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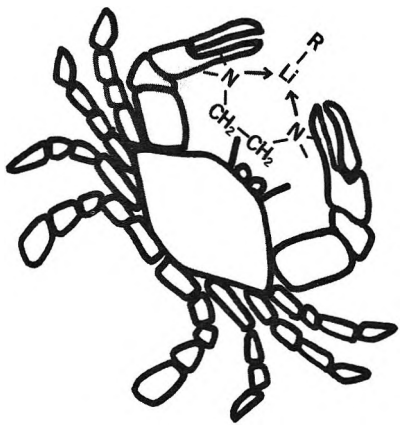

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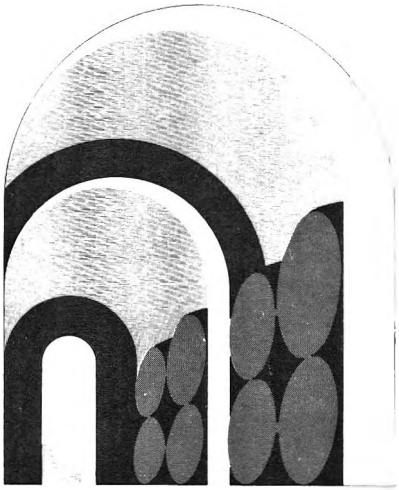

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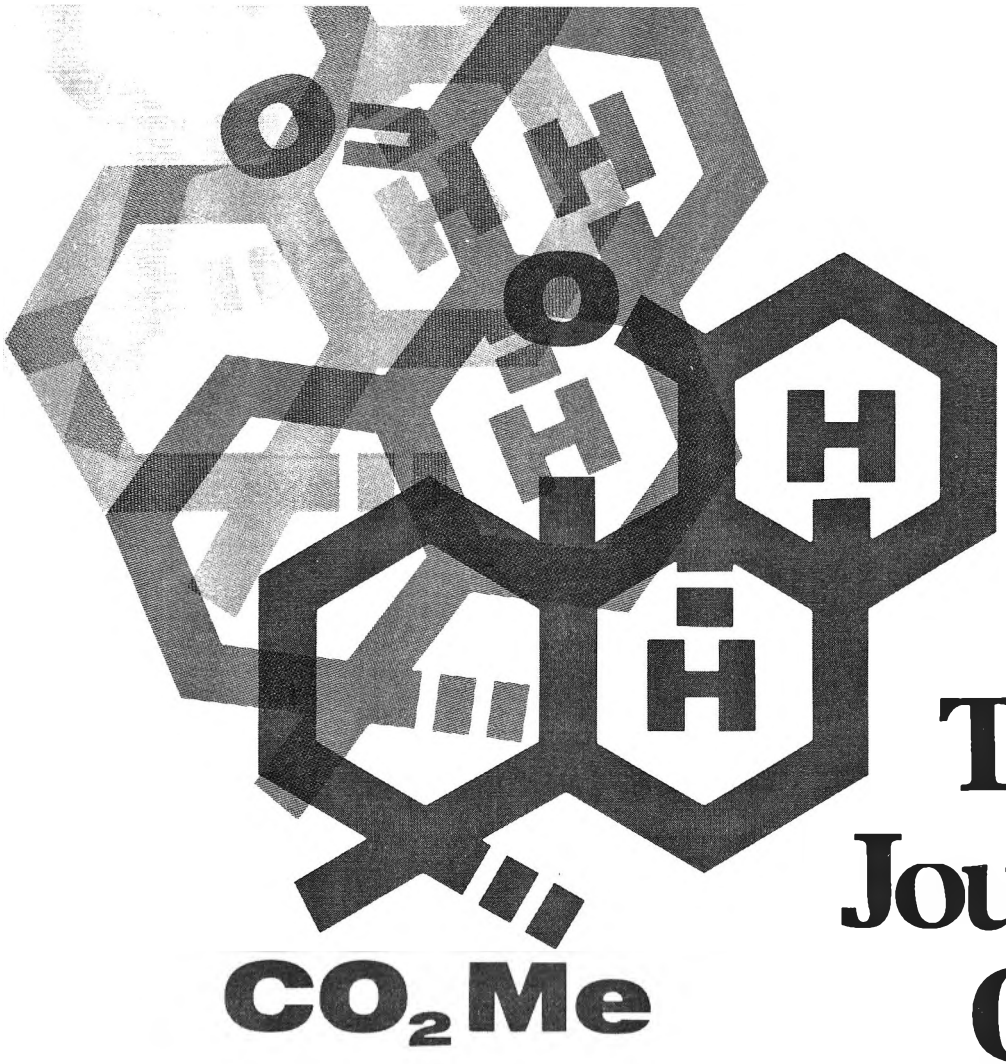

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Stereoselective Synthesis of Alkyl (2*E*, 4*E*)- and (2*Z*, 4*E*)-3,7,11-Trimethyl-2,4-dodecadienoates. Insect Growth Regulators with Juvenile Hormone Activity[1]

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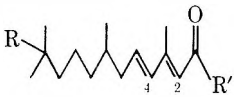
Received July 30, 1974

A general synthetic method is described suitable for the preparation, in excellent overall yield, of alkyl (2*E*, 4*E*)- and (2*Z*, 4*E*)-3,7,11-trimethyl-2,4-dodecadienoates of high stereochemical purity. The method involves the condensation of dialkyl 3-methylglutaconates with the aldehydes **2** to give the diacids **4**. Decarboxylation (*via* **7**) affords the pure 2*Z*, 4*E* isomers **9** which are equilibrated with the 2*E*, 4*E* isomers **10**. The latter are then separated *via* their insoluble ammonium salts. Methods are discussed for the conversion of the 2*Z*, 4*E* stereoisomers to the 2*E*, 4*E* stereoisomers. Benzenethiol by itself is shown to be an excellent equilibration catalyst for olefins.

The alkyl 3,7,11-trimethyl-2,4-dodecadienoates[2,3] are potent insect growth regulators with juvenile hormone activity and their efficacy as control agents for several pest insect species has been demonstrated in large scale field tests. Zoecon Corporation has obtained an experimental use permit from the Environmental Protection Agency for compound **1a** (Altosid insect growth regulator; ZR-0515;



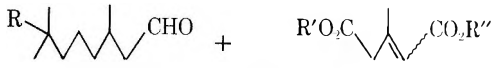
1a, R = OMe; R′ = $OCH(Me)_2$ (ZR-0515)
b, R = H; R′ = OEt (ZR-0512)
c, R = OMe; R′ = SEt (ZR-0619)
d, R = H; R′ = $OCH_2C{\equiv}CH$ (ZR-0777)
e, R = OH; R′ = OEt (ZR-0587)

methoprene; ENT 70460)[4] and we wish to describe here an outline of a procedure[5] which may be used to prepare **1a** and related compounds.

Since the 2*E*, 4*E* stereoisomer shows considerably higher biological activity than the other three possible stereoisomers,[2,6] a useful synthesis must produce principally this isomer as the final product. We also required a synthetic route that would be sufficiently versatile to enable us to prepare a variety of esters, thioesters, amides, and related analogs. We had initially investigated along with a phosphonate route[2,7] a variety of other methods[8] for the synthesis of **1a** and **1b** and related compounds. However, it soon became apparent that the glutaconate route described below was to be preferred.

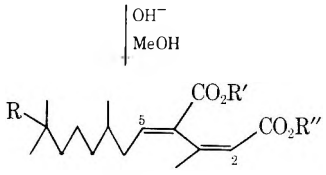
Any efficient synthesis of 3-methyl-2,4-dienoic acids could be applicable to the preparation of **1** since equilibration[8] of all four stereoisomers[6] of **1b** (or of the corresponding acids) with benzenethiol gives the same mixture containing *ca.* 65% of the 2*E*, 4*E* isomer, *ca.* 35% of the 2*Z*, 4*E* isomer, and only trace amounts of the two 4*Z* isomers. Furthermore, as demonstrated below, the 2*E*, 4*E* isomer can be readily separated from such an equilibrium mixture and the 2*Z*, 4*E* isomer can be recycled.

It has been known for some time that diethyl and dimethyl 3-methylglutaconates (**3**) condense with aliphatic and aromatic aldehydes under alkaline conditions (methanolic KOH) to give variable yields of 4-alkylidene (or 4-arylidene)-3-methylglutaconic acids.[9-12] The intermediate diacids, which were finally assigned[12] the "cis,cis" configuration (2*Z*, 4*E* as in **4**), have been decarboxylated, with inversion at C-4, to give (2*Z*, 4*E*)-3-methyl-2,4-dienoic



2a, R = OMe
b, R = H
c, R = OH

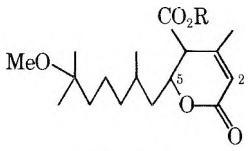
3a, R′ = R″ = Me
b, R′ = R″ = Et
c, R′ = Me; R″ = Et, R′ = Et; R″ = Me, and **3a**



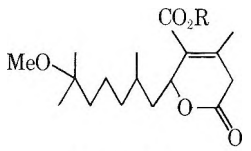
4a, R = OMe; R′ = R″ = Na
b, R = OMe; R′ = R″ = K
c, R = OMe; R′ = R″ = H
d, R = OMe; R′ = R″ = Et
e, R = OMe; R′ = Me; R″ = H
f, R = OMe; R′ = R″ = Me
g, R = OH; R′ = R″ = H
h, R = H; R′ = R″ = H

acids.[10-12] However, the reported yields have been highly variable and the reaction mechanisms of both the condensation and the decarboxylation steps have not been clarified.[12a] It was noted by Cawley[10b] that half-esters of the diacid may have been formed as intermediates in the conden-

sation and that both pure Z and E isomers of dimethyl 3-methylglutaconate gave the same diacid on condensation with cinnamaldehyde. Wiley and Ellert[11] found that on acidification of the condensation reaction product both diacids and the previously unnoticed isomeric carboxy-δ-lactones (assigned structures such as **5a**) were obtained. The

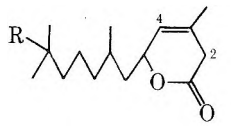


5a, R = H
b, R = Et
c, R = Me

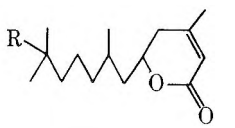


6a, R = H
b, R = Et
c, R = Me

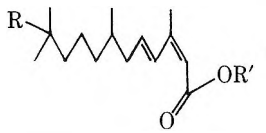
type of product obtained could apparently be correlated, by these authors, with the type of aldehyde used. Although the diacids were reported to decarboxylate by heating at 145–160° in quinoline alone,[10c] the preferred method of decarboxylation was found by Cawley, *et al.*,[10] to be heating with 2,4-dimethylpyridine in the presence of copper or cupric acetate at 90–120°. However, Wiley and Ellert[11] obtained poor yields of monoacid and/or δ-lactone under these conditions and preferred to decarboxylate in hot acetic acid to give δ-lactones, assigned the 5,6-dihydro-2-pyrone structure (*cf.* 8). We have investigated this reaction sequence in considerable detail and have developed it into a very useful general synthesis of (2*Z*, 4*E*)- and of (2*E*, 4*E*)-3-methyl-2,4-dienoic acids.



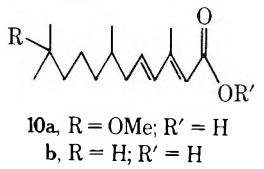
7a, R = OMe
b, R = H



8a, R = OMe
b, R = H



9a, R = OMe; R′ = H
b, R = H; R′ = H
c, R = OH; R′ = H
d, R = OMe; R′ = Me
e, R = OMe; R′ = Et
f, R = OMe; R′ = $CH(Me)_2$
g, R = H; R′ = Me

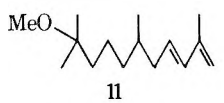


10a, R = OMe; R′ = H
b, R = H; R′ = H
c, R = OH; R′ = H
d, R = OMe; R′ = Me
e, R = OMe; R′ = Et
f, R = H; R′ = Me

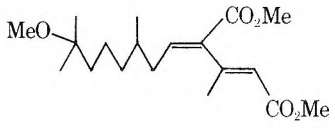
Results and Discussion

The condensation of dialkyl 3-methylglutaconates (**3**)[13] with the aldehydes **2** in the presence of excess alcoholic sodium or potassium hydroxide proceeded rapidly. For example, treatment of a mixture of **2a** and **3a** in dry methanol with sodium hydroxide in methanol and heating under reflux for 1 hr gave the precipitated disodium salt (**4a**) in 90% isolated yield (3.5–4 equiv of NaOH was required to obtain this optimum yield). Acidification of **4a** afforded the diacid **4c** which could be esterified to the stable diesters (**4d** and **f**). The free diacid lactonized readily to a mixture of **5a** and **6a** on heating or on standing at room temperature for long periods (*cf.* ref 11). The initial product of lactonization appeared to be mostly **6a**, with isomerization to **5a** occurring subsequently. However, under the above condensation conditions it was necessary to isolate the disodium or dipotassium salt by filtration, in order to obtain pure **4c**. Examination of the filtrate (after acidification) showed it to contain three additional diacid isomers of **4c** (see below). The presence of two 2*E* isomers (*ca.* 4% of the total condensation product) was detrimental as it was found that they did not decarboxylate readily in the following steps and hence contaminated the product or the recycle. It was found that the isomerization occurred subsequent to condensation (*cf.* ref 12a, c, and d) and thus could be avoided by modifying the reaction conditions. Thus addition of 1 equiv of 50% aqueous sodium hydroxide solution to a mixture of **2a** and **3a** in methanol at 5° followed by standing 1 hr at room temperature gave the half-ester **4e.** Addition of a further 2 equiv of sodium hydroxide in water and heating at 65° for 1 hr gave, after acidification, the diacid **4c** in 95% yield in >96% purity. The initial rapid formation of the half-ester indicated that **5c** (or **6c**) was probably an intermediate in the condensation reaction. On standing, the isolated half-ester lactonized to give a mixture of **5c** and **6c.** The initial product of lactonization of **4e** could be seen by nmr to be **6c;** however, subsequent isomerization to **5c** occurred readily on mild basic treatment and on chromatography of **6c** on silica gel tlc plates.

Decarboxylation of the diacid **4c** in the presence of 10% 2,4-dimethylpyridine began at 80° (neat or in toluene) and proceeded readily at 100° to a mixture of **7a, 8a,** and **9a** with **7a** generally predominating (in toluene). In contrast to the published work,[10,11] it was found that *the presence (or absence) of a copper salt had no detectable effect* on the decarboxylation. It was possible to convert the diacid **4c** directly to the 2*Z*, 4*E* monoacid **9a** by prolonged heating at 100–130° using no solvent other than an excess of an organic base such as pyridine or 2,4-dimethylpyridine (*cf.* ref 10c). The initial decarboxylation took place readily but the subsequent conjugation and opening of the lactone ring to give **9a** was slow and often incomplete. These latter steps proceeded more rapidly in alcoholic sodium alkoxide[8,15] and hence it was found much more efficient to carry out the reaction in two steps (*cf.* ref 11). Thus the diacid **4c** was heated in toluene with 2,4-dimethylpyridine (0.1 equiv) at 100° until carbon dioxide evolution ceased, and then 1.1 equiv of sodium methoxide in methanol was added and the mixture heated at 70° for a further hour. This procedure gave the 2*Z*, 4*E* monoacid **9a** in >90% yield in high purity. The lactone acids **5a** and **6a,** which *were probably intermediates in the decarboxylation,* also gave **9a** under the above conditions (*cf.* ref 11). It was noted that although no decarboxylation occurred upon heating the diacid **4c** in excess 2 *N* NaOH, when the diacid was half-neutralized with aqueous NaOH and the solution heated to reflux (pH gradually increased from 6.5 to 8.5) a 50% yield of **9a** was obtained, along with 13% of the diene **11,** 9% of the lactone **8a,** and 20% of the starting diacid. Prolonged heating of the 2*Z*, 4*E* monoacid **9a** above 100° gave the diene **11** along with lesser amounts of **8a** (plus **7a**). The alkyl esters of **9a** and of **10a** were considerably more thermally stable.



11



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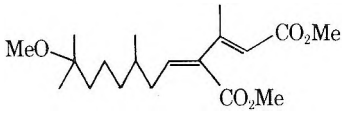

13

The isomerization of the acid **9a** was studied with a variety of catalysts (see below). The best catalyst for equilibra-

tion was found to be benzenethiol. Thus heating the acid **9a** neat in the presence of 0.5–1.0% by weight of benzenethiol at 100° for 1–2 hr gave in 95% yield a mixture of 35% of **9a** and 65% of **10a.** It is particularly interesting that the presence of light or of AIBN [2,2′-azobis(isobutyronitrile)][16] was *not necessary* (see below).

We have already noted[2] that pure (2*E*,4*E*)-2,4-dienoic acids could be islated *via* their *S*-benzylisothiuronium salts. For purification of **10a** we now found that treatment of the isomerization mixture in ether (or in hexane, or dichloromethane for **10b** and **10c**) with anhydrous ammonia gas gave a crystalline precipitate of the pure 2*E*,4*E* ammonium salt which was collected. The filtrate from this procedure was recycled to the isomerization step above to convert the unprecipitated 2*Z*,4*E* acid to an equilibrium mixture of **9a** and **10a.** The ammonium salt was now acidified and the recovered pure 2*E*,4*E* acid converted *via* its acid chloride (prepared with thionyl chloride in dimethylformamide) into the corresponding ester or thioester (see Experimental Section). This overall scheme has been used to prepare pure **1a, b, c,** and **d** (purity 90–98% by internal standard glc analysis), *without any distillation of intermediates or final products.*

In connection with the isomerization of **9a** discussed above, we found that heating olefins without solvent with 0.5% by weight of benzenethiol at 100° was an excellent method for equilibration. The presence of a hydrocarbon solvent increased both the time required to reach equilibrium and the amount of benzenethiol which had to be used. We have used these conditions for equilibrating many olefins. For example, treating (*Z*)-11-tetradecen-1-yl acetate[17] with 1% by weight of benzenethiol for 1 hr at 100° followed by removal of the thiol by codistillation with a high boiling solvent, gave a mixture of the *Z* and *E* isomers in the ratio 25:75, respectively, in 92% yield. Other workers have reported the isomerization of olefins with thiyl radicals generated from benzenethiol in the presence of AIBN (at 65°).[16] It has been reported that when the benzenethiyl radicals were produced thermally (in the dark) from excess benzenethiol, diphenyl disulfide, or diphenyl sulfide it was necessary to heat to 200° in order to have a reasonable isomerization rate of (*Z*,*Z*)-1,8-cyclotetradecadiene.[18] These workers also noted that double bond migration occurred under these conditions whereas benzenethiyl radicals produced photochemically ($\lambda > 300$ nm) from diphenyl disulfide (or from diphenyl sulfide) gave rapid equilibration at room temperature without double bond migration. Photochemical *Z*–*E* isomerization with diphenyl disulfide has been used successfully by other workers.[19-21]

The reversibility of the thiyl radical addition to the olefinic double bond,[22] especially in the case of a resonance-stabilized radical like benzenethiyl, is presumably the basis for the thiyl-catalyzed cis–trans isomerization discussed above. Even though the isomerization probably proceeds through a transitory radical adduct we did not detect any permanent thiol adduct in these reactions and our yields of pure products were always high. No polymerization or other decomposition took place during the benzenethiol-catalyzed isomerization.

Of the other catalysts[21] investigated for the equilibration of **9a** (and of **9b**) without solvent, it was found that Na_2S (20 mol %; 17 hr at 120°) and LiSCN (20 mol %; 22 hr at 120°) gave predominantly the lactone **8a.** Butadiene sulfone[20,21] (25 mol %; 7 hr at 120°) and ruthenium trichloride trihydrate (20 mol %; 2 hr at 120°) gave deconjugation to the 3,5-diene and some loss of the 11-methoxy group. Heating with thiobenzoic *S*-acid[20] (30 mol %; 24 hr at 120°), Al_2S_3 (20 mol %; 19 hr at 120°), or with diphenyl disulfide (20 mol % plus 10 mol % AIBN; 3 hr at 80°) gave slow isomerization without attainment of equilibrium under these conditions, whereas heating with dibenzyl disulfide (10 mol % plus 10 mol % AIBN; 3 hr at 80°) produced no change. Diphenyl disulfide did result in equilibration at a higher temperature (20 mol %; 5 hr at 120°), but benzenethiol, for comparison, gave rapid equilibrium *with* (5 mol % plus 1 mol % AIBN; 2 hr at 80°) *or without* (2 mol %; 1 hr at 100°) the use of AIBN. Heating with sulfur[21,23] (20 mol %; 25 hr at 115°) gave only partial isomerization. Heating with thioacetic *S*-acid (20 mol %; 6.5 hr at 120°) gave the equilibrium mixture (**9a:10a** in ratio 35:65, respectively) but the reaction was not as rapid or as clean as with benzenethiol and required considerably more catalyst. Treatment with thioglycolic acid (10% by weight; 22 hr at 100°) also gave the equilibrium mixture.

Isomerization of the esters **1a, 1b, 9e, 9f,** and **9g** was also investigated. Again benzenethiol was a satisfactory catalyst.[8] Thus heating either **1a** or **9f** with 1% by weight of benzenethiol and 0.5% AIBN at 80° for 2 hr gave a mixture of **1a** and **9f** in the ratio 67:33, respectively. Heating the 2*Z*,4*E* esters with alkoxides such as potassium *tert*-butoxide or sodium isopropoxide in dimethylformamide and also in 2-propanol for the latter gave very little isomerization, although addition of catalytic amounts of sodium ethoxide in ethanol to a solution of **1b** in dimethylformamide at 25° (overnight) did produce isomerization at C-2. Heating the ester **9g** (without solvent) with sulfur[21,23] (20 mol %; 4.5 hr at 115°) gave rapid equilibration to the 65:35 mixture of **10f** and **9g,** respectively. Sodium sulfide and also sodium hydrosulfide (20 mol %) gave equilibration after 20 hr at 115° (no solvent). Ruthenium trichloride (20 mol %; 48 hr at 115°) was slower and most other catalysts (no solvent; 115°) also gave either slow isomerization (*e.g.*, NaSMe, $LiSCH_3$, or $KSCH_3$), no isomerization (*e.g.*, KF or NaOMe), or caused decomposition (*e.g.*, I_2 or $PdCl_2$).

The configuration of the intermediate **4c** was assigned the 2*Z*,4*E* stereochemistry in agreement with previous assignments,[12] based on the following result. Methylation of the disodium salt **4a** with excess methyl iodide in dimethylformamide gave the dimethyl ester **4f.** Treatment of this diester with benzenethiol (10 mol % plus 0.05% AIBN) gave a mixture of three isomers (glc–ms) in the ratio 42:46:12. Partial separation by preparative tlc (and hplc) and examination of the nmr spectra enabled the assignment of the structures **4f, 12,** and **13,** respectively. The mixture of the two 2*E* isomers **12** and **13** could not be easily separated by preparative tlc but treatment of a mixture of **12** and **13** (in the ratio 78:22, respectively) with benzenethiol as above gave the same equilibrium mixture (**4f:12:13** in the ratio 40:48:12, respectively) as obtained from **4f.** In the nmr spectrum (CCl_4) of **4f** the 2-H absorbed at 5.85, the 5-H at 6.70, and the C-3 methyl group at 1.98 ppm. Similarly the 5-H of **12** absorbed at 6.76 whereas the C-3 methyl group absorbed at 2.22 ppm (*cf.* ref 2 and 6). In **13** and C-3 methyl group signal appeared at 2.27 but the signal due to the 5-H was shifted upfield to 6.08 ppm.[6,12]

The condensation of **3a** with **2a** using 4 equiv of sodium hydroxide *under reflux* gave mainly **4a** (90% yield) but the filtrate after the collection of the disodium salt **4a,** as mentioned above, contained (after acidification) three additional isomers of **4c,** in the ratio *ca.* 1:1:3. Methylation of the diacids with diazomethane and comparison with the isomerization products of **4f,** showed that one of the minor isomers was identical with **12,** and that a negligible amount of **13** was present. The major by-product diacid appeared to decarboxylate readily to give the same product as did **4c** and thus probably had the 2*Z* configuration (the other two

isomers did not decarboxylate readily). From an examination of the mass spectra of the dimethyl esters it appeared that both this major by-product isomer and the other minor isomer possessed 2,5-dienoate (or 3,5-dienoate) structures (both contained a major fragment at *m/e* 162 whereas **4f** and **12** had a typical strong peak at *m/e* 183 which was of low intensity in these two by-product isomers).

In conclusion the glutaconate route described above is a versatile general method for the preparation of (2*E*,4*E*)- and (2*Z*,4*E*)-3-methyl-2,4-dienoic acids, and of a variety of esters and related analogs. The chemical starting materials are readily available and the by-products are ecologically innocuous. The solid disodium salts (*e.g.*, **4a**) and the ammonium salts (of **10**) allow easy purification of the intermediates and thus the product esters are obtained in high purity without distillation. The process can be run in high concentrations and can be readily scaled up.

Experimental Section

All substances described herein are racemic compounds; the prefix *dl* is omitted. Preparative thin-layer chromatography was carried out with Merck (Darmstadt) silica gel PF-254. Nmr spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200G spectrophotometer. Mass spectra were measured on a Varian Mat CH-7 spectrometer, at 20 or 70 eV ionization potential. Gas–liquid chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. Solvents were dried over activated 4A molecular sieves.

Dimethyl 3-Methylglutaconate (3a). To a solution of 273 g (1.5 mol) of methyl isodehydracetate in 250 ml of dry methanol was added 34 g (0.16 mol) of 25% sodium methoxide in methanol, and the mixture was heated under reflux for 1 hr in a dry nitrogen atmosphere. The solvent was removed at reduced pressure and the residue was distilled *in vacuo* to give 232 g (90%) of **3a**, bp 100° (3 mm).

Substitution of 300 g (1.46 mol) of ethyl isodehydracetate for the methyl ester in the above reaction, gave 242 g (86.5%) of a fraction of mixed esters 3c of 3-methylglutaconate, bp 99–115° (3 mm), which can be used directly in the condensation step. Diethyl 3-methylglutaconate was prepared, as above, from ethyl isodehydracetate with sodium ethoxide in dry ethanol.

Disodium (2*Z*,4*E*)-4-Carboxylato-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (4a). To a solution of 308 g (1.65 mol) of aldehyde **2a** and 284 g (1.65 mol) of dimethyl 3-methylglutaconate (**3a**) in 150 ml of dry methanol was added over 15 min with stirring, a solution of 267 g (6.68 mol; 4.05 equiv) of sodium hydroxide dissolved in 1.1 l. of dry methanol. The mixture was then heated under reflux for 1 hr and allowed to cool. The precipitate was filtered off, dried with suction, and then slurried in 1.8 l. of 2-propanol and the salt was collected by filtration. The filter cake was allowed to drain well and dried in a vacuum desiccator. The yield of the disodium salt **4a** was 529 g (90%). Ether can be used in place of 2-propanol to wash the salt (the solubility of **4a** in 2-propanol at room temperature was found to be 2.1 g/l.; the solubility in methanol was *ca.* 15 g/l.).

The disodium salt was dissolved in 1.5 l. of water, acidified to pH 1 with 4 *N* sulfuric acid and the mixture was extracted with ether (3 × 1 l.). The combined organic layers were washed with water and brine and dried ($MgSO_4$) and the solvent was removed *in vacuo* to give **4c** (446 g) as a viscous oil: nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.13 (s, C-11 CH_3 + H-12), 2.05 (br s, C-3 CH_3), 3.22 (s, OCH_3), 5.97 (m, H-2), and 6.92 ppm (t, separation = 7.5 Hz, H-5). On standing at room temperature or on mild heating the diacid lactonized. Thus after standing 1 month, *ca.* 70% of the diacid had been converted to **6a** (and **5a**). Partial lactonization even occurred on removal of the ether solvent used to extract the diacid after acidification (the $CDCl_3$ nmr spectrum of **4c** above contained signals at 2.23 and 5.40 ppm due to **6a**). Extraction of the diacid into CCl_4 after acidification of the disodium salt, followed by washing with water and drying ($CaSO_4$), gave a pure *solution* of **4c** containing no lactone: nmr δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.08 (s, C-11 CH_3 + H-12), 2.01 (d, J = 1.3 Hz, C-3 CH_3), 3.10 (s, OCH_3), 5.85 (m, H-2), and 6.82 ppm (br t, "J" = 7.5 Hz, H-5).

Use of 4 equiv of potassium hydroxide in the above reaction gave the solid dipotassium salt **4b.**

Substitution of 2a with 3,7-dimethyl-1-octanal (**2b**) or with 7-hydroxy-3,7-dimethyl-1-octanal (**2c**) in the above reaction gave the corresponding disodium salts in high yield (*ca.* 95%). The diacids recovered from these two salts solidified at room temperature.

If toluene was used in place of ether to extract the diacid after acidification, then the dried, filtered toluene extract could be used directly in the decarboxylation step.

Ethylation of the diacid **4c** with 1-ethyl-3-*p*-tolyltriazene[24] in ether and purification by silica gel preparative tlc gave the corresponding diethyl ester **4d:** bp (bath, short path) 146° (0.05 mm); ir (film) 1725, 1715, 1660, and 1635 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 3, J = 6 Hz, C-7 CH_3), 1.13 (s, 6, C-11 CH_3 + H-12), 2.00 (d, 3, J = 1.5 Hz, C-3 CH_3), 3.18 (s, 3, OCH_3), 4.11 (q, 2, J = 7 Hz, OCH_2CH_3), 4.23 (q, 2, J = 7 Hz, OCH_2CH_3), 5.93 (m, 1, H-2), and 6.82 ppm (t, 1, separation = 7.5 Hz, H-5); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 368 (~0), 354 (~0), 291 (3), 290 (2), 244 (5), 229 (3), 211 (31), 183 (12), 167 (10), 73 (100).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.45; H, 9.85. Found: C, 68.16; H, 9.96.

To 6.01 g (0.017 mol) of the disodium salt **4a** in 25 ml of dimethylformamide was added 9.6 g (0.068 mol) of methyl iodide and the solution heated at 56° for 8 hr under N_2. After cooling the mixture was poured into water and extracted with ether–hexane. The organic layer was washed with water, 10% Na_2CO_3, water, and brine and dried ($CaSO_4$). Removal of the solvent *in vacuo* gave 5.14 g (89% yield) of the dimethyl ester **4f:** bp (bath, short path) 130° (0.05 mm); nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.10 (s, C-11 CH_3 + H-12), 1.98 (d, J = 1.5 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.60 (s, CO_2CH_3), 3.70 (s, CO_2CH_3), 5.85 (m, H-2), and 6.70 ppm (t, "J" = 7.5 Hz, H-5); mass spectrum *m/e* (rel intensity) M^+ 340 (~0), 325 (2), 309 (~0), 308 (~0), 277 (3), 276 (3), 261 (7), 244 (10), 229 (8), 183 (60), 153 (18), 123 (8), 73 (100).

Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.94; H, 9.44.

Methylation of **4c** with diazomethane in ether, followed by purification by preparative tlc, also gave **4f.**

4-Ethoxycarbonyl-5-(6-methoxy-2,6-dimethylheptyl)-3-methyl-2-penten-5-olide (5b). Removal of the solvent from a sample of the diacid **4c,** which had been stored in ether solution at room temperature for 50 days, and examination of the residue by ir and nmr spectroscopy showed it to contain a considerable proportion of the lactone **5a** (and the 3-pentenolide isomer **6a**). A 2.15-g sample of this material was esterified with 1-ethyl-3-*p*-tolyltriazene[24] in ether. Chromatography on preparative thin-layer plates gave 0.50 g of the diester **4d** (upper band) and 0.50 g of **5b** (containing a small amount of **6b**): bp (bath, short path) 160° (0.05 mm); ir (CCl_4) 1740 and 1735 cm^{-1}; nmr ($CDCl_3$) δ 0.93 (d, J = 6 Hz, CH_3CH), 1.14 [s, $(CH_3)_2C$], 2.01 (d, J = 1.3 Hz, C-3 CH_3), 3.13 (m, H-4), 3.20 (s, OCH_3), 4.24 (q, J = 7 Hz, OCH_2CH_3), 4.28 (q, J = 7 Hz, OCH_2CH_3), 4.6 (br m, H-5), and 5.98 ppm (m, H-2); mass spectrum (20 eV) *m/e* (rel intensity) 325 (~0), 269 (~0), 183 (3), 73 (100).

Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 67.12; H, 9.58.

(2*Z*,4*E*)-4-Carboxy-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic Acid (4c). To a solution of 28.60 g (0.15 mol) of 3,7-dimethyl-7-methoxy-1-octanal (**2a**) and 28.32 g (0.15 mol) of dialkyl 3-methylglutaconate (analyzed mixture of methyl and ethyl esters) in 90 ml of methanol cooled in an ice–water bath was added, over 10 min, a solution of 12.0 g (0.15 mol) of 50% aqueous sodium hydroxide solution in 20 ml of methanol. After the mixture was stirred for 1 hr at room temperature, a solution of 12.0 g (0.30 mol) of sodium hydroxide in 48 ml of water was added and the reaction mixture was heated at 65° under reflux for 1 hr. After cooling, water was added and the mixture was extracted with hexane (discarded). The aqueous layer was acidified, and extracted with ether. The ether solution was washed with water and brine, dried ($MgSO_4$), and evaporated to give 44.71 g (95% yield) of **4c.** Methylation of a sample with diazomethane (before removal of the solvent) and glc analysis of the resulting diester **4f** indicated a purity of >96% by peak normalization. This product can be used directly in the decarboxylation step.

(2*Z*,4*E*)-11-Methoxy-4-methoxycarbonyl-3,7,11-trimethyl-2,4-dodecadienoic Acid (4e). To a solution of 2.86 g (15 mmol) of methoxycitronellal (**2a**) and 2.58 g (15 mmol) of dimethyl 3-methylglutaconate (**3a**) in 10 ml of dry methanol was added, with stirring and cooling in an ice–water bath, a solution of 1.2 g (15 mmol) of 50% aqueous sodium hydroxide solution in 2 ml of methanol.

The reaction mixture was then stirred at room temperature for 1 hr, and then diluted with water and acidified with cold aqueous sulfuric acid, and then extracted with CCl_4. The organic layer was washed with water and dried ($MgSO_4$), to give a CCl_4 *solution* of pure **4e**; ir (CCl_4) 1730, 1700, 1660, 1635 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.08 (s, C-11 CH_3 + H-12), 2.00 (d, J = 1.3 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.70 (s, CO_2CH_3), 5.83 (m, H-2), and 6.67 ppm (t, "J" = 7.5 Hz, H-5). When the CCl_4 was removed *in vacuo* partial lactonization to **6c** occurred. The residue was dissolved in ether and the solution heated under reflux for 48 hr and the solvent removed *in vacuo*. The residue now contained a mixture of **4e** and **6c** in the ratio *ca.* 1:1 [the nmr spectrum in $CDCl_3$ showed peaks at 2.21 (C-3 CH_3) and 5.40 (H-5) due to **6c**]. When an aliquot of this material in ether was shaken with aqueous NH_4OH, the **6c** was converted mostly into **5c.** When the mixture of **4e** and **6c** above was chromatographed on silica gel preparative thin-layer plates, the recovered lactone fraction consisted of mostly **5c:** ir (CCl_4) 1735 and 1660 cm^{-1}; nmr (CCl_4) δ 0.93 and 0.97 (two d, J = 6 Hz, CH-CH_3), 1.10 [s, $(CH_3)_2C$], 1.99 (d, J = 1.3 Hz, C-3 CH_3), 3.03 (m, H-4), 3.12 (s, OCH_3), 3.76 (s, CO_2CH_3), 4.50 (br m, H-5), and 5.83 ppm (m, H-2).

Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 65.80; H, 9.03.

(2*Z*,4*E*)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoic Acid (9a). A solution of 104.0 g (333 mmol) of the diacid **4c** and 2.0 g (19 mmol) of 2,4-dimethylpyridine in 270 ml of dry toluene was heated, under nitrogen, at 100° until decarboxylation was complete (3 hr; the reaction was followed by tlc). The solution was cooled to 70°, purged with nitrogen, 82 g (380 mmol) of 25% sodium methoxide in methanol was added, and the resulting solution was held, under nitrogen at 70°, until reaction was complete (*ca.* 1 hr). To the cooled, stirred solution was added 500 ml of water and 30 ml of 1 *N* aqueous NaOH. After removal of the organic phase (discarded), the aqueous phase was acidified to pH 1 with 4 *N* sulfuric acid and extracted with 300 ml of hexane. The hexane extract was washed twice with water, once with brine, dried ($MgSO_4$), and the solvent was evaporated *in vacuo* up to 58° (1 mm) to give 83.5 g (93%) of (2*Z*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoic acid (**9a**) (analysis by glc showed a purity of 96%) as a yellow oil: ir ($CHCl_3$) 1685 (C=O), 1635, and 1600 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.13 (s, C-11 CH_3 + H-12), 2.01 (d, J = 1.3 Hz, C-3 CH_3), 3.17 (s, OCH_3), 5.63 (br s, H-2), 6.15 (d of t, J = 7 and 16 Hz, H-5), and 7.55 ppm (d, J = 16 Hz, H-4).

Methylation of a sample with diazomethane and analysis by glc showed it to contain <0.5% of the 2*E*,4*E* isomer **10d.**

To a solution of 2.0 g (0.0075 mol) of the acid **9a** in 10 ml dry ether, and 0.8 ml of thionyl chloride at 10°, was added 0.3 ml of dimethylformamide. The mixture was then allowed to warm to room temperature and was stirred for 1 hr. The upper layer of the now two-phase mixture was decanted and the solvent removed from it *in vacuo* (the lower phase was discarded). The residue was taken up in 15 ml of fresh ether and 2.3 g (0.038 mol) of 2-propanol was added. The mixture was then stirred at room temperature overnight, ether (45 ml) and water (50 ml) were added, and the mixture was made basic with aqueous 15% potassium carbonate solution. The organic layer was separated and washed twice with water, brine, and then dried ($CaSO_4$). Solvent removal *in vacuo* yielded 1.8 g (77%) of the isopropyl ester **9f:** bp (bath, short path) 136° (0.04 mm); nmr (CCl_4) δ 0.92 (d, J = 6 Hz, C-7 CH_3), 1.08 (s, C-11 CH_3 + H-12), 1.22 [d, J = 6 Hz, $OCH(CH_3)_2$], 1.95 (d, J = 1.3 Hz, C-3 CH_3), 3.08 (s, 3, OCH_3), 4.97 [m, 1, J = 6 Hz, $-OCH(CH_3)_2$], 5.50 (br s, H-2), 6.00 (d of t, J = 7 and 16 Hz, H-5), and 7.58 ppm (d, J = 16 Hz, H-4); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 310 (~0), 153 (25), 137 (15), 111 (40), 109 (15), and 73 (100).

Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.04. Found: C, 73.66; H, 10.97.

Decarboxylation of 4c to the Lactones 7a and 8a. To 12.95 g (0.0415 mol) of the diacid **4c** in 80 ml toluene was added 0.44 g (0.0041 mol) of 2,4-dimethylpridine. The solution was stirred and heated to 100° (evolution of CO_2 began at 80°) and held at 100° until CO_2 evolution ceased (*ca.* 90 min). The solvent was then removed *in vacuo* to give a residue of 10.5 g (94% yield) of a mixture of **7a, 8a,** and **9a** with the lactone **7a** predominating. Separation into acidic and neutral fractions and purification of a sample of the latter by preparative tlc gave the lactone **7a** (containing only a small amount of **8a**): nmr (CCl_4) δ 0.95 (d, J = 6 Hz, CH_3CH), 1.10 [s, $(CH_3)_2CO$], 1.80 (br s, C-3 CH_3), 2.83 (m, H-2), 3.10 (s, OCH_3), 4.87 (br m, H-5), and 5.50 ppm (m, H-4); mass spectrum (20 eV) *m/e* 254, 198, 197, 111, 109, 107, 97, 95, 81, 73 (base peak), 69, and 55.

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.67; H, 10.38.

Repetition of the above experiment with the addition of cupric acetate monohydrate (0.002 mol) gave identical results.

Decarboxylation of 4c Directly to 9a. A mixture of 60.6 g (0.194 mol) of the diacid **4c,** 0.966 g (0.0048 mol) of cupric acetate monohydrate, and 187 g (1.7 mol) of dry 2,4-dimethylpyridine was heated at 80–85° until evolution of carbon dioxide ceased (*ca.* 1 hr). The temperature (oil bath) was then increased to 130° and held there for 1 hr. After cooling, ether and water were added and the mixture was then acidified with cold aqueous 3 *N* H_2SO_4. The aqueous layer was separated and extracted twice with ether. The combined ether layers were washed with aqueous saturated $CuSO_4$ solution, water, and brine and then dried ($CaSO_4$). Solvent removal *in vacuo* gave 50.8 g of a mixture of the lactones **7a** and **8a,** and the acid **9a** with the *acid* predominating.

Heating a sample of the diacid **4c** in excess pyridine as the solvent (no added copper salt) at 100° under a N_2 atmosphere for 2 hr gave a 20% yield of **7a** (plus some **8a**) and a 66% yield of **9a.** In general decarboxylation using 2,4-dimethylpyridine was found to be faster than when pyridine was used.

Heating the lactone acid **5a** (containing some **6a**) in excess 2,4-dimethylpyridine for 2 hr at 100 to 120° gave a similar yield of a mixture of **7a, 8a,** and **9a.**

Opening of the Lactone 7a. A solution of 21.9 g (0.082 mol) of **7a** in 40 ml of ethanol was added to a solution of NaOEt (from 2.3 g of Na; 0.1 mol) in 100 ml of ethanol, and the solution stirred for 18 hr at room temperature. The ethanol was then removed *in vacuo,* and the residue was dissolved in water (150 ml) and extracted with ether (discarded). The aqueous phase was acidified (pH 1) with 4 *N* H_2SO_4 and extracted with ether. The ether extract was washed with water and brine and dried ($MgSO_4$) and the solvent removed to give 21.02 g (96% yield) of **9a.**

(2*Z*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoic Acid (9b). A solution of the lactone **7b** (1.065 g; 0.0045 mol) prepared from **4h** by the procedure given above for **7a,** in 5 ml of ethanol was added slowly to a solution of NaOEt (from 0.115 g of Na; 0.005 mol) in 7.5 ml ethanol at 5° under a N_2 atmosphere. After 20 hr at room temperature the solvent was removed *in vacuo,* water was added and the solution was extracted with ether (discarded). The aqueous phase was separated, acidified with aqueous HCl and the mixture was extracted with ether. The organic layer was washed with water and brine and dried (Na_2SO_4) and the solvent removed *in vacuo* to give 0.92 g (86% yield) of the acid **9b,** which crystallized on standing at room temperature, mp 28–30°. Recrystallization from pentane gave material with mp 31.5–32°: nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 2.03 (d, J = 1.3 Hz, C-3 CH_3), 5.63 (br s, H-2), 6.17 (d of t, J = 7 and 16 Hz, H-5), and 7.55 ppm (d, J = 16 Hz H-4).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.97; H, 11.02.

(2*Z*,4*E*)-11-Hydroxy-3,7,11-trimethyl-2,4-dodecadienoic Acid (9c). In an analogous sequence of reactions, condensation of **2c** with **3a** gave **4g.** Decarboxylation in 2,4-dimethylpyridine at 85–120°, and treatment of the isolated product with NaOEt in dry ethanol gave in similar yields (to above) the acid **9c:** ir (film) 1695 (C=O), 1635, and 1600 cm^{-1}; nmr ($CDCl_3$) δ 0.90 (d, J = 6 Hz, C-7 Me), 1.20 (s, C-11 CH_3 + H-12), 2.02 (br s, C-3 Me), 5.65 (br s, H-2), 6.17 (m, H-5), and 7.56 ppm (d, J = 16 Hz, H-4).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.36; H, 10.60.

This acid was best stored below 5° in sealed containers under N_2 or argon. Slightly impure samples were found to decompose readily at room temperature in air.

Decarboxylation of the Mono Salt of 4c. To 3.56 g (0.01 mol) of the disodium salt **4a** in 20 ml of water was added 2.77 ml (0.01 mol) of 3.60 *N* sulfuric acid (the pH of the resulting solution was 6.5). The solution was heated under reflux for 7 hr (after which time the pH was 8.5), and then allowed to stand overnight at room temperature. The mixture was made basic with 2 *N* sodium hydroxide and extracted with ether. The organic layer was washed with water and dried ($MgSO_4$) and the solvent removed to give 0.53 g of a colorless oil, which by tlc, glc, and nmr analysis was a 55:45 mixture of 11 and **8a,** respectively.

The aqueous phase was acidified with 3.6 *N* sulfuric acid and extracted three times with ether. The combined ether layers were dried ($MgSO_4$) and the solvent was removed. The residue (2.04 g) was composed of a 2:1 mixture of **9a** and the starting acid **4c,** respectively.

10-Methoxy-2,6,10-trimethyl-1,3-undecadiene (11). On heat-

ing a sample of the 2*Z*,4*E* acid **9a** at 120° without solvent both the lactone **8a** and the diene **11** began to appear. After 22 hr the three compounds **9a**, **8a**, and **11** were present in about equal amounts. At 150° the acid **9a** disappeared and the diene **11** began to predominate.

A 3.3-g sample of **9a** was heated without solvent at 130° for 27 hr under N_2. After the sample had cooled, the nmr spectrum (and the glc analysis of a diazomethane treated aliquot) showed the presence of a mixture of **11**, **8a**, and **9a**. A 1.85-g portion of this mixture was chromatographed on silica gel preparative thin-layer plates developed with ether–hexane (7:93). The upper band gave 0.45 g of the diene **11** (analysis by glc showed a purity of 96%): bp (bath, short path) 65° (0.04 mm); uv max (hexane) 230 nm (ϵ 25,600); ir (film) 3080, 1610, 970, and 885 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-6 CH_3), 1.10 (s, C-10 CH_3 + H-11), 1.82 (m, C-2 CH_3), 3.10 (s, OCH_3), 4.83 (br s, H-1), 5.57 (m, H-4), and 6.11 ppm (d, J = 16 Hz, H-3); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 224 (~0), 209 (1), 192 (6), 177 (7), 149 (16), 136 (8), 124 (13), 123 (23), 121 (13), 109 (20), 107 (27), 95 (10), 93 (15), 81 (20), 73 (100), 69 (27), and 55 (10).

Equilibration of the 2*Z*,4*E* Acid 9a. To 123 g (0.46 mol) of **9a** was added with stirring under N_2, 1.23 g (11 mmol) of benzenethiol and the mixture was heated at 100° in an oil bath for 1 hr (reaction was followed by glc analysis of diazomethane methylated aliquots). To the mixture was then added 60 g of odorless hydrocarbon solvent of bp 176–207° (Soltrol 130, from Phillips Petroleum Co) and the solution distilled *in vacuo* at 3 mm (up to 90°) to remove the benzenethiol. The residue was then cooled and to it was added hexane (100 ml), water (400 ml), and 37 g (0.55 mol) of 58% NH_4OH. After thorough mixing the aqueous layer was separated and acidified with 4 *N* H_2SO_4 and then was extracted with hexane. The organic layer was washed with water and brine and dried ($MgSO_4$) and the solvent removed at 1 mm (up to 60°) to give 117.3 g (95% yield) of a mixture containing 32% of **9a** and 65.4% of **10a** (determined by glc analysis of a diazomethane treated aliquot, on OV-101 or PDEAS).

In the equilibration reaction and during the benzenethiol removal, the temperature of the pot was kept below 102° to prevent any loss of **9a** by decarboxylation to **11**.

Under the same conditions **9b** and **9c** were equilibrated to the corresponding 65:35 mixtures of 2*E*,4*E* and 2*Z*,4*E* isomers, respectively.

Equilibrations of **9a** were also carried out using 5 mol % benzenethiol plus 1 mol % 2,2′-azobis(isobutyronitrile) with heating at 80° for 2 hr, to give a mixture of **9a**:**10a** in the ratio 32:68, respectively.

Equilibration of (*Z*)-11-Tetradecen-1-yl Acetate. A mixture of 10.36 g of (*Z*)-11-tetradecen-1-yl acetate[17] and 0.104 g of benzenethiol was heated in an oil bath at 100° with stirring for 80 min under a N_2 atmosphere. After cooling, 15 ml of Soltrol 130 (a mixture of hydrocarbons; bp 176–207°) was added and a Soltrol 130–benzenethiol mixture was distilled off *in vacuo* [max bp 54° (3.6 mm)]. The residue was chromatographed on silica gel (activity III; 200 g), and elution with 5% ether in hexane gave 9.35 g (90% yield) of pure 11-tetradecen-1-yl acetate, as a mixture of the *E* and *Z* isomers in the ratio of 75:25, respectively.

Similarly heating (*Z*)-8-dodecen-1-yl acetate[25] with 1% by weight of benzenethiol at 100° for 1 hr and working up as above gave a *E*:*Z* ratio of 77:23, respectively.

Ammonium (2*E*,4*E*)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoate. Over a stirred solution of 242.5 g (0.904 mol) of a 65:35 mixture of **10a**:**9a** (respectively) from equilibration, in 1.2 l. of diethyl ether, was passed dry NH_3 gas until the solution ceased to absorb the gas. After a further 2 hr stirring in a NH_3 atmosphere the mixture was filtered, and the collected solid was resuspended in 750 ml of fresh ether and the mixture was filtered again. Residual ether was removed from the salt under reduced pressure to give 130 g (0.46 mol) of the salt as a white solid. The ammonium salt slowly evolved NH_3 but was stable stored in air-tight containers.

The ether filtrates from above were combined and stirred with excess aqueous 4 *N* H_2SO_4. The organic layer was washed with water and brine and dried and the solvent removed to give a 116.3 g (0.43 mol) of residue (**9a** plus **10a**) which was recycled through the equilibration procedure.

The solubility of the ammonium salt of **10a** in dry ether, at 25°, was found to be 2.1 g/l., and the solubility in hexane was *ca.* 1 g/l.

In a like manner the ammonium salts of **10b** and **10c** were precipitated from dichloromethane.

(2*E*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoic Acid (10b). To a solution of 197 g (0.77 mol) of the ammonium salt of **10b** in 350 ml of water was added 850 ml of hexane and 275 g (0.1 mol) of 4 *N* H_2SO_4 with stirring. After 15 min the organic layer was washed with brine and dried ($CaSO_4$) and the solvent was removed to give 180 g (0.76 mol) of **10b** as a crystalline solid, mp 42–44° (lit.[2] mp 44°). Analysis by glc (of a diazomethane methylated sample) showed that the acid contained a negligible amount (<0.5%) of the 2*Z*,4*E* isomer **9b**.

Similarly recovery from the corresponding salts (as above) gave pure **10a**,[2] and also the pure 2*E*,4*E* acid **10c**: ir (film) 1697, 1635 and 1610 cm^{-1}; nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.17 (s, C-11 CH_3 + H-12), 2.27 (d, J = 1 Hz, C-3 CH_3), 5.68 (m, H-2), and 6.03 ppm (m, H-4 and H-5).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.45; H, 10.03.

Methylation of **10c** with diazomethane gave methyl (2*E*,4*E*)-11-hydroxy-3,7,11-trimethyl-2,4-dodecadienoate: bp (bath, short path) 115° (0.04 mm); nmr (CCl_4) δ 0.88 (d, J = 6 Hz, C-7 CH_3), 1.18 (s, C-11 CH_3 + H-12), 2.26 (d, J = 1 Hz, C-3 CH_3), 3.67 (s, CO_2CH_3), 5.65 (br s, H-2), and 6.10 ppm (m, H-4 and H-5).

Ethylation of **10c** with diazoethane gave the corresponding ethyl ester **1e**: bp (bath, short path) 102° (0.01 mm).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71; O, 16.99. Found: C, 72.40; H, 10.77; O, 16.96.

Isopropyl (2*E*,4*E*)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoate (1a). To a solution of 285.4 g (1.0 mol) of the ammonium salt of **10a** in 450 ml of water was added 900 ml of hexane and 375 ml of 4 *N* H_2SO_4 with stirring. The organic layer was washed with brine and dried ($CaSO_4$) and the solvent was removed *in vacuo*. The dry residue was dissolved in 146 g (2 mol) of dimethylformamide under a N_2 atmosphere in an apparatus equipped with a reflux condenser, and 137 g (1.15 mol) of $SOCl_2$ was added (exothermic) dropwise with stirring, at such a rate that the temperature did not exceed 35°. After a further 1 hr at 35° the mixture was cooled and 350 ml of pentane was added (gas evolution occurred) followed by the dropwise addition of 81 g (1.35 mol) of 2-propanol (exothermic; temperature was controlled by the refluxing solvent). After a further 1 hr stirring, 400 ml of pentane was added followed by the slow addition of 300 ml of water, with cooling in a cold water bath. The organic phase was washed with 2 *N* NaOH, water, and brine and dried ($MgSO_4$) and the solvent removed to give 277 g (89% yield) of **1a**[2] (analysis by glc showed it to contain 95.1% of **1a** and 2.1% of the 2*Z*,4*E* isomer **9f**): bp 135–136° (0.06 mm).

Since the starting ammonium salt of **10a** contained negligible 2*Z*,4*E* isomer, a small amount of isomerization at C-2 obviously occurred under the above rather vigorous esterification conditions. Heating the acid chloride (above) at 110° for 2 hr with excess thionyl chloride caused equilibration at C-2.

***S*-Ethyl (2*E*,4*E*)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienethioate (1c).** To a solution of 135 g (0.50 mol) of **10a** in 73 g (1.0 mol) of dimethylformamide under N_2 was added dropwise 68.5 g (0.58 mol) of $SOCl_2$ while maintaining the temperature at ≤35°. After a further 1 hr at 35° the mixture was cooled and 200 ml of pentane was added with stirring (gas evolution occurred). On settling, the lower dimethylformamide layer was drained off, additional pentane (250 ml) was added to the upper phase which was then cooled to 15°. To this solution was added slowly 34 g (0.55 mol) of ethanethiol followed by careful addition (exothermic) of 48 ml (0.60 mol) of pyridine dissolved in pentane (100 ml) with cooling to maintain the temperature below 30°. After the addition was completed the mixture was stirred for 1 hr at room temperature and then 300 ml of water was added. The organic phase was washed with 4 *N* H_2SO_4, water, 2 *N* NaOH, water, and brine and dried ($CaSO_4$) and the solvent removed to give 147 g (94% yield) of **1c**. Internal standard glc analysis gave a purity of 93% **1c**: bp 155–156° (0.09 mm); nmr (CCl_4) δ 0.88 (d, 3, J = 6 Hz, C-7 CH_3), 1.10 (s, 6, C-11 CH_3 + H-12), 1.27 (t, 3, J = 7.5 Hz, SCH_2CH_3), 2.24 (d, 3, J = 1 Hz, C-3 CH_3), 2.88 (q, 2, J = 7.5 Hz, SCH_2CH_3), 3.10 (s, 3, OCH_3), 5.90 (m, 1, H-2), and 6.10 ppm (m, 2, H-4 and H-5).

Anal. Calcd for $C_{18}H_{32}O_2S$: C, 69.19; H, 10.32. Found: C, 69.40; H, 10.35.

2-Propynyl (2*E*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoate (1d). To a solution of 85.4 g (0.36 mol) of **10b** in 52 g (0.71 mol) of dimethylformamide under N_2 was slowly added 48.8 g (0.41 mol) of $SOCl_2$ keeping the temperature ≤35°. After a further 1 hr at 35°, 300 ml of pentane was added to the cooled reaction mixture with stirring (gas evolution). The lower phase was discarded and then 27.5 g (0.49 mol) of 2-propyn-1-ol was slowly added (exothermic) to the upper pentane phase with cooling and stirring. After

the addition was completed the solution was stirred for an additional 1 hr at room temperature, then washed with water, 2 *N* NaOH, water, and brine and dried ($CaSO_4$) and the solvent was removed to give 97.8 g (98% yield) of crude product. Analysis by glc showed it to be 97.2% pure **1d**: bp (bath, short path) 121° (0.01 mm); ir (film) 1725, 1640, and 1615 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 2.31 (d, J = 1 Hz, C-3 CH_3), 2.45 (t, 1, J = 2.5 Hz, C≡CH), 4.74 (d, 2, J = 2.5 Hz, $OCH_2C{\equiv}CH$), 5.76 (m, 1, H-2), and 6.17 ppm (m, 2, H-4 and H-5).

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.10; H, 10.12.

Substitution of dry ethanol for 2-propyn-1-ol in the above preparation gave **1b**.[2]

Isomerization of Dimethyl Ester 4f. To 2.01 g of the ester **4f** was added 0.065 g of benzenethiol and 0.045 g of 2,2′-azobis(isobutyronitrile) [AIBN] and the mixture heated at 88° for 2.25 hr under N_2. Analysis by glc showed the presence of 48% of **4f**, 34% of the isomer **12**, and 13% of the isomer **13**. A further 0.065 g of benzenethiol and 0.049 g of AIBN were added and the mixture was heated at 88° for 2 hr. Glc analysis now showed the presence of 42% of **4f**, 46% of **12**, and 12% of **13**. Further addition of 0.065 g of benzenethiol and 0.048 g of AIBN and heating again at 85° for 2 hr did not produce any further change in the isomer ratio. No evidence was seen (nmr and glc) for the presence of the fourth possible isomer (2*Z*,4*Z*). The product was chromatographed on preparative thin-layer silica gel plates (1.5 mm thick) developed with ether–hexane (3:7). The lower band gave the starting ester **4f** and the upper band gave 0.70 g of a mixture of **12** and **13** in the ratio 78:22, respectively. Attempted separation of a portion of this mixture by hp liquid chromatography on LiChrosorb (20 μ, lm) in ether–pentane (1:4) gave two fractions, the first containing **12** and **13** in the ratio 31:69 and the second fraction containing **12** and **13** in the ratio 89:11, respectively. **12**: nmr (CCl_4) δ 0.93 (d, J = 6 Hz, C-7 CH_3), 1.10 (s, C-11 CH_3 + H-12), 2.22 (d, J = 1.5 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.70 (s, CO_2CH_3), 3.73 (s, CO_2CH_3), 5.54 (m, H-2), and 6.76 ppm (t, "J" = 7.5 Hz, H-5).

13: nmr (CCl_4) δ 0.93 (d, J = 6 Hz, C-7 CH_3), 1.10 (s, C-11 CH_3 + H-12), 2.27 (d, J = 1.5 Hz, C-3 CH_3), 3.10 (s, OCH_3), 3.66 (s, CO_2CH_3), 3.76 (s, CO_2CH_3), 5.62 (m, H-2), and 6.08 ppm (t, "J" = 7.5 Hz, H-5).

The mass spectra of **12** and **13** (obtained from glc–ms) were almost identical with that obtained from **4f**.

To 0.20 g of a mixture of **12** and **13** (in the ratio 78:22, respectively) were added 0.007 g of benzenethiol and 0.006 g of AIBN and the mixture was heated at 80° for 2 hr under N_2. A further 0.007 g of benzenethiol and 0.006 g of AIBN were added and the mixture heated again at 80° for 2 hr. Glc analysis (after removal of the benzenethiol in high vacuum) showed the presence of 40% of **4f**, 48% of **12**, and 12% of **13**.

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Registry No.—**1a**, 41205-06-5; **1c**, 53023-54-4; **1d**, 53023-55-5; **1e**, 53023-56-6; **2a**, 53023-57-7; **3a**, 52313-87-8; **3b**, 924-59-4; **3c** (R′ = Me, R″ = Et), 53023-58-8; **3c** (R′ = Et, R″ = Me), 53092-54-9; **4a**, 53023-59-9; **4c**, 53023-60-2; **4d**, 53023-61-3; **4e**, 53023-62-4; **4f**, 53023-63-5; **5a**, 52313-83-4; **5b**, 53092-48-1; **5c**, 53092-49-2; **6c**, 53023-64-6; **7a**, 52313-82-3; **7b**, 52313-78-7; **8a**, 52313-85-6; **9a**, 53023-65-7; **9a** NH_3 salt, 53042-19-6; **9b**, 53092-50-5; **9c**, 53092-51-6; **9f**, 53108-97-7; **10a**, 53092-52-7; **10a** NH_3 salt, 53023-66-8; **10b**, 53023-67-9; **10b** NH_3 salt, 53023-68-0; **10c**, 53092-53-8; **10c** NH_3 salt, 53154-32-8; **10c** methyl ester, 53154-33-9; **11**, 53023-69-1; **12**, 53023-70-4; **13**, 53023-71-5; methyl isodehydracetate, 41264-06-6; ethyl isodehydracetate, 3385-34-0; 1-ethyl-3-*p*-tolyltriazene, 50707-40-9; (*Z*)-11-tetradecen-1-yl acetate, 20711-10-8; (*E*)-11-tetradecen-1-yl acetate, 33189-72-9; (*Z*)-8-dodecen-1-yl acetate, 28079-04-1; (*E*)-8-dodecen-1-yl acetate, 38363-29-0; 2-propanol, 67-63-0; 2-propyn-1-ol, 107-19-7.

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Approaches to the Synthesis of the Insect Juvenile Hormone Analog Ethyl 3,7,11-Trimethyl-2,4-dodecadienoate and Its Photochemistry[1]

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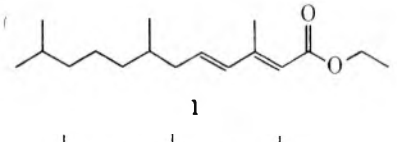
Three alternate synthetic schemes for the preparation of ethyl 3,7,11-trimethyl-2,4-dodecadienoate are described. Methods are discussed for the conversion of the 4*Z* to the 4*E* isomers and the thermodynamic equilibrium was established for the isomers. A study was made of both the direct and the sensitized photochemical *Z*–*E* isomerization of the 2*E*,4*E* and the 2*Z*,4*E* isomers. The Rose Bengal sensitized photooxygenation of the 2*E*,4*E* isomer **1** gave the 3-hydroxy-2-pyrone **19**.

In related papers[3,4] we have discussed synthetic methods for the preparation of each of the four stereoisomers of the alkyl 3,7,11-trimethyl-2,4-dodecadienoates,[5] a class of insect growth regulators in which the 2*E*,4*E* isomers (*e.g.*, **1**) have potent juvenile hormone activity.[4,5] In the preceding paper[3] we described a general stereoselective route to these compounds. The present paper describes three of the other synthetic routes which we have investigated for the preparation of **1**.



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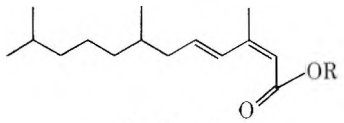


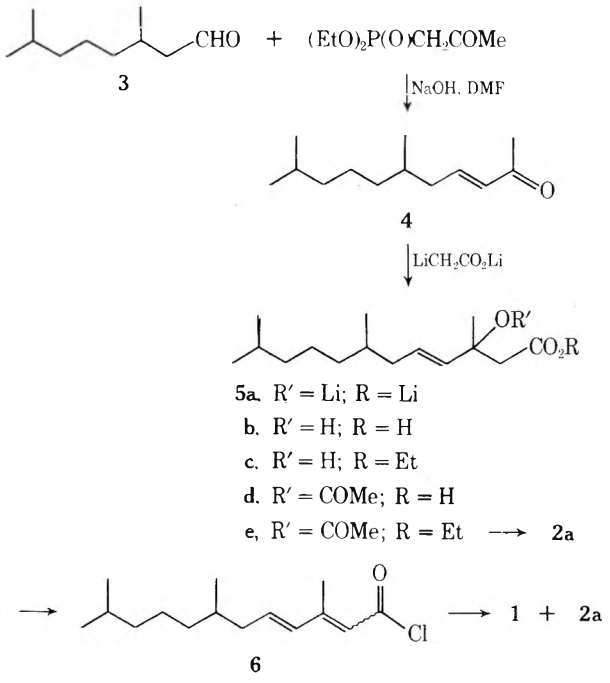
2a, R = Et
b, R = H

Method I. The condensation of a conjugated ketone such as **4** with an acetic acid derived reagent was one potential route to **1**. Reaction of the aldehyde **3** with the anion of diethyl 2-oxopropylphosphonate gave **4** in high yield with nearly exclusive *E* stereochemistry. Treatment of **4** with the dilithium salt of acetic acid[6] gave, after protonation, the hydroxy acid **5b** which could be esterified to **5c** (*cf.* Reformatsky reaction[7]) (Scheme I). Dehydration of **5c** with either phosphoryl chloride in pyridine[7a] or phosphorus pentoxide[7c] in benzene gave a mixture of **1** and **2a**, as well as variable amounts (*ca.* 40%) of isomers (presumably 3,5-dienes **16**; and perhaps some 4,6-dienes) in which the ester was no longer conjugated with the diene system (*cf.* ref 7). Reaction of **5b** with thionyl chloride or with phosphorus trichloride[7b] gave impure **6** containing up to 50% 3,5-diene isomers. However, if formation of the acid chloride was carried out in the presence of the hindered tertiary amine *N*-ethyldiisopropylamine,[8] subsequent treatment with ethanol gave a mixture of **1** and **2a** containing <10% of the 3,5-dienoate isomers. If the impure acid chloride above, prepared with thionyl chloride, was allowed to stand in the presence of *N*-ethyldiisopropylamine for 3 days before treatment with ethanol, a similar mixture of **1** and **2a** was obtained (*cf.* ref 7b).

Acetylation of the intermediate dilithium salt **5a** gave **5d** which was esterified with diazoethane to give **5e**. Treatment of the acetoxy ester **5e** with potassium *tert*-butoxide[9] in tetrahydrofuran gave a mixture of **1** and **2a** in approximately equal amounts. Both **1** and **2a** can be equilibrated readily with benzenethiol to a mixture containing 65% of **1**.[3]

Reaction of **4** with the anion of triethyl phosphonoacetate under a variety of conditions gave negligible yields of **1** and **2a**, in contrast to the result obtained with the corresponding 3-yn-2-one analog of **4**.[4]

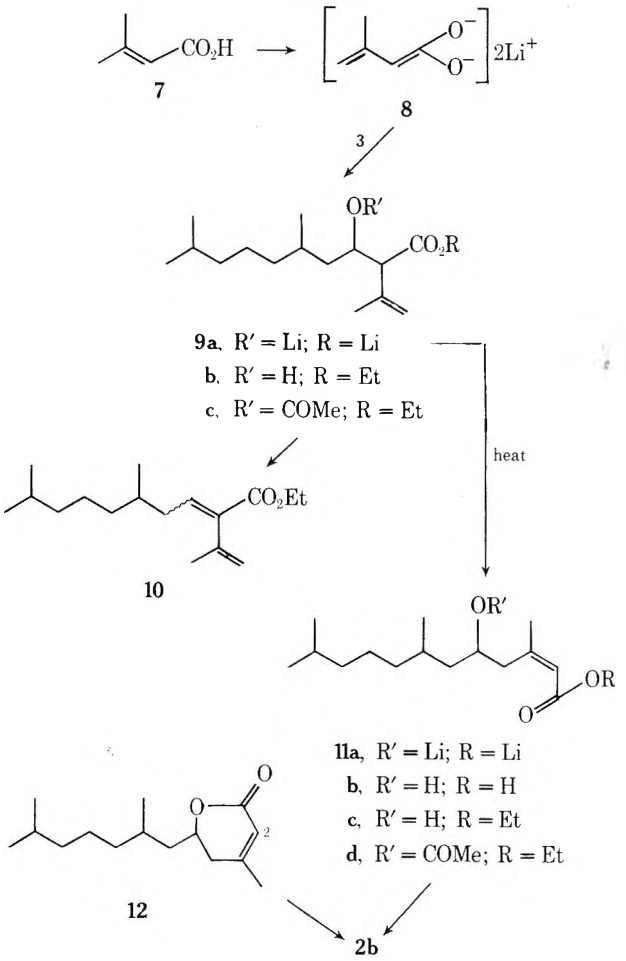
Scheme I



Method II. The direct condensation of esters of 3-methyl-2-butenoic acid (**7**) with aldehydes in the presence of alkali amides in either liquid ammonia or in ether has been reported to give (after hydrolysis) 3-methyl-2,4-dienoic acids.[10] However, the yields in our hands from such direct condensations with *saturated* aldehydes such as **3** were very poor (*cf.* ref 10b, c, and e). Alkylation reactions of the reactive metalated esters of **7** have been reported, with attack occurring predominately at the α position.[11] A recent report has also appeared on the condensation reaction of the relatively stable disalts of **7** with benzaldehyde.[12]

Dimetalation of **7** to give **8** occurred readily with lithium diisopropylamide in tetrahydrofuran (Scheme II). Reaction of **8** with the aldehyde **3** at room temperature (or at −70°) afforded predominantly the intermediate salt **9a**. Protonation of the reaction mixture and esterification with 1-ethyl-3-*p*-tolyltriazene gave **9b** (plus some **11c** and **12**). Acetylation of **9b** gave **9c** (a mixture of diastereoisomers) which could be converted to the dienoic ester **10** with potassium *tert*-butoxide in tetrahydrofuran. Heating a solution of the intermediate dilithium salt **9a** in tetrahydrofuran under reflux gave a *mixture containing ca. 95% of the isomer* **11a** *and only ca. 5% of* **9a**. Acetylation of the dilithium salt **11a** and then esterification of the recovered acetoxy acid

Scheme II

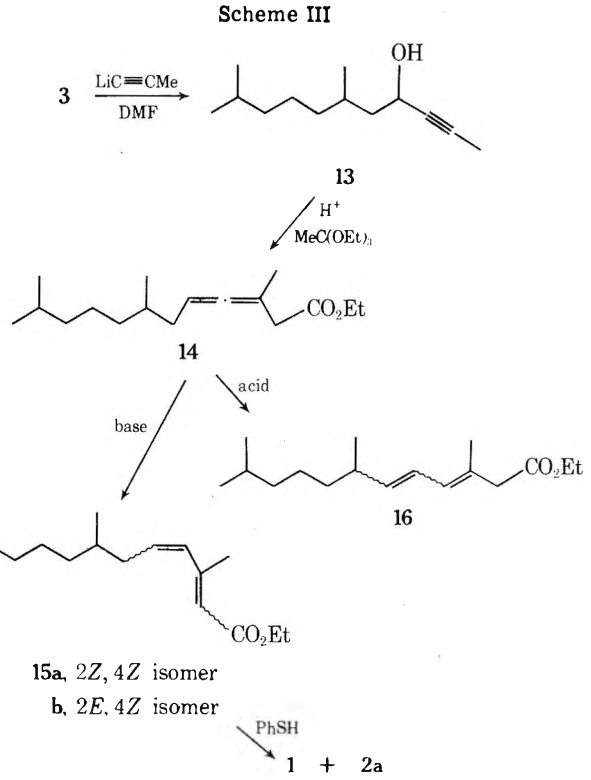


with diazoethane gave the acetoxy ester **11d** as a mixture of the *Z* and *E* isomers in the ratio 9:1, respectively. Treatment of **11d** with potassium *tert*-butoxide in tetrahydrofuran, however, gave only a slow conversion to **2a** (plus **1**) (*cf.* ref 9 and 13a).

Direct acidification of the disalt **11a** gave a mixture of the acid **11b** and the lactone **12**[3] with the latter usually predominating. The hydroxy acid **11b** lactonized readily to **12** under mild acidic conditions. Opening the lactone **12** with sodium ethoxide in ethanol[3,13] gave a high yield of the 2*Z*,4*E* acid **2b** which can be converted to **1**.[3]

It was reported by Watanabe, *et al.*,[14] that the reaction of the dilithium salt of crotonic acid with ketones gave only the 5-hydroxy-2-enoic acids. Repetition of this work by a different group[15] showed that in fact, under the conditions used by Watanabe, *et al.*, a mixture of ~40% α isomer and 60% γ isomer is obtained. Similarly it has been recently reported[12] that the disalts of 3-methyl-2-butenoic acid (**7**) react with benzaldehyde to give mixtures of the α and γ products and that the product distribution could be correlated with the nature of the two metals used to form the disalt, and with the solvent. However, none of these authors noticed that *there is an equilibrium between the disalts of the products,* and that the α product (*e.g.*, **9a**) can be converted to a mixture containing mainly the γ product (*e.g.*, **11a**) by further heating of the reaction mixture. Recently the Reformatsky reaction of alkyl γ-bromocrotonates has been reinvestigated. It was noticed that at 0° the β-hydroxy ester was obtained and that when the alkoxide corresponding to this hydroxy ester was heated, an equilibrium was established which upon hydrolysis gave the δ-hydroxy ester, corresponding to the thermodynamically more stable zinc salt.[16]

Scheme III



Method III. It has been shown by Crandall and Tindell[17] and by us[18] that reaction of aliphatic propynyl alcohols such as 2-methyl-3-butyn-2-ol with trialkyl orthoacetates gives β-allenic ester derivatives which can be rearranged under mild alkaline conditions[18] to give alkyl 5-methyl-2,4-hexadienoates. We have also investigated this reaction as a possible route to alkyl 3,7,11-trimethyl-2,4-dodecadienoates such as **1**.[19]

Reaction of aldehyde **3** with propynyllithium in dimethylformamide gave **13** in 29% yield after spinning band distillation (Scheme III). Treatment of **13** with triethyl orthoacetate (*cf.* ref 20) and a catalytic amount of propionic acid at 125° under conditions of continuous ethanol removal gave the allenic ester **14** in 83% isolated yield. The rearrangement of **14** to the 3-methyl-2,4-dienoate isomers was studied under a variety of conditions. Treatment of **14** with various acidic catalysts gave mixtures of **1**, **2a**, and the 3,5-dienoate isomers **16** with the latter predominating.[21,22] Rearrangement of **14** with basic catalysts (Table I) generally gave mixtures of **1**, **2a**, and the 4*Z* isomers, **15a** and **15b**,[4] with the 4*Z* isomers often predominating. Small variations in the basic conditions gave different ratios of **1**, **2a**, **15a**, and **15b**. The use of tetrahydrofuran or ethanol as the reaction solvent gave fewer by-products than did the use of dimethylformamide, dimethyl sulfoxide, or of dioxane. The allenic ester isomerized rapidly under basic conditions and the composition of the initially formed mixture of isomers did not generally change appreciably with time under the various conditions used. Thus addition of a catalytic amount of sodium ethoxide in ethanol to a solution of **14** in dimethylformamide gave complete reaction of the starting material in less than 10 min at 0° (or 2 hr at −20°) and produced a mixture of **1**, **2a**, and **15a** + **15b** in the ratio *ca.* 45:20:35, respectively. Little further change in the isomer ratio occurred after another 15 hr of reaction time at room temperature.

Rearrangement of **14** with Triton B in ethanol at room temperature for 2 days gave a mixture of **1** (23%), **2a** (7%), and the 4*Z* isomers (21% of **15a** and 49% of **15b**), in high yield. Further treatment of this mixture with a catalytic

Table I
Catalytic Rearrangement[a] of Ethyl 3,7,11-Trimethyl-3,4-dodecadienoate (14)

Catalyst	Solvent	Temp, °C (time, hr)	Product ratio[b] (15a + 15b)	2a	1	16
NaOEt	EtOH	24 (1)	35	50	15	
NaOEt	EtOH	24 (68)	65	15	20	
NaOEt	EtOH	50 (70)	65	15	20	
NaOEt[c]	DMF	−70 (2)				
NaOEt	DMF	−20 (2)	40	15	45	
NaOEt	DMF	−15 (48)	55	10	35	
NaOEt	DMF	0 (0.25)	35	20	45	
NaOEt	THF	24 (3)	50	30	15	5
KO-*t*-Bu	THF	24 (2)	55	40	5	
KO-*t*-Bu	*p*-Dioxane	24 (22)[e]	35	40	5	5
Triton B[d]	EtOH	24 (5)	65	10	25	
Triton B	*p*-Dioxane	24 (24)[e]	40	10	20	15
Triton B	DMSO	24 (24)[e]	30	10	20	30
Triton B	DMF	153 (18)[e]	15	10	15	40
KF	EtOH	60 (11)	40	35	15	10
DBN[f]	THF	60 (190)	30	50	10	10
Me_4N·OCOMe[c]	THF	60 (120)				
p-TsOH·H_2O	CH_2Cl_2	40 (5)		15	30	55
H_2SO_4	EtOH	60 (190)[e]		15	25	40
BF_3·Et_2O[g]	Et_2O	24 (48)				

[a] All rearrangements were monitored by glc analysis using *n*-docosane as an internal standard. [b] Duplicate runs varied by up to ± 10% in isomer ratio. [c] No rearrangement occurred. [d] $C_6H_5CH_2N(Me)_3OH$. [e] About 10–20% of 14 remained unreacted under these conditions. [f] 1,5-Diazabicyclo[4.3.0]non-5-ene. [g] Starting material was partially destroyed.

amount of benzenethiol[3] in the presence of a trace of 2,2′-azobis(isobutyronitrile) [AIBN] at 85° for 2 hr in the absence of solvent gave equilibration[3] to a mixture of **1** and **2a** in the ratio 67:33, respectively, with only traces (≤1%) of the 2*Z*,4*Z* isomer (**15a**) and the 2*E*,4*Z* isomer (**15b**). The latter two isomers have been prepared by an alternative route.[4] We have also shown that the same equilibrium mixture of **1** and **2a** was obtained on treatment of either pure **1** or **2a** with benzenethiol (2% by weight) and a trace of AIBN at 80° for 2 hr (*cf.* ref 3). Thus at thermodynamic equilibrium the 4*Z* stereochemistry is not favorable. Indeed examination of Dreiding stereomodels of **15a** and **15b** indicates considerable steric crowding might be expected in these isomers (*cf.* ref 4).

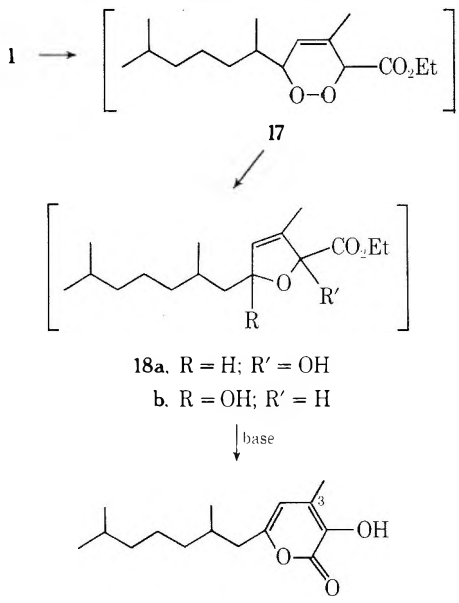
The allenic ester **14** was recovered completely unchanged after attempted isomerization with benzenethiol under the above conditions. Even more vigorous treatment such as heating **14** with 2% by weight of benzenethiol at 100° for 16 hr, gave recovered allene with no decomposition or isomerization detectable by ir, nmr, or glc.

The synthetic routes described above appear to be less useful than the 3-methylglutaconate route described in the preceding paper,[3] for the commercial production of 3,7,11-trimethyl-2,4-dodecadienoates and related analogs. The above schemes involve more steps, are more linear in outline and are less versatile.

Photochemistry. Photochemical *Z*–*E* isomerization of the α,β-double bond was essentially the only process observed in solution under the conditions used, when the (2*E*,4*E*)-dienoate **1** or its 2*Z*,4*E* isomer **2a** was directly irradiated, or irradiated in the presence of a suitable photosensitizer. The direct irradiation of **1** [λ_{max} (hexane) 259 nm (ε 26,400)] or of **2a** [λ_{max} (hexane) 262 nm (ε 20,900)] or of a mixture of both using a medium-pressure mercury lamp whose light was filtered through *ca.* 2–3 mm of Pyrex glass, gave a photostationary state in which the ratio of **1** to **2a** was *ca.* 44:56, respectively. Only traces (<2%) of the 4*Z* isomers **15a** and **15b** could be detected and no other photoprocesses such as photodeconjugation, including allene formation (*i.e.*, **14**), were observed under these conditions.[23] It is interesting that when 4-methyl-3,5-heptadienone was irradiated in a dilute solution in ether, only photoisomerization about the α,β-double bond was reported to occur, in contrast to the results obtained with analogous compounds lacking the 4-methyl group.[24]

Irradiation of mixtures of **1** and **2a** (*ca.* 7:3, respectively) with a medium-pressure mercury lamp (whose light was filtered through 5–12 mm of Pyrex) in the presence of triplet-state sensitizers with triplet-excitation energies ≥53 kcal/mol gave rapid *Z*–*E* isomerization at C-2 to give mixtures of **1** and **2a** in the ratio *ca.* 1:1. For sensitizers with triplet-state energies below 53 kcal/mol the energy transfer efficiency rapidly decreased with decreasing E_t (see Experimental Section). Thus a triplet excited state of the dienoic ester with a triplet-state energy of *ca.* 46–48 kcal/mol is probably involved in this photoisomerization (*cf.* ref 25). Our inability to find an appropriate quencher with a triplet-state energy <49 kcal/mol and not absorbing uv light in the region, where the dienoic esters **1** and **2a** absorb, prevented our doing quenching experiments. Thus it was not possible to ascertain if in the case of direct irradiation, the photoisomerization could, at least in part, have occurred *via* a singlet excited state.

The Rose Bengal sensitized photooxygenation[26] of a mixture of **1** and **2a** (in the ratio 4:1, respectively) was studied using ethanol as the solvent. The reaction of singlet oxygen with the 2*E*,4*E* isomer was quite slow while the 2*Z*,4*E* isomer appeared to be completely unreactive. In a typical experiment, after 163 hr of irradiation only 57% of **1** had reacted. Analysis by tlc showed the formation of only one main product which after work-up and then chromatography gave the hydroxypyrone **19**. The formation of **19** can be rationalized *via* the initial formation of the cyclic peroxide **17** which rearranged to **18a** or to **18b** and then to **19**. Products analogous to **17** and **18a** have been obtained on photosensitized oxygenation of some carotenoid analogs.[27] Photosensitized oxygenation of **1** in d_4-deuteriomethanol in an nmr tube showed that **19** was *not* primarily formed during the irradiation. The initial product showed nmr signals (in



19

CD_3OD) at 1.73 (triplet, J = 2 Hz) and at 5.83 ppm (broad peak) and the addition of a few drops of sodium deuteriomethoxide solution caused the rapid appearance of nmr signals due to **19** and to the liberated ethanol (see Experimental Section). The initial product appeared to be **18a** or **18b** and the conversion to **19** occurred not only with base but also upon heating or prolonged treatment with alumina or even silica gel. The formation of **19** also occurred in the injection port of the gas chromatograph. The nmr, ir, mass spectra, and uv spectra of **19** agree with that expected for the assigned 3-hydroxy-2-pyrone structure (*cf.* ref 28). Recently the analogous 3-hydroxy-2-pyrone has been obtained from the photosensitized oxygenation of isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate.[29]

Experimental Section

All substances described herein are racemic compounds; the prefix *dl* is omitted. Preparative thin-layer chromatography was carried out with Merck (Darmstadt) silica gel PF-254. Nmr spectra were determined on a Varian T-60 spectrometer. Infrared spectra were measured on a Unicam SP 200G spectrophotometer. Mass spectra were measured on a Varian Mat CH-7 spectrometer, at either 20 or 70 eV ionization potential. Gas–liquid chromatographic analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. Solvents were dried over activated molecular sieves.

(*E*)-6,10-Dimethyl-3-undecen-2-one (4). To a mixture of 118.0 g (0.76 mol) of 3,7-dimethyl-1-octanal and 160.5 g (0.83 mol) of diethyl 2-oxopropylphosphonate[30] in 350 ml of dimethylformamide cooled in an ice bath under N_2 was added 31.8 g (0.80 mol) of finely ground sodium hydroxide. After 30 min the cooling bath was removed and after a further 1 hr at room temperature the mixture was diluted with 1400 ml of ice–water and 1000 ml of hexane. The organic layer was separated, washed twice with 600-ml portions of brine, then dried ($CaSO_4$). Solvent removal *in vacuo* yielded 153.1 g of crude product which was purified by distillation through a 15-cm Vigreux column to give 130.0 g (87% yield) of ketone **4** [analysis by glc showed a purity of >90% with a negligible (<2%) amount of the *Z* isomer present]: bp 67–73° (0.07 mm); ir (film) 1700, 1680 (C=O), and 1630 cm^{-1} (C=C); nmr (CCl_4) δ 2.17 (s, 3, $COCH_3$), 5.97 (d, 1, J = 16 Hz, H-3), and 6.71 ppm (2t, 1, J = 16 Hz and 7 Hz, H-4); mass spectrum (20 eV) *m/e* (rel intensity) 197 (~0), 196 (~0), 181 (2), 153 (3), 111 (12), 95 (10), 84 (100), 71 (40), 69 (32), 57 (46), 43 (30).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.75; H, 12.23.

(*E*)-3-Hydroxy-3,7,11-trimethyl-4-dodecenoic Acid (5b). To a solution of 7.9 g (0.078 mol) of diisopropylamine in 400 ml tetrahydrofuran, at 0° under N_2 was slowly added 51 ml (0.079 mol) of 1.55 *M* *n*-butyllithium in hexane solution. The mixture was stirred at 0° for 1 hr, and at room temperature for 3 hr. Then 2.26 g (0.038 mol) of acetic acid in 25 ml of tetrahydrofuran was added at 0°; the mixture was stirred 0.5 hr, heated, and stirred an additional 1.5 hr at 45°. After cooling to 0°, 7.34 g (0.037 mol) of the ketone **4** in 25 ml of tetrahydrofuran was added. The ice bath was then removed and the mixture was stirred at room temperature overnight. After removal of most of the solvent *in vacuo* aqueous 1 *N* hydrochloric acid was added and the mixture extracted with ether. The ether extract was washed with 0.1 *N* aqueous NaOH (4X) and the combined alkaline washings were acidified with 3 *N* hydrochloric acid and extracted thoroughly with ether. The combined organic extracts were washed with brine and dried ($CaSO_4$) and the solvent removed to give 7.21 g of **5b**: low melting solid; ir (film) 3600–2400 (CO_2H and OH) and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.88 (d, 9, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 1.37 (s, 3, C-3 CH_3), 2.63 (s, 2, H-2), and 5.65 ppm (m, 2, H-4 and H-5).

To 1.9 of **5b** in 25 ml of ether was added 2.38 g of 1-ethyl-3-*p*-tolyltriazene[31] and a boiling chip and the mixture heated under reflux for 3.5 hr. To the solution was added slowly aqueous 10% hydrochloric acid and then the organic layer was washed with further aqueous acid, 10% Na_2CO_3, and brine, and dried ($CaSO_4$) and the solvent was removed. Short path distillation of the residue gave 1.1 g of hydroxy ester **5c**: bp (bath) 110° (0.1 mm); ir (film) 3540 (OH) and 1725 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.87 (d, 9, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 1.25 (t, 3, J = 7 Hz, OCH_2CH_3), 1.32 (s, 3, C-3 CH_3), 1.95 (m, 2, H-6), 2.55 (s, 2, H-2), 4.16 (q, 2, J = 7 Hz, OCH_2CH_3), and 5.58 ppm (m, 2, H-4 and H-5); mass spectrum (20 eV) *m/e* (rel intensity) 269 (10), 223 (3), 84 (92), 71 (100), 69 (45), 57 (80), 43 (60).

Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.76; H, 11.20.

Ethyl (*E*)-3-Acetoxy-3,7,11-trimethyl-4-dodecenoate (5e). To about 0.025 mol of the dilithium salt **5a** in 275 ml of THF (prepared as described above for **5b**) at room temperature, under N_2 was added 5.2 g (0.051 mol) of acetic anhydride. The mixture was stirred 6 hr and then boiled overnight. After concentration *in vacuo* aqueous 1 *N* hydrochloric acid was added and the mixture was extracted twice with ether. The organic layer was then extracted with 10% aqueous Na_2CO_3 solution and the basic washes were acidified with cold 3 *N* aqueous HCl and extracted with ether. The organic layer was washed with brine and dried ($CaSO_4$) and the solvent removed *in vacuo* to give 9.56 g of acetoxy acid **5d**: ir (film) 3500–2500 (COOH), 1745, 1720, and 1615 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 9, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 1.65 (s, 3, C-3 CH_3) 2.02 (s, 3, CH_3CO), 3.02 (br s, 2, H-2), and 5.75 ppm (m, 2, H-4 and H-5).

A sample of the acetoxy acid **5d** was esterified with excess diazoethane in ether and the product purified by preparative tlc to yield the ester **5e**: ir (film) 1745 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.88 (d, 9, J = 6.0 Hz), 1.27 (t, 3, J = 7.0 Hz), 1.63 (s, 3, C-3 CH_3), 2.02 (s, 3, CH_3CO), 2.97 (s, 2, H-2), 4.14 (q, 2, J = 7.0 Hz, OCH_2CH_3), and 5.73 ppm (m, 2, H-4 and H-5).

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 70.06; H, 10.45.

Ethyl 3,7,11-trimethyl-2,4-dodecadienoate (1 and 2a). A. From 5b with Phosphorus Trichloride. To a solution of 1.0 g (3.9 mmol) of hydroxy acid **5b** in 10 ml of benzene was added a solution of 0.91 g (6.6 mmol) of phosphorus trichloride in 5 ml of benzene, and the mixture was stirred at room temperature for 3 days. Ethanol (5 ml) and pyridine (10 ml) were then added and the mixture was stirred at room temperature for 2 hr. The reaction mixture was then diluted with ether and water and acidified with 3 *N* aqueous H_2SO_4. The organic layer was washed with 10% aqueous Na_2CO_3, water, saturated aqueous $CuSO_4$, water, and brine, and dried ($CaSO_4$) and the solvent was removed *in vacuo* to give 0.30 g of a mixture. Analysis by glc[21] showed it to contain **1**, **2a**, and **16**[22] in the ratio of *ca.* 1:1:2, respectively.

Repetition of the above procedure using ether as the solvent under reflux overnight gave, apart from 10% **5c**, a mixture of **1**, **2a**, and **16** in the ratio 1.5:1.2, respectively.

B. From 5b with Thionyl Chloride. To a mixture of 7.2 g (28 mmol) of **5b**, 100 ml of benzene, and 7.64 g (59 mmol) of *N*-ethyldiisopropylamine at 0° was added 5.1 ml (70 mmol) of thionyl chloride. The ice bath was then removed and the mixture was stirred at room temperature overnight. Glc analysis at this point revealed very little starting material to be present. The mixture was cooled to 0°, 6.5 g (141 mmol) of ethanol was added, and the mixture was allowed to warm to room temperature and then stirred for 4 hr. The product was then isolated as in A to yield 5.1 g of product. Distillation gave 3.54 g, bp 137–142° (0.3 mm), containing (glc analysis[21]) 5% of **5c**, 27% of **2a**, 50% of ester **1**, and 10% of the deconjugated esters **16**.

This procedure was repeated with 0.1 g (0.4 mmol) of **5b** without initial addition of the tertiary amine. After stirring overnight at room temperature an aliquot was worked up (with ethanol treatment) and analyzed by glc.[21] In addition to some **5b**, there was present a mixture of **1** + **2a** and **16** in the ratio 4:3. To the reaction mixture was now added 0.26 g (2 mmol) of *N*-ethyldiisopropylamine and the reaction followed by glc. The proportion of **16** decreased during the first few hours. After 3 days the mixture was worked up as in A and shown to contain mostly **1** and **2a** with less than 5% of **16**.

C. From 5c with Phosphoryl Chloride. To a solution of 0.10 g (0.35 mmol) of hydroxy ester **5c** in 2 ml of pyridine at 0° was added 0.05 g (0.33 mmol) of phosphoryl chloride. The mixture was allowed to warm to room temperature and stand 4 days. At this point glc analysis[21] revealed the presence of about equal amounts each of the esters **5c**, **1**, **2a**, and **16**.

D. From 5c with Phosphorus Pentoxide. To a mixture of 1.0 g (3.52 mmol) of **5c** in 25 ml benzene, was added 0.50 g (3.52 mmol) of phosphorus pentoxide and the mixture was stirred at 65° for 12 hr, then cooled to room temperature and an additional 0.50 g of phosphorus pentoxide was added. After the mixture had remained at room temperature for 4 days it contained, according to glc analysis,[21] a mixture of **5c**, **1**, **2a**, and **16**[22] in the ratio of 1:1:1:2, respectively.

E. From 5e. To a solution of 0.10 g (0.31 mmol) of the acetoxy ester **5e** in 5 ml of tetrahydrofuran was added 0.04 g (0.36 mmol) of potassium *tert*-butoxide. The solution was stirred at room temperature for 60 hr after which time the mixture contained[21] about 20% starting material **5e** and approximately equal amounts of the 2,4-dienoates **1** and **2a**.

Ethyl 3-Hydroxy-2-isopropenyl-5,9-dimethyldecanoate (9b). To 3.32 g (32.8 mmol) of diisopropylamine and 150 ml of tetrahydrofuran at 0° under N_2 was added 21 ml (33.4 mmol) of 1.59 *M n*-butyllithium in hexane solution. The mixture was stirred 1 hr at 0° and then 3 hr at room temperature. After cooling to 0°, 1.56 g (15.6 mmol) of 3-methyl-2-butenoic acid in 25 ml of THF was added; the solution was stirred 0.5 hr at 0° and then 1.5 hr at 45°. The solution was then recooled to 0° and 2.43 g (15.6 mmol) of 3,7-dimethyl-1-octanal (**3**) in 20 ml of THF was added. After the mixture was stirred 0.5 hr at 0°, it was slowly allowed to warm to room temperature overnight. Aqueous 1 *N* hydrochloric acid was then added with cooling in an ice–water bath and the mixture was extracted thoroughly with ether. The combined organic layers were extracted three times with aqueous 0.1 *N* sodium hydroxide and the combined alkaline washes were acidified at 0° with aqueous 3 *N* hydrochloric acid. The mixture was then extracted with ether and the organic layer washed with brine and dried ($CaSO_4$) and the solvent removed *in vacuo* to give 4.26 g of crude 3-hydroxy-2-isopropenyl-5,9-dimethyldecanoic acid as a low melting solid: ir (film) 1710 (C=O), 1650 (C=C), and 900 cm^{-1}; nmr (CCl_4) δ 0.88 [d, J = 6 Hz, $(CH_3)_2CH$-], 2.99 (br d, $J \sim 7$ Hz, H-2), 4.1 (m, H-3), and 4.97 ppm (m, C=CH_2). A sample of the crude hydroxy acid was esterified with 1-ethyl-3-*p*-tolyltriazene[31] in ether (at reflux temperature) to give crude **9b** contaminated with about 25% of a mixture of **11c** and **12**. Purification by preparative tlc gave pure **9b**: bp (bath, short-path) 120° (0.1 mm); ir (film) 3550 (OH), 1725 (C=O), 1650 (C=C), and 915 cm^{-1} (C=CH_2); nmr ($CDCl_3$) δ 0.88 (d, 6, J = 6 Hz, C-9 CH_3 + H-10), 0.93 (d, 3, J = 6 Hz, C-5 CH_3), 1.27 (t, 3, J = 7 Hz, OCH_2CH_3), 1.87 (m, 3, CH_3C=), 3.03 (br d, 1, $J \sim 7$ Hz, H-2), 4.1 (m, 1, H-3), 4.21 (q, 2, J = 7 Hz, OCH_2CH_3), and 5.02 ppm (m, 2, C=CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 128 (100), 113 (15), 100 (55), 83 (60), 82 (65), 69 (18), 57 (30), 55 (40).

Anal. Calcd for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34. Found: C, 71.78; H, 11.30.

A similar result was obtained when the aldehyde **3** was allowed to react with 8 at −70° for 2 hr followed by quenching at −70° with aqueous hydrochloric acid. Esterification of the product gave a mixture **9b** and **12** in the ratio 88:12, and a negligible amount of **11c**.

Ethyl 3-Acetoxy-2-isopropenyl-5,9-dimethyldecanoate (9c). To a mixture of 2.58 g (9.1 mmol) of hydroxy ester **9b** and 5.9 ml (73 mmol) of pyridine at 0° was added 1.7 ml (18 mmol) of acetic anhydride. The ice bath was then removed and the mixture was stirred at room temperature overnight. The mixture was then cooled to 0° and stirred for 1 hr with 3.5 ml of water. The ester was then isolated with ether in the usual manner to give 2.0 g of crude acetoxy ester which was purified by preparative tlc. Two samples (0.48 g and 0.56 g) were separated, both exhibiting identical ir, nmr, and mass spectra but each containing equal amounts of two components, all differing in glc retention times. These proved to be the four diastereoisomers of **9c** which had been partially separated into two groups: bp (bath, short-path) 80° (0.06 mm); ir (film) 1745 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, J = 6.0 Hz), 1.27 (t, J = 7 Hz, OCH_2CH_3), 1.82 (br s, 3, CH_3C=C), 2.02 (s, 3, CH_3CO), 3.24 (d, 1, J = 9 Hz, H-2), 4.19 (q, 2, J = 7 Hz, OCH_2CH_3), 4.98 (br s, 2, C=CH_2), 5.52 ppm (m, 1, H-3); mass spectrum (20 eV) *m/e* (rel intensity) 221 (4), 170 (10), 128 (100), 127 (22), 100 (10), 43 (32).

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50; Found: C, 69.72; H, 10.35.

Ethyl 2-Isopropenyl-5,9-dimethyl-2-decenoate (10). A mixture of 0.30 g (0.92 mmol) of acetoxy ester **9c**, 10 ml of tetrahydrofuran and 0.11 g (0.98 mmol) of potassium *tert*-butoxide was stirred at room temperature overnight under N_2. Volatile material was then removed *in vacuo* and the residue diluted with 50 ml of ether and 50 ml of water. The aqueous layer was then removed and extracted with 50 ml of ether. The combined ether layers were washed with aqueous 5% sodium bicarbonate solution and water and then dried ($CaSO_4$) and the solvent was removed *in vacuo* to give 0.14 g of product **10** which was short-path distilled: bp (bath) 80° (0.06 mm); ir (film) 3080, 1725 (C=O), 1635 (C=C), and 905 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 9, J = 6.0 Hz, C-5 CH_3 + C-9 CH_3 + H-10), 1.28 (t, J = 7 Hz, OCH_2CH_3), 1.90 (br s, 3, CH_3C=C), 2.2 (m, 2, H-4), 4.24 (q, 2, J = 7 Hz, OCH_2CH_3), 4.78 and 5.18 (br s, C=CH_2), and 6.87 ppm (t, 1, "J" = 7.5 Hz, H-3); mass spectrum (20 eV) *m/e* (rel intensity) 266 (8), 221 (7), 195 (5), 153 (100), 140 (30), 126 (43), 125 (50), 107 (33), 95 (33), 81 (35), 69 (22), 57 (34), 43 (21).

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.52; H, 11.20.

The stereochemistry of the 2-ene bond in **10** is unknown.

(*Z*)-5-Hydroxy-3,7,11-trimethyl-2-dodecenoic Acid (11b). A solution of 9.72 g (62.2 mmol) of 3 was added to 700 ml of a solution of about 62 mmol of the dilithium salt of 3-methyl-2-butenoic acid (prepared as described above, under N_2). The mixture was stirred 0.5 hr at 0° and 4 hr at room temperature, and then heated overnight (16 hr) under reflux. The hydroxy acid was then isolated as described above to give 8.5 g of a mixture of the hydroxy acid **11b** and the lactone **12** in the ratio 60:40 plus about 5% of the 2-isopropenyl-3-hydroxy acid, as estimated from the nmr spectrum (the ratio of **11b**:**12** obtained varied in different experiments).

Ethyl (*Z*)-5-Hydroxy-3,7,11-trimethyl-2-dodecenoate (11c) and 3-Methyl-(2,6-dimethylheptyl)-2-penten-5-olide (12). A 2.0-g sample of crude hydroxy acid above was esterified with 1-ethyl-3-*p*-tolyltriazene[31] and the product was purified by short-path distillation followed by preparative tlc, to give hydroxy ester **11c** [about 90% *Z* and 10% *E* isomers by glc]: {bp (bath, short-path) 120° (0.1 mm); ir (film) 3450 and 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 6, J = 6 Hz, C-11 CH_3 + H-12), 0.93 (d, 3, J = 6 Hz, C-7 CH_3), 1.28 (t, 3, J = 7 Hz, OCH_2CH_3), 1.97 (d, 3, J = 1.3 Hz, C-3 CH_3), 3.95 (br m, 1, H-5), 4.18 (q, 2, J = 7 Hz, OCH_2CH_3) and 5.87 ppm (m, 1, H-2)} and the **lactone 12** {bp (bath, short-path) 110° (0.05 mm); ir (CS_2) 1730, 1655 cm^{-1}; nmr ($CDCl_3$) δ 0.88 [d, 6, J = 6 Hz, $(CH_3)_2CH$], 0.93 (d, 3, J = 6 Hz, CH_3CH), 2.00 (br s, 3, C-3 CH_3), 2.28 (d, 2, J = 7 Hz, H-4), 4.47 (br m, 1, H-5), and 5.80 ppm (m, 1, H-2); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 238 (~0), 125 (7), 112 (8), 111 (100), 109 (5), 100 (5), 97 (5), 95 (5), 83 (17), 82 (22), 81 (8), 71 (9), 69 (9), 57 (14), 55 (8)}.

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.66; H, 10.83.

Ethyl (*Z*)-5-Acetoxy-3,7,11-trimethyl-2-dodecenoate (11d). To a solution of about 20 mmol of the dilithium salt **11a** in tetrahydrofuran was added 3.7 ml (39 mmol) of acetic anhydride and the mixture stirred at room temperature for 6 hr and then boiled overnight. The acetoxy acid was isolated in the usual manner to give 6.5 g of crude acetoxy acid. A 1.4-g sample of the latter was treated with excess diazoethane to give the acetoxy ester **11d** [about 90% *Z* and 10% *E* stereoisomers by glc]: bp (bath, short path) 100° (0.03 mm); ir (film) 1740 (C=O), 1715 (C=O), 1650 (C=C), and 1245 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, J = 6 Hz), 1.28 (t, 3, J = 7 Hz, OCH_2CH_3), 1.94 (d, 3, J = 1.3 Hz, C-3 Me), 2.00 (s, 3, $COCH_3$), 2.92 (m, 2, H-4), 4.25 (q, 2, J = 7 Hz, OCH_2CH_3), 5.17 (br m, 1, H-5), and 5.77 ppm (br s, 1, H-2); mass spectrum (20 eV) *m/e* (rel intensity) 266 (~0), 170 (9), 139 (38), 128 (100), 111 (12), 100 (18), 83 (14), 82 (14), 69 (9), 57 (14).

Anal. Calcd for $C_{19}H_{34}O_4$: C, 69.90; H, 10.50. Found: C, 69.99; H, 10.33.

Ethyl 3,7,11-Trimethyl-2,4-dodecadienoate (1 plus 2a). A mixture of 0.10 g (0.31 mmol) of acetoxy ester **11d** [*ca.* 90% *Z* and 10% *E* isomers by glc], 5 ml tetrahydrofuran, and 0.04 g (0.36 mmol) of potassium *tert*-butoxide was stirred at room temperature for 60 hr, at which time it contained (glc) about 80% of starting material **11d** and a mixture of the dienoates **1** plus **2a** in the ratio about 1:9, respectively.

6,10-Dimethyl-2-undecyn-4-ol (13). To a mixture of 46 g (1 mol) of 1-propynyllithium (from Foote Mineral Co) and 700 ml of dimethylformamide at 0° under N_2 was added 60 g (0.38 mol) of 3,7-dimethyl-1-octanal in 300 ml of dimethylformamide over a period of 3 hr; the ice bath was then removed and the mixture was stirred at room temperature overnight. Saturated aqueous NH_4Cl was then added with ice–water cooling and the mixture was extracted with ether–pentane (1:1). The combined organic layers were washed with water and brine and dried ($CaSO_4$), and the solvent was removed *in vacuo* to give 72.4 g of crude product which was purified by distillation through a 15-cm Vigreux column, followed by distillation on a spinning-band column to give 21.5 g (29% yield) of pure alcohol **13**: bp 68.0° (0.025 mm); ir (film) 3360 (OH) and 2220 cm^{-1} (C≡C); nmr (benzene-d_6) δ 0.88 (d, 9, J = 6 Hz, C-6 Me + C-10 Me + H-11), 1.55 (d, 3, J = 2 Hz, C≡CCH_3), and 4.40 ppm (br m, 1, H-4); nmr ($CDCl_3$) δ 0.87 (d), 1.83 (d, J = 2 Hz, H-1), and 4.4 ppm (br m, H-4); mass spectrum (20 eV) *m/e* 195 ($M^+ - 1$), 69.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.46; H, 12.24.

Ethyl 3,7,11-Trimethyl-3,4-dodecadienoate (14). A mixture of 4.0 g (20 mmol) of the alcohol **13**, 23 g (142 mmol) of triethyl orthoacetate, and 0.05 g (0.7 mmol) of propionic acid was heated at 135° with stirring for 5 hr with a slow stream of argon being allowed to pass over the surface of the liquid such that ethanol plus some triethyl orthoacetate slowly distilled off (reaction was followed by glc). The product was then distilled *in vacuo* directly from the reaction flask after excess triethyl orthoacetate had been removed at 20 mm. There was obtained 4.4 g (83%) of the ester **14** (analysis by glc showed a purity of >96%): bp 100–101° (0.10 mm); ir (film) 1955 (C=C=C), 1740 (C=O), and 1190 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 9, J = 6 Hz, C-7 Me + C-11 Me + H-12), 1.27 (t, 3, J = 7 Hz, OCH_2CH_3), 1.76 (d, 3, J = 3 Hz, C-3 Me), 2.96 (br d, 2, H-2), 4.17 (q, 2, J = 7 Hz, OCH_2CH_3), and 5.03 ppm (br m, 1, H-5); mass spectrum (20 eV) *m/e* (rel intensity) 266 (1), 81 (100).

Anal. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.53; H, 11.21.

Isomerization of 14. Small samples (25–30 mg) of **14** in 1 ml of solvent were treated with 10–30 mol % of various catalysts (Table I) and the progress of the reaction was followed by glc analysis[21] using *n*-docosane (20–30 mg) as an internal standard and using previously prepared, authentic samples of esters **1, 2a, 16, 15a,** and **15b** for comparison purposes. Some of the products were analyzed carefully by glc–mass spectrometry for confirmation of the results.

Isomerization of 14 and Equilibration of Ethyl 3,7,11-Trimethyl-2,4-dodecadienoate Stereoisomers. To a solution of 0.20 g (0.75 mmol) of ester **14** in 2 ml of ethanol at room temperature under N_2 was added 2 drops of *N*-benzyltrimethylammonium hydroxide ("Triton B"; 40% solution in methanol). After 2 days the mixture was acidified with aqueous 2 *N* sulfuric acid and the solvent removed *in vacuo*. The residue was treated with 20 ml of ether and 20 ml of water, the ether layer was separated, washed with water and brine and dried ($CaSO_4$), and the solvent was removed to give 0.16 g of product containing (in their glc elution order)[21] 21% of ester **15a**, 49% of ester **15b**, 7% of ester **2a**, and 23% of ester **1**.

To 50 mg the above ester mixture was added with stirring, 4.6 mg of benzenethiol and 2.9 mg of 2,2′-azobis(isobutyronitrile) and the mixture was heated at 85° for 2 hr under N_2. Volatile materials were then removed *in vacuo* and the mixture was examined by glc.[21] In addition to several trace impurities already present in the starting ester mixture, the final material was found by careful glc analysis to contain 31% of ester **2a** and 64% of ester **1** and very little (<1%) of the 4*Z* esters (**15a** and **15b**).

Photochemical *Z*–*E* Isomerization of 1 and 2a. A. Direct Irradiation. A 44-mg sample of the pure 2*E*,4*E* isomer **1** was dissolved in 3 ml of hexane in a Pyrex tube. The solution was degassed and maintained under an atmosphere of argon, and then irradiated with a 200-W Hanovia medium-pressure mercury arc lamp (S654A-36) with the light filtered through a total of *ca.* 2–3 mm of Pyrex glass. The reaction was followed by glc and after 73 hr of irradiation of photostationary state was reached with **1** and **2a** present in the ratio 44:56, respectively. No trace of the allene **14** could be detected and ≤2% each of the 2*Z*,4*Z* isomer **15a** and of the 2*E*,4*Z* isomer **15b** were present.

An identical result was obtained on repeating the above irradiation starting with the pure 2*Z*,4*E* isomer **2a** in hexane (80 hr). Very little loss of material was observed due to polymerization.

Irradiation of a mixture of **1** and **2a** (in the ratio 70:30, respectively) in either hexane or in methanol as above but in presence of air, gave essentially the same result. After 21-hr irradiation in methanol a mixture of **1** and **2a** was obtained in the ratio 48:52, respectively. Irradiation of a 30-mg sample of dienoates **1** + **2a** (70:30) in a mixture of 2 ml of hexane and 1 ml of (*E*)-1,3-pentadiene (E_t = 59 kcal/mol) in an air atmosphere gave after 21 hr, a mixture of **1** and **2a** in the ratio 44:56, respectively, as above. Thus no quenching was observed.

B. Photosensitized Isomerization. A 30-mg sample of **1** + **2a** (70:30, respectively) was dissolved in a mixture of 1 ml of hexane and 1 ml of acetophenone. The solution was irradiated as above but through a total of 12 mm of Pyrex glass. Isomerization was rapid and after 5.5 hr a photostationary state was reached containing a mixture of **1** and **2a** in the ratio 53:47, respectively. After a further 25 hr of irradiation the ratio had not altered. No allene **14** could be detected and only trace amounts of the 4*Z* isomers **15a** and **15b** were present.

Similarly 50-mg samples of a mixture of **1** + **2a** (78:22, respectively) in degassed tetrahydrofuran (5 ml) under an argon atmosphere were irradiated as above in the presence of 10–20 equiv of a variety of sensitizers, for 2–3 hr with the light filtered through 5–7 mm of Pyrex glass. Under these conditions no change at all occurred in the absence of a sensitizer. The concentrations of the sensitizers were chosen so that they would absorb >99% of the light above 300 nm. The sensitizers used with their triplet energies[32] in kcal/mol in parentheses were acetophenone (73.6), carbazole (70.1), benzophenone (68.5), fluorene (67.6), biphenyl (65), phenanthrene (62.2), 1′-acetonaphthone (56.4), biacetyl (54.9), benzil (53.7), pyrene (48.7), 1,2-benzanthracene (47), and phenazine (44). Most of the sensitizers with triplet energies ≥53 kcal/mol gave rapid isomerization under these conditions to mixtures of **1** and **2a** in *ca.* 50:50 ratio. Some decomposition of the sensitizer was noted in the experiments using phenazine, 1′-acetonaphthone, and phenanthrene, and in the experiment using benzophenone the dienoates were consumed. After 3 hr the run with pyrene contained a mixture of **1**:**2a** in the ratio 61:39, and after 2 hr that with 1,2-benzanthracene contained a ratio of 73:27 (**1**:**2a**). Phenazine under these conditions (2 hr) gave a ratio of 78:22, unchanged from that in the starting sample (some decomposition of the sensitizer did, however, occur).

Photosensitized Oxygenation of 1. A sample of 9 g of dienoate (containing **1** and **2a** in the ratio 4:1, respectively) and 500 mg of Rose Bengal were dissolved in 300 ml of dry ethanol. The photooxidation was conducted in a water-jacketed reaction flask into which the oxygen was dispersed by an extracoarse gas dispersion tube. The solution was irradiated externally with a Smith-Victor Corp (Ind.) Model Q-1 movie light containing a Type DYH 600-*W* GE quartz tungsten–iodine lamp, installed 20 cm from the flask. Efficient water cooling of the jacket kept the reaction temperature below 15° during the reaction period. The reaction was followed by glc analysis of a known aliquot diluted with a solution of *n*-docosane as an internal standard. After 163 hr of irradiation glc analysis demonstrated that whereas the amount of **2a** had remained practically constant, the 2*E*,4*E* isomer **1** had reacted to the extent of *ca.* 57%. Only one main reaction product could be detected by tlc. The solvent was then removed *in vacuo* at a bath temperature below 40°. The residue was chromatographed on 1200 g of silica gel (activity II). Elution with hexane–ether (10:3) gave 1.5 g of **19**: bp (bath, short-path) 100° (0.1 mm); uv max (hexane) 296 nm (ϵ 6500); ir (film) 3370, 1695, 1660, and 1585 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (d, 9, J = 6 Hz, C-7 CH_3 + C-11 CH_3 + H-12), 2.12 (s, 3, C-3 CH_3), and 5.87 ppm (s, 1, H-4); mass spectrum (20 eV) *m/e* (rel intensity) M^+ 252 (10), 140 (100).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.29; H, 9.67.

The nmr spectra of some of the fractions of **19** obtained from the above chromatography, contained a triplet signal at 1.73 ppm due to the presence of an impurity (see below).

In another experiment a 2-g sample of the dienoate (**1**:**2a** in ratio 4:1) was photooxidized at 10° with Rose Bengal (100 mg) for 115 hr as above and the ethanol removed *in vacuo*. Ether was added to the residue and the Rose Bengal was removed by filtration through a column of cellite. The solvent was then evaporated and the residue examined by nmr. The spectrum ($CDCl_3$) showed the presence of **1** and **2a** in about equal amounts (C-3 CH_3 as doublets at 2.28 and 2.00 ppm, respectively) and two new signals, a triplet (J = 2 Hz) at 1.73 ppm and a broad peak at 5.88 ppm. The singlet at 2.12 due to **19** could not be seen. Half of this crude product was distilled *in vacuo* (0.1 mm) at a bath temp of 110° to give 0.87 g of an oil. The nmr spectrum ($CDCl_3$) of this distilled product now contained (apart from signals due to **1** and **2a**) singlets due to **19** at 2.12 and 5.87 ppm. The triplet at 1.73 ppm was considerably diminished in intensity. Analysis by glc showed that the amount of **19** present was *ca.* 15%.

Chromatography of the crude photooxygenation product on alumina (Activity IV) also gave some **19**. Addition of triphenylphosphine or of hexamethylphosphorous triamide to the ethanol solution after irradiation gave after work-up, lower yields of **19** along with complex by-product mixtures.

Photosensitized Oxygenation of 1 in an Nmr Tube. To a 100-mg sample of the dienoate (containing **1** and **2a** in the ratio 4:1) in 0.5 ml of CD_3OD in an nmr tube was added 10 mg of Rose Bengal and the solution irradiated as above in a cooling bath. The oxygen was bubbled through *via* a fine glass tube. The temperature was maintained at 8°, and the reaction was followed by taking occasional nmr spectra. After irradiation for 10 hr the nmr spectrum showed that the majority of **1** had reacted to give a new product which absorbed at 1.73 ppm (triplet, J = 2 Hz) and at 5.83 ppm (broad multiplet peak). Addition of a few drops of NaOD in CD_3OD produced a complete change in the spectrum with loss of the 1.73 and 5.83 ppm signals and the appearance of singlets at

2.03 and 5.87 ppm characteristic of **19**. A quartet at 3.63 ppm (J = 7 Hz) was now observed which was probably due to liberated free ethanol.

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Registry No.—**1**, 41205-09-8; **2a**, 53042-55-0; **3**, 5988-91-0; **4**, 53042-56-1; **5a**, 53042-57-2; **5b**, 53042-58-3; **5c**, 53042-59-4; **5d**, 53042-60-7; **5e**, 53042-61-8; **8**, 53042-62-9; **9b**, 53042-63-0; **9b** free acid, 53042-64-1; **9c** isomer A, 53042-65-2; **9c** isomer B, 53109-13-0; **9c** isomer C, 53109-14-1; **9c** isomer D, 53109-15-2; **10**, 53042-66-3; **11a**, 53042-67-4; **11b**, 53042-68-5; **11c**, 53042-69-6; **11d**, 53042-70-9; **12**, 53042-71-0; **13**, 40770-70-5; **14**, 40770-71-6; **15a**, 53042-72-1; **15b**, 53042-73-2; **19**, 53042-74-3; diethyl 2-oxopropylphosphonate, 1067-71-6; 1-ethyl-3-*p*-tolyltriazene, 50707-40-9; 3-methyl-2-butenoic acid, 541-47-9; triethyl orthoacetate, 78-39-7.

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(22) Spectral data (ir, nmr, and mass spectra) showed the presence of two major isomers in which the carbonyl function was not in conjugation with the diene system. Since proof of actual structure in this case is not trivial, we have tentatively assigned their structures as 3,5-dienoates (*cf.* ref 7). In the mass spectra of **1**, **2a**, **15a**, and of **15b**, the base peak is at *m/e* 139. In the mass spectra of the isomers **16**, the base peak is at *m/e* 107. Partial deconjugation of **1** can readily be carried out by treatment with triphenylmethyllithium in tetrahydrofuran at −30° followed by protonation with water to give some **16**; addition of excess deuterium oxide to the anion solution at −70° gives **16** containing one deuterium atom at C-2 (in the mass spectrum the base peak is now at *m/e* 109 with a peak at 108 of 93% of the base peak intensity).
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Photochemical Reactivity of Imino Lactones. Photoreduction and Photoelimination

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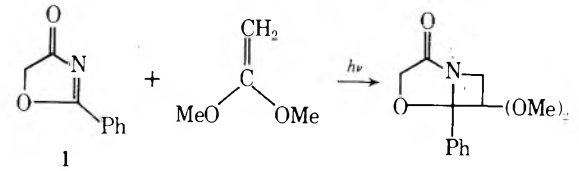
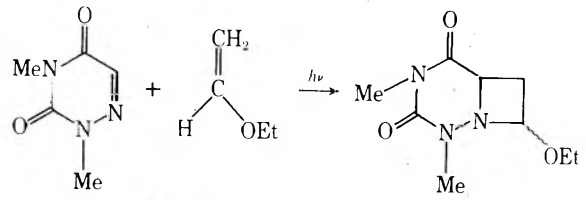
The photochemical reactivity of three imino lactones, 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**), 5,6-dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one (**3b**), and 3-butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (**3c**), is described. Oxazinones **3a** and **3b** are photostable with respect to the [2 + 2] photocycloaddition reaction to the carbon–nitrogen double bond. Oxazinone **3a** undergoes photoreductive dimerization in 2-propanol solvent, oxazinone **3c** photoeliminates propene to give **3a**, and **3b** is photostable. Possible mechanisms for the reductive dimerization and elimination reactions are discussed.

In our exploration of the photochemical reactivity of conjugated imines and imino ethers, we have synthesized and studied three imino lactones. These chromophores were prepared as systems which might illustrate the elusive

[2 + 2] photocycloaddition reaction of carbon–nitrogen double bonds to olefins. We have reported this mode of photoreactivity with keto imino ethers such as 2-phenyloxazolin-4-one (1),[1] and Hyatt and Swenton have observed similar reactivity with 1,3-dimethyl-6-azauracil (2).[2] Al-



1

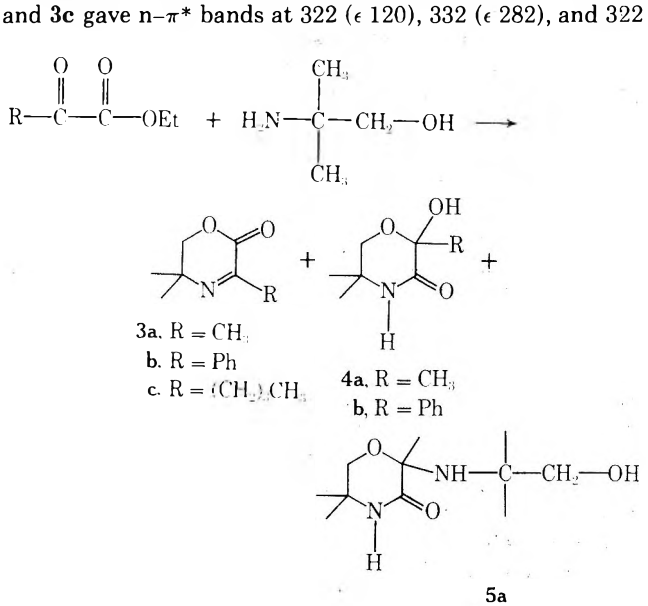


2

though the imino lactones described here, 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**), 5,6-dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one (**3b**), and 3-butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (**3c**), resemble the azauracil of Hyatt and Swenton, their photochemical reactivity with olefins is not competitive with decay processes and photoreduction.

Results and Discussion

Synthesis of Reactants. 5,6-Dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one (**3b**) was prepared by the reaction of ethyl benzoylformate with 2-amino-2-methylpropanol as described by Biekert and Sonnenbichler.[3] 5,6-Dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**) and 3-butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (**3c**) were prepared by an analogous procedure from the reaction of 2-amino-2-methylpropanol with ethyl pyruvate and ethyl hexan-2-onate, respectively, in refluxing toluene. Products **3a** and **3c** were characterized by strong carboxyl and medium intensity imine stretching bands at 1735 and 1640 cm^{-1} in the infrared, strong mass spectral parent ions at *m/e* 141 and 183, respectively, and the nmr data reported in the Experimental Section. In the uv in ethanol solvent, **3a, 3b,** and **3c** gave n–π^* bands at 322 (ϵ 120), 332 (ϵ 282), and 322



3a, R = CH_3
b. R = Ph
c. R = $(CH_2)_3CH_3$

4a, R = CH_3
b, R = Ph

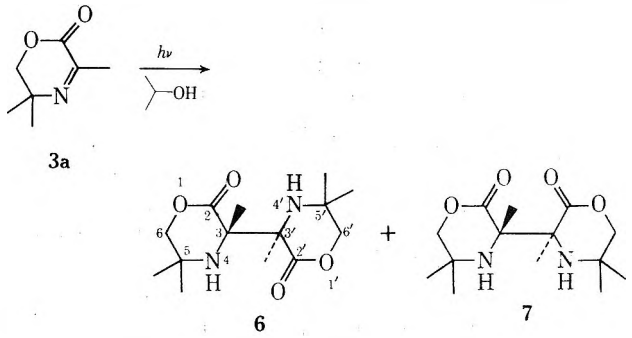
5a

nm (ϵ 135), respectively. The π–π^* band of **3b** appeared at 266 nm (ϵ 7560) and **3a** and **3c** showed only strong end absorption for the π–π^* transitions.

As noted by Biekert and Sonnenbichler,[3] 5,5-dimethyl-2-hydroxy-2-phenylmorpholin-3-one (**4b**) was a by-product of the synthesis of **3b.** Similarly, 2-hydroxy-2,5,5-trimethylmorpholin-3-one (**4a**) was obtained as a by-product of the synthesis of **3a.** An additional by-product, **5a,** was also isolated. It was characterized from the spectroscopic data reported in the Experimental Section and by synthesis from **4a** and 2-amino-2-methylpropanol. Like **4b,** the hemiketal **4a** exists in equilibrium with an isomeric, acyclic, hydroxy ketoamide as shown by nmr analysis.

Photochemical Reactions. Irradiation of **3a** or **3b** with a 450-W, mercury lamp through a Pyrex filter in nonhydrogen donating solvents of varying polarity such as 2-methyl-2-propanol, benzene, and cyclohexane resulted only in recovered starting material as indicated by ir, nmr, and glpc. Similarly, irradiation of **3a** and **3b** in the presence of electron rich and electron neutral olefins such as 1,1-dimethoxyethene and cyclohexene, respectively, in these solvents gave only recovered starting materials. At 77°K, irradiation of a glass of **3a** or **3b** in a low-temperature infrared cell[4] with a 200-W Bausch and Lomb, super pressure, mercury source through a Corning CSO-54 filter gave no destruction of starting material as evidenced by infrared analysis.

When **3a** was irradiated at −15° with a 450-W, mercury lamp through a Pyrex filter in a hydrogen-donating solvent such as 2-propanol, reductive type dimers were isolated in 57% yield. These were assigned the meso and *dl* structures **6** and **7** and were formed in the ratio of 3:2 (meso:*dl*). The



3a

6 7

meso and *dl* dimers were separated using a Chromatronix liquid chromatography column of tlc grade alumina eluting at medium pressure. They were characterized by the nmr data shown in Table I, carboxyl and N–H stretching bands at 1710 and 3360 cm^{-1} in the infrared, and a weak parent ion in the mass spectrum at *m/e* 284 with a base peak at *m/e* 142 corresponding to homolytic cleavage of the 3–3′ bond. The assignment of stereochemistry was accomplished by observing changes in the nmr spectra of **6** and **7** in the presence of the optically active europium shift reagent, tris(3-(trifluoromethylhydroxymethylene)-*d*-camphorato)europium(III).[5] As shown in Table I the nmr absorption by the methyl protons at ring positions 3(3′) and the methylene protons at 6(6′) of the *d* and the *l* isomers were separated in the presence of the optically active shift reagent, thus distinguishing the *dl* from the meso dimer. Irradiation of **3b** under similar conditions in reducing solvents did not lead to reductive dimerization and only starting material was recovered.

The photoreduction of **3a** occurs with a quantum yield of destruction of 0.005 and is quenched by *cis*-piperylene. When the quantum yield data in the presence and absence of quencher (Table II) were plotted in the Stern–Volmer fashion a linear plot was obtained with a slope of 10 l./mol. Analysis of the piperylene by glpc indicated that it was isomerized to *trans*-piperylene during the quantum yield experiments. These results suggest that the photoreduction of **3a** occurs *via* a triplet state.

Table I
Nmr Data

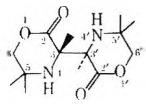
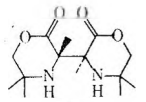
Compd	Solvent	Ring positions 3(3')	5(5')	6(6')
 6	$CDCl_3$	1.53 s (3 H)	1.12 s (3 H), 1.31 s (3 H)	3.90 d (1 H), 4.27 d (1 H), J = 10 Hz
6 + shift reagent	$CDCl_3$	1.62 s (3 H)	1.17 s (3 H), 1.38 s (3 H)	3.99 d (1 H), 4.38 d (1 H), J = 10 Hz
 7	$CDCl_3$	1.68 s (3 H)	1.15 s (3 H), 1.30 s (3 H)	3.94 d (1 H), 4.46 d (1 H), J = 10 Hz
7 + shift reagent	$CDCl_3$	2.07 s (1.5 H), 2.09 s (1.5 H)	1.23 s (3 H), 1.40 s (3 H)	4.08 d (0.5 H), 4.71 d (0.5 H), J = 10 Hz; 4.13 d (0.5 H), 4.71 d (0.5 H), J = 10 Hz

Table II
Quantum Yield of Destruction of 3a in 2-Propanol

[3a][a]	[cis-Piperylene][a]	$A_{initial}$[b]	A_{final}[b]	Φ
0.021	0.00	2.549	2.320	0.0049
0.021	0.01	2.618	2.417	0.0043
0.021	0.05	2.565	2.432	0.0028
0.021	0.10	2.601	2.492	0.0023
0.021	0.15	2.576	2.483	0.0020

[a] Concentrations are given in moles/liter. [b] Average of six measurements of the initial and final optical densities at 322 nm of the oxazinone (3a) solutions.

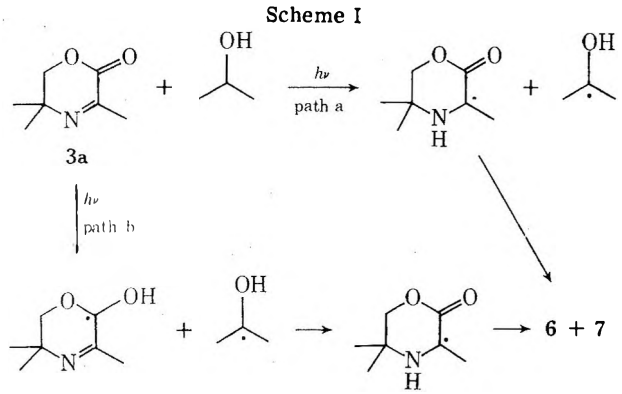
Table III
Quantum Yield of Formation of 3a from 3c

[3c][a]	Φ	[3c][a]	Φ
0.0255	0.0011	0.102	0.0021
0.0408	0.0013	0.204	0.0023

[a] Concentrations are given in moles/liter.

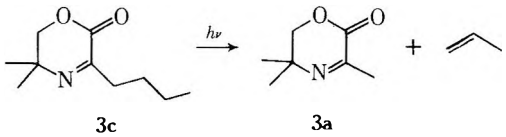
There are two reasonable photochemical events which might ultimately lead to the reductive dimers **6** and **7**. Excited **3a** might abstract a hydrogen atom from 2-propanol at the nitrogen of the imine functional group (path a, Scheme I) or at the carbonyl oxygen of the carboxyl functional group (path b, Scheme I). If initial hydrogen atom abstraction occurred at the carboxyl group, a subsequent intra- or intermolecular hydrogen atom transfer would be required prior to radical combination. The latter path is similar to the chemical sensitization mechanism proposed by Padwa[6] and others[7] to explain the photoreduction of imines in the presence of carbonyl compounds.

Scheme I



3-Butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (**3c**) was studied in order to gain some evidence for distinguishing between these two pathways for reductive dimerization. It was theorized that if the nitrogen of the imine functional group of **3a** had a propensity for hydrogen atom abstraction (*i.e.*, path a, Scheme I), **3c** would undergo a photoreaction analogous to the Norrish Type II photoelimination reaction of ketones. This would occur *via* intramolecular γ-hydrogen abstraction from the butyl side chain by the nitrogen of the imine functional group followed by elimination of propene.

Oxazinone (**3c**) was irradiated in 2-methyl-2-propanol solvent with a 450-W, mercury lamp through a Pyrex filter. 2-Methyl-2-propanol was chosen as the solvent for this experiment because it has a polarity similar to 2-propanol without being a reducing solvent. Under these conditions the only product isolated was **3a**, the product of photoelimination, in 44% yield. Propene was identified as a by-product of the irradiation by nmr and mass spectrometry.

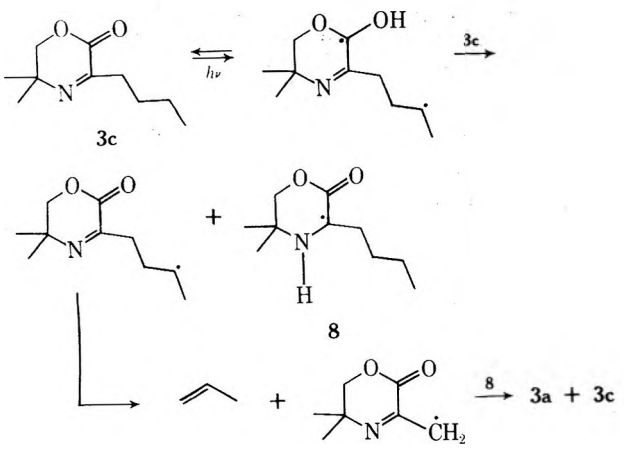


3c **3a**

The formation of **3a** and propene from irradiation of **3c** was in itself most consistent with initial hydrogen atom abstraction by the nitrogen of the imine functional group. Hydrogen atom abstraction from the side chain of **3c** by the carbonyl oxygen of the carboxyl functional group would most likely lead to a cyclization product rather than the products of elimination.[8]

If the photoreaction of **3c** occurred by a Norrish Type II mechanism involving initial hydrogen atom abstraction by the nitrogen of the imine functional group, the quantum yield of **3a** formation should be independent of the concentration of starting **3c**. The quantum yield data for this experiment are reported in Table III. Contrary to the result

Scheme II



predicted by the imine Norrish Type II mechanism, the quantum yield of product formation was concentration dependent and the reciprocal of quantum yield was linear in reciprocal of **3c** concentration, least-squares slope 1.54 ± 0.17 × 10^{-5} mol/l. This result coupled with the low quantum yield prompts us to reconsider the chemical sensitization mechanism and other more complex mechanisms for the elimination reaction as well as for the reductive dimerization. A possible chemical sensitization route to photoelimination consistent with the results of Table III is shown in Scheme II. A rationale for the second step of this mechanism is the documented stability of radicals such as 8.[9]

It is interesting to speculate about the photostability of **3a** and **3b** with respect to the [2 + 2] photocycloaddition reaction with olefins. Danilov and coworkers[10] have suggested that the photostability of the 6-aza analogs of thymine to [2 + 2] dimerization results from an unreactive low-energy n,π^* state. This suggestion has been challenged by the work of Hyatt and Swenton.[2] However, in our exploration of the photoreactivity of keto imino ethers, we have concluded that molecules which are reactive in the [2 + 2] photocycloaddition to carbon–nitrogen double bonds have low-energy π,π^* states and those which are unreactive have low-energy n,π^* states.[1,11,12] At least in the singlet manifold, **3a**, **3b**, and **3c** have lowest energy n,π^* states.

Experimental Section

Apparatus and Instruments. Melting points and boiling points are uncorrected. Melting points were measured with a Thomas-Hoover Unimelt apparatus. A Perkin-Elmer 337 spectrophotometer was used to determine ir spectra. Uv spectra were measured with Cary 14 and 17 spectrophotometers, and nmr spectra were recorded with a JEOL PS-100 and Varian A-60A and HA-100 spectrometers. Chemical shifts are reported in parts per million on the δ scale from internal tetramethylsilane. Mass spectra were obtained with a Varian Mat CH-5 spectrometer. Glpc analyses and isolations were performed with Varian Aerograph (Model 200 and 1500) gas chromatographs equipped with thermal conductivity detectors, and peak areas were measured by Disc integration. Microanalyses were performed by Atlantic Microlab, Atlanta, Georgia.

Synthesis of 5,6-Dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one (3b). 5,6-Dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one was prepared by the method of Biekert and Sonnenbichler.[3] The oxazinone (**3b**) was purified by glpc using a 10 ft × 0.375 in. column of 5% SE-30 on 60–80 mesh Chromosorb W at 185° (He 80 cm^3/min) and gave the following spectral data: nmr ($CDCl_3$) δ 1.32 (s, 6 H), 4.18 (s, 2 H), 7.35 (m, 3 H), and 7.92 ppm (m, 2 H); ir (neat) 1740 and 1605 cm^{-1}; mass spectrum (70 eV) *m/e* 203 (60), 159 (27), 146 (12), 145 (92), 105 (52), 104 (base), 103 (35), 77 (65); uv λ_{max} (95% EtOH) 332 sh (282), 330 sh (271), and 266 nm (7560).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.00; H, 6.45; N, 6.88.

In addition to the oxazinone (**3b**), a precipitate was formed during the reaction which was removed by suction filtration and recrystallized from 2-propanol, mp 125–126° (lit.[3] mp 122°), and identified as 5,5-dimethyl-2-hydroxy-2-phenylmorpholin-3-one (**4b**). In dimethyl sulfoxide solution at ambient temperature **4b** existed in equilibrium with *N*-(2-(1-hydroxy-2-methylpropyl))benzoylformamide as a 86:14 mixture (**4b**:formamide) as indicated by the nmr spectrum. As the temperature of the solution was increased, the percentage of formamide in the mixture increased. At 140° the ratio was 33:67. The following spectral data were obtained: nmr (DMSO-d_6) morpholinone **4b** δ 1.17 (s, 3 H), 1.36 (s, 3 H), 3.49 and 4.03 (AB pattern, J = 12 Hz), 7.14 (s, 1 H), 7.2–7.6 (m, 5 H), and 7.92 ppm (broad, 1 H); the peaks at δ 7.14 and 7.92 ppm disappeared upon exchange with D_2O; formamide δ 1.31 (s, 6 H), 3.50 (d, J = 6 Hz, 2 H), 4.90 (t, J = 6 Hz, 1 H), 7.52 (m, 3 H), 7.89 (m, 2 H), and 8.2 ppm (broad, 1 H); upon addition of D_2O the peaks at δ 4.90 and 8.2 ppm disappeared and the doublet at δ 3.50 ppm collapsed to a singlet; ir (KBr) 3190 and 1645 cm^{-1}; mass spectrum (70 eV) *m/e* 204 (0.5), 193 (2.5), 190 (3.8), 123 (9.5), 116 (15), 105 (65), 77 (41), 73 (17), 58 (base), and 56 (20).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.13; H, 6.92; N, 6.27.

Synthesis of 5,6-Dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (3a). 5,6-Dihydro-3,5,5-trimethyl-1,4-oxazin-2-one was prepared by a procedure similar to the one described for **3b**. A solution of 58 g (0.50 mol) of ethyl pyruvate in 75 ml of toluene was added dropwise to 44.5 g (0.50 mol) of 2-amino-2-methylpropanol in 200 ml of refluxing toluene. The reaction was carried out under a nitrogen atmosphere and a Dean-Stark trap was used to remove the water. After completion of the addition (3 hr), the refluxing was continued overnight. The reaction mixture was transferred to a distillation apparatus and the toluene was removed by distillation through a 20-cm Vigreux column. After the theoretical amount of toluene was collected the pressure was reduced and the product was distilled. Oxazinone (20.0 g) distilling at 90° (25 mm) was collected. Redistillation of the recovered toluene yielded an additional 8.7 g of product for a total yield of 36.7%. Nmr ($CDCl_3$) showed δ 1.30 (s, 6 H), 2.27 (s, 3 H), and 4.23 ppm (s, 2 H); ir (neat) 1735 and 1640 cm^{-1}; uv λ_{max} (95% EtOH) 322 nm (120); mass spectrum (70 eV) *m/e* 141 (52), 83 (91), 56 (68), 42 (72), 41 (base).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.65; H, 7.88; N, 9.95.

Continued distillation of the reaction residue gave 13.1 g (0.057 mol) of 2-*N*-(1′-hydroxy-2′-methyl-2′-propyl)amino-2,5,5-trimethylmorpholin-3-one (**5a**), bp 90° (0.02 mm). The viscous liquid gradually crystallized and was recrystallized twice from ether: mp 90–92°; nmr (CCl_4) δ 1.20 (s, 3 H), 1.22 (s, 3 H), 1.30 (s, 6 H), 1.42 (s, 3 H), 3.40 and 3.61 (AB pattern, J = 8 Hz), 3.50 (s, 2 H), and 6.85 ppm (broad, 1 H); nmr (DMSO-d_6) δ 1.10 (s, 3 H), 1.19 (s, 3 H), 1.22 (s, 6 H), 1.37 (s, 3 H), 3.01 (s, 1 H), 3.36 (d, J = 5 Hz, 2 H), 3.46 (s, 2 H), 5.01 (t, J = 5 Hz, 1 H), and 7.53 ppm (broad, 1 H); upon treatment with D_2O the latter spectrum changed as follows, δ 3.01, 5.01, and 7.53 ppm disappeared while δ 3.36 ppm collapsed to a singlet; ir (CCl_4) 3380, 3300, and 1668 cm^{-1}; mass spectrum (70 eV) *m/e* 200 (4.2), 199 (68), 143 (2.7), 127 (2.7), 115 (32), 114 (base), 98 (5.5), 83 (8.2), 72 (64).

Anal. Calcd for $C_{11}H_{22}N_2O_3$: C, 57.37, H, 9.63; N, 12.16. Found: C, 57.43; H, 9.70; N, 12.11.

Another compound formed in low yields in this reaction was identified as 2-hydroxy-2,5,5-trimethylmorpholin-3-one (**4a**), mp 168–170° (sealed tube), after recrystallization from 2-propanol. As the temperature of a solution of **4a** in dimethyl sulfoxide was increased to 80° new peaks appeared in the nmr spectrum which were assigned to the compound *N*-(2-(1-hydroxy-2-methylpropyl))acetylformamide. At 140° the composition of the mixture was 66:34 (**4a**:formamide) as determined by nmr. The following spectral data were obtained: nmr (DMSO-d_6) morpholinone (**4a**) δ 1.07 (s, 3 H), 1.19 (s, 3 H), 1.35 (s, 3 H), 3.30 and 3.81 (AB pattern, J = 11.5 Hz), 6.39 (s, 1 H), and 7.7 ppm (broad, 1 H); the peaks at δ 6.39 and 7.7 ppm disappeared upon exchange with D_2O; formamide δ 1.22 (s, 6 H), 2.30 (s, 3 H), 3.38 (d, J = 6 Hz, 2 H), 4.97 (t, J = 6 Hz, 1 H), and 7.5 ppm (broad, 1 H); upon addition of D_2O the peaks at δ 4.97 and 7.5 ppm disappeared and the doublet at δ 3.38 ppm collapsed to a singlet; ir (KBr) 3190 and 1650 cm^{-1}; mass spectrum (70 eV) *m/e* 142 (3), 131 (2), 116 (3), 114 (2), 74 (9), 61 (6), 58 (base), 56 (32).

Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.89; H, 8.29; N, 8.89.

The addition of ethyl pyruvate to 2-amino-2-methylpropanol in refluxing benzene yielded 16% 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**), 33% 2-hydroxy-2,5,5-trimethylmorpholin-3-one (**4a**), and none of product **5a**.

Reaction of 2-Hydroxy-2,5,5-trimethylmorpholin-3-one (4a) with 2-Amino-2-methylpropanol. 2-Hydroxy-2,5,5-trimethylmorpholin-3-one (2.0 g, 0.013 mol) was dissolved in 50 ml of dry toluene. 2-Amino-2-methylpropanol (2.3 g, 0.026 mol) was added and the mixture was refluxed for 24 hr using a Dean-Stark trap for removal of water. Analysis by glpc using a 5 ft × 0.25 in. column of 5% SE-30 on 60–80 mesh Chromosorb W at 140° (He 60 cm³/min) showed some unreacted alcohol and a large peak with the same retention time as the morpholinone **5a**. Distillation under vacuum gave 1.85 g of a slightly yellow viscous liquid, bp 85–90° (0.02 mm), which crystallized when seeded with a crystal of **5a**. Recrystallization from ether gave 1.6 g (54%) of white crystals, mp 89–91°, mixture melting point with morpholinone **5a**, 89–91°. The spectra of this compound were identical with those of the previously isolated **5a**.

Synthesis of 3-Butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (3c). 3-Butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one was synthesized in a manner similar to the synthesis of oxazinone **3b**. A 1000-ml three-neck flask, equipped with a Dean-Stark trap, stirrer, dropping funnel, and nitrogen inlet, was charged with 350 ml of toluene and 32 ml (0.34 mol) of 2-amino-2-methylpropanol and brought to reflux. Ethyl hexan-2-onate[13] (38.1 g, 0.24 mol) was added dropwise over a period of 2 hr to the mixture and the reaction refluxed overnight. The toluene was distilled off at atmospheric pressure and the product was distilled at 110° (8 mm), yielding 27.5 g (63%) of pure product. Nmr (CCl_4) showed δ 0.83 to 1.82 (m, 7 H), 1.29 (s, 6 H), 2.54 (t, J = 7 Hz, 2 H), and 4.19 ppm (s, 2 H); ir (neat) 1735 and 1640 cm⁻¹; mass spectrum (70 eV) *m/e* 183 (8.4), 141 (28), 126 (14), 125 (58), 84 (37), 83 (29), 82 (11), 68 (13), 58 (17), 57 (19), 56 (base); uv λ_{max} (95% EtOH) 322 nm (135).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.53; H, 9.39; N, 7.69.

Photodimerization of 5,6-Dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (3a) in 2-Propanol. Oxazinone **3a** (25.3 g) dissolved in 500 ml of 2-propanol, distilled from anhydrous calcium sulfate, was degassed with nitrogen and irradiated with a 450-W, mercury, immersion lamp through Pyrex under a nitrogen atmosphere. Throughout the reaction the photochemical apparatus was immersed in a bath kept at −15°. At this temperature the dimers formed a thick, gelatinous precipitate during the reaction. Every 24 hr the photolysis was interrupted, the precipitate removed by vacuum filtration, and the filtrate returned for continued irradiation. After 5 days no more precipitate formed and the solvent was removed on a rotary evaporator using a Dry Ice–acetone condenser, maintaining the water bath at 10°. Combined yield was 14.4 g (57%) of mixed reductive dimers (**6** and **7**), mp 142–143°, in the ratio of 3:2, meso to *dl*.

The meso and *dl* dimers were separated using medium pressure liquid chromatography. A Chromatronix glass column, 23 × 0.5 in. was packed with Woelm, neutral, tlc grade alumina and activated by first eluting with methanol and then with benzene followed by Skelly B. Solvent was pumped by means of a Milton Roy mini-Pump, and fractions were collected with a time-controlled fraction collector. The entire apparatus was kept in a cold room at 7°. In a typical run, 100 mg of crude dimer mixture was dissolved in 4.5 ml of 5% MeOH in benzene and injected onto the column using a Chromatronix injection system. The eluting solvent was 1% MeOH and 5% Skelly B in benzene at a flow rate of 60 cm³/hr with fractions changing every 5 min. The fastest moving of the dimers was eluted in 70 min and the slower moving in 85 min. Fractions were analyzed using 4 × 7 cm Brinkmann silica gel N-HR tlc sheets, developing with 10% MeOH in benzene at 7° and visualizing with iodine vapor. R_f values were 0.15 and 0.4 for meso and *dl* dimers, respectively. Total recovery of material was better than 95%.

Physical properties of the dimers were as follows: meso dimer, mp 148–150°, *dl* dimer, mp 155–156°; nmr, see Table I; meso and *dl* dimers, ir (KBr) 3360 and 1710 cm⁻¹; meso and *dl* dimers, mass spectrum (70 eV) *m/e* 284 (1), 253 (24), 144 (20), 143 (60), 142 (base), 88 (41), 56 (44), 55 (31).

Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85. Found for meso: C, 59.26; H, 8.46; N, 9.79. Found for *dl*: C, 59.33; H, 8.59; N, 9.80.

Irradiation of 5,6-Dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (3a) in Ethanol. 5,6-Dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (1.4 g) in 130 ml of absolute ethanol was degassed with nitrogen for 0.5 hr and irradiated with a 450-W mercury lamp with a Pyrex immersion well for 26 hr under nitrogen. Throughout the reaction the water bath was kept at 20°. The irradiation mixture was then concentrated on a rotary evaporator keeping the water bath at about 15°. After most of the ethanol was removed 40 ml of cold Skelly B was added and the precipitate of dimers was collected by suction filtration. The filtrate was washed with another 20-ml portion of cold Skelly B, and 0.64 g (45%) of mixed reductive dimers (**6** and **7**), mp 138–140°, was obtained. Nmr analysis showed the meso to *dl* ratio to be 2:1.

Irradiation of 5,6-Dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one (3b). A 0.2-mm path length ir solution cell was filled with a benzene solution of 5,6-dihydro-5,5-dimethyl-3-phenyl-1,4-oxazin-2-one of a concentration such that the carboxyl stretching band at 1740 cm⁻¹ gave an absorbance of 1. The solution was irradiated at ambient temperature with a Bausch and Lomb, 200 W, super pressure mercury lamp through a Corning CSO-54 filter for 30 min. Subsequent scanning of the ir showed no change in the spectrum. A solution of **3b** and 1,1-dimethoxyethene was similarly prepared and irradiated for 90 min with the CSO-54 filtered light. Again irradiation resulted in no change of the infrared absorption spectrum of **3b**. When a solution of **3b** was irradiated with a 450-W, mercury lamp with a Pyrex immersion well in ethanol or 2-propanol solvent as described for **3a**, no destruction of starting material occurred.

Irradiation of 3-Butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (3c). 3-Butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (1.0 g) mixed with 150 ml of 2-methyl-2-propanol was irradiated with a 450-W, mercury lamp through Pyrex for 48 hr at 30°. The reaction was monitored by glpc using a 5 ft × 0.25 in. column of 5% SE-30 on 60–80 mesh Chromosorb W at 120° (He 60 cm³/min). A steady decrease in starting oxazinone and a simultaneous formation of a new product at shorter retention time was observed. The solvent was removed by distillation at atmospheric pressure and the product was distilled at 65° (12 mm), yielding 0.34 g (44%). The physical properties of the product were identical with those of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**).

Irradiation of 3-Butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (3c) in an Nmr Tube. 3-Butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one, 0.25 g, and 0.5 cm³ of benzene-d_6 were placed in an nmr tube, freeze–thaw degassed to a residual pressure of 10^{-4} mm. The tube was sealed and attached to the Pyrex water jacket of a 450-W, medium pressure, mercury lamp and irradiated for 24 hr. The terminal nmr spectrum showed that there was about 50% conversion to 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**) by integration of the *gem*-dimethyl singlets at δ 1.29 (**3c**) and 1.30 (**3a**) ppm. In addition to the appearance of absorptions due to (**3a**), peaks were observed which were due to dissolved propene, as identified by comparison with an authentic sample.

The gaseous product from the nmr tube was collected in a liquid nitrogen trap and identified as propene by comparison of the mass spectral fragmentation patterns with those reported in the literature.[14]

Reagents Used for Quantum Yield Experiments. 5,6-Dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**) and 3-butyl-5,6-dihydro-5,5-dimethyl-1,4-oxazin-2-one (**3c**) were purified by preparative glpc using a 10 ft × 0.375 in. column of 5% SE-30 on 60–80 mesh Chromosorb W at 140 and 165°, respectively (He 80 cm³/min). Spectrograde 2-propanol and Spectrograde benzene were used without further purification. *cis*-Piperylene (Chemical Samples) was purified by glpc collection from a 1t ft × 0.25 in. column of 25% β,β′-oxydipropionitrile on 80–100 mesh Chromosorb P at ambient temperature (He 60 cm³/min).

Quantum Yield Measurements. Quantum yield measurements were performed in a rotating photochemical apparatus[15] immersed in a 15 gal constant temperature bath held at 25.0 ± 0.5°. Light from a Hanovia, 550-W, mercury lamp contained in a Pyrex immersion well was passed through a solution filtering system to isolate the 313-nm band. The filter was constructed from three concentric quartz cylinders, 12.5, 8.8, and 6.0 cm in diameter, sealed between two anodized aluminum disks with Neoprene rubber gaskets. The path length in the inner cell was 1.25 ± 0.5 cm and was filled with 0.8 *M* cobalt sulfate solution. The outer cell had a path length of 1.65 ± 0.05 cm and was filled with 6×10^{-4} *M* potassium chromate solution. The chemical filters were found to be stable to the conditions of the experiment. Potassium ferrioxalate actinometry was used to measure the light output of the system during the experiments.[16]

Quantum yield calculations for destruction of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one were based on the change in the optical density of the oxazinone (**3a**) solutions after irradiation.

Samples of **3a** in 2-propanol solvent (3.0 ml) were placed in the round-tube portion of a two-compartment cell and freeze–thaw degassed to a residual pressure of 10^{-4} mm. The cell was constructed from Pyrex glass tubing with a tubular compartment 13 mm o.d. by 55 mm and a cuvette compartment from 10 mm i.d. by 55 mm Trubore square tubing. Irradiations were carried out with the solution in the 13-mm tube and uv analyses were performed after transfer of the solution to the cuvette portion. *cis*-Piperylene, present at the concentrations shown in Table II, was employed as a triplet quencher for the photoreduction. At the end of the experiment formation of *trans*-piperylene was detected by glpc using the β,β'-oxydipropionitrile column (*vide supra*). Samples of **3c** in benzene solvent (3.00 ml) of the various concentrations shown in Table III were placed in Pyrex tubes (13 × 70 mm) and freeze–thaw degassed to a residual pressure of 10^{-5} mm. After irradiation in the quantum yield apparatus formation of 5,6-dihydro-3,5,5-trimethyl-1,4-oxazin-2-one (**3a**) was measured by glpc using a 6 ft × 0.25 in. column of 5% FS-1265 on 30–60 mesh Haloport F at 115° (He 60 cm^3/min) using benzisoxazole as an internal standard. The quantum yields of formation of **3a** as a function of the initial concentration of **3c** are reported in Table III.

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Registry No—**3a,** 53153-46-1; **3b,** 53153-47-2; **3c,** 53153-48-3; **4a,** 53153-49-4; **4b,** 53153-50-7; **5a,** 53153-51-8; **6,** 53153-52-9; **7,** 53153-53-0; *N* - (2 - (1 - hydroxy-2-methylpropyl))benzoylformamide, 53153-54-1; ethyl pyruvate, 617-35-6; *N* - (2-(1-hydroxy-2-methylpropyl)acetylformamide, 53153-55-2; 2-amino-2-methylpropanol, 124-68-5; ethyl hexan-2-onate, 5753-96-8.

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Photochemistry of Acid Hydrazides. Determination of Modes of Reaction and Identification of Photoproducts[1a,b]

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The photochemical reaction pathways of a number of benzoic and acetic acid hydