-one would then give the correct functionality for **4** in rings A, B, and C (Scheme I).

This leaves the problem of introducing the 15β-alcohol into the molecule. One standard method of oxygenating C-15 is the hydroboration of a Δ^{14} double bond to give a 15α-alcohol.[9] Subsequent oxidation of this alcohol and stereospecific reduction should then produce the desired 15β-alcohol configuration (Scheme II).

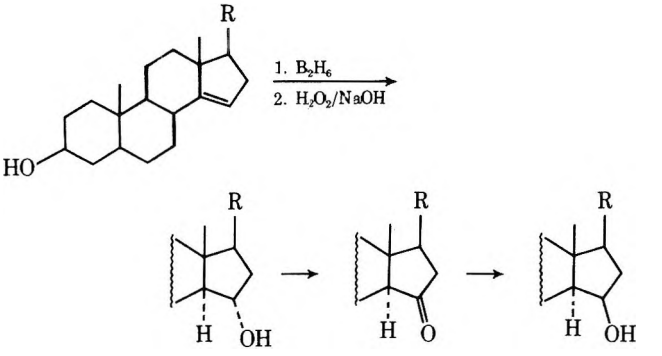
With these two schemes in mind, the starting material chosen for the synthesis of **4** was cholesta-7,14-dien-3β-ol benzoate (**7a**),[10] obtained from the acid-catalyzed double-bond isomerization of 7-dehydrocholesterol benzoate.[11] Sondheimer and co-workers have reported that the hydroboration of steroidal 7,9(11)-dienes produces Δ^7-11α-alcohols in good yield.[12] The selectivity and stereospecificity of this reaction was accounted for by their observation that Δ^7 double bonds are unreactive and $\Delta^{9(11)}$ steroids yield the 11α-hydroxy compounds in the hydroboration reaction. These results suggested that the hydroboration of a 7,14-diene should produce the Δ^7-15α-alcohol. This reaction would then serve to link Schemes I and II by oxygenating C-15 while leaving the Δ^7 double bond for functionalizing ring C.[13]

Hydroboration of cholesta-7,14-dien-3β-ol (**7b**), obtained from the saponification of the benzoate **7a**, followed by oxidation with alkaline peroxide did, in fact, afford in 78% yield a product shown to be the desired 14α-cholest-7-ene-3β,15α-diol (**8**). The assignment of structure **8** to this enediol is based on the analogy to the 7,9(11)-diene system and the expected overall *cis* addition of water to the α side of the Δ^{14} double bond.[9] Strong supporting evidence for this structure is provided by the NMR spectrum which exhibits a signal at

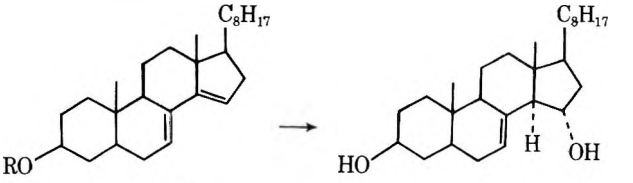
Scheme I



Scheme II



δ 5.44 ppm for the vinyl proton at C-7 and signals at δ 3.57 and 4.20 ppm assigned to the 3α- and 15β-protons, respectively. The signal at 4.20 ppm is consistent with a 15β-proton which has an expected chemical shift at ca. 4.13 ppm, rather than a 15α proton which resonates further upfield at ca. 3.95 ppm.[14a] The chemical shifts observed for the C-18 and C-19 angular methyl groups also show good agreement with the values calculated for **8**.[14,15]



7a, R = Bz
7b, R = H

8

Additional confirmation of the α configuration of the C-15 alcohol in compound **8** is furnished by a consideration of the molecular rotation contribution of this alcohol. The $\Delta[M]_D$ value going from cholest-7-en-3β-ol to **8** is +172°. This value

and to the Upjohn Company (Kalamazoo, Mich.) for steroid starting materials.

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(8) 3,6-Dioxobisnor-4-cholenaldehyde (**13**): mp 142–145 °C; $[\alpha]_D$ −15° [c 4.12, $CHCl_3$] (mixture of epimers at C-20); NMR signals (100 MHz) at 6.13 (1 H, H-5), 1.175 (3 protons, C-19 methyl), 1.124 and 1.057 (d, J = 5 Hz, together 3 protons, C-21 methyl), 0.772 and 0.733 ppm (s, together 3 protons, C-18 methyl); UV_{EtOH} λ_{max} (nm) 312 (ϵ 0.3 × 10^4), 250 (ϵ 1.0 × 10^4); CD_{EtOH} $[\theta]$ 297 [14 360], and 238.5 nm [41 180]; MS *m/e* 342 (37, M^+), 327 (16), 324 (11), 314 (33), 300 (15), 285 (14), 243 (27), 191 (28), 175 (10), 173 (11), 165 (12), 163 (17), 161 (12), 152 (20), 151 (10), 149 (12), 148 (11), 147 (19), 137 (100), 136 (67), 135 (14), 134 (16), 133 (30), 131 (11), 123 (11), 122 (12), 121 (15), 119 (14), 110 (14), 109 (29), 108 (20), 107 (26), 105 (23), 95 (22), 94 (11), 93 (27), 91 (34), 81 (38), 80 (50), 79 (45), 78 (10), 77 (26), 69 (15), 68 (11), 67 (28), 66 (16), 65 (11), 56 (15), 55 (50), 53 (21); structural assignment based on comparison of the spectral data with compound **14**.
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Phosgene Iminium Chloride

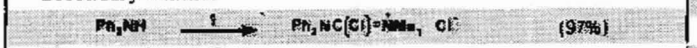
Phosgene iminium ("PI") salts are highly reactive electrophiles which enable the synthesis of a variety of interesting compounds. Extensive reviews by Viehe and Janousek attest to the current interest in this unusual class of compounds.[1-3]

Probably the most versatile PI salt is **phosgene iminium chloride**

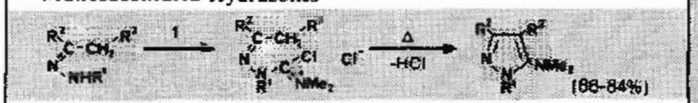
1, Phosgene Iminium Chloride

(1), a white, hygroscopic powder which is stable in a dry atmosphere, but which is hydrolyzed readily by adventitious moisture. **Phosgene iminium chloride** undergoes reaction with a variety of substrates, some of which are shown below.

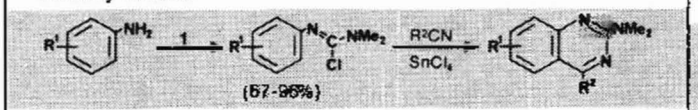
Secondary Amines[4]



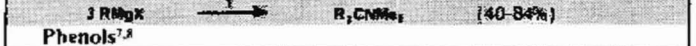
Monosubstituted Hydrazones[5]



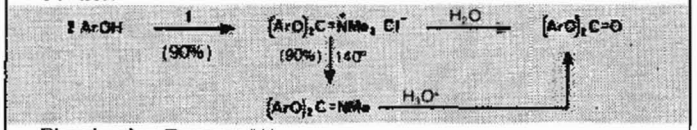
Primary Amines[6]



Grignard Reagents[1]

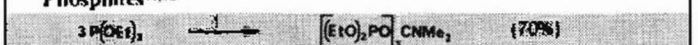


Phenols[7,8]

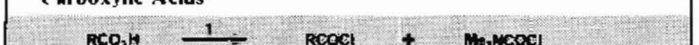


Fluorinating Reagents[9,10]

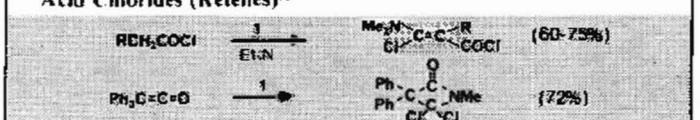
Phosphites[11,12]



Carboxylic Acids[1]

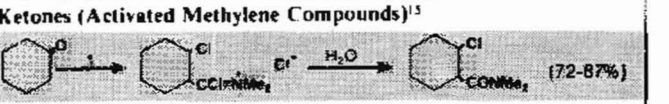


Acid Chlorides (Ketenes)[13]

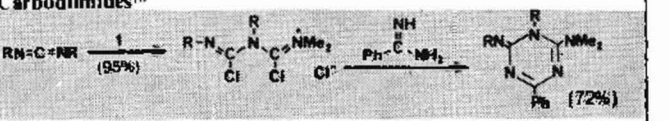


Acetophenones[14]

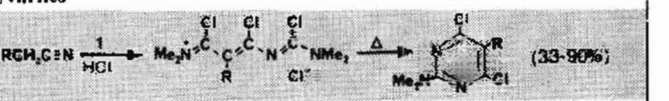
Ketones (Activated Methylene Compounds)[15]



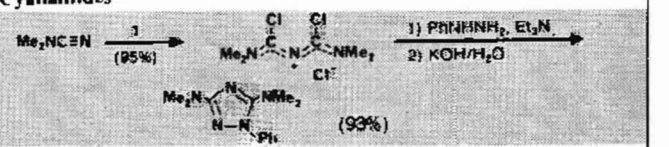
Carbodiimides[16]



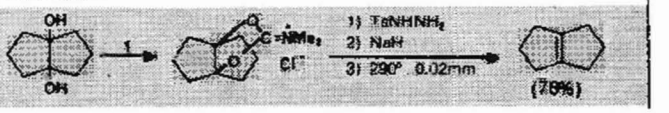
Nitriles[17]



Cyanamides[18]



Vic-Diols[19]



These few examples provide assurance that **phosgene iminium chloride** will continue to enjoy widespread application in synthetic organic chemistry.

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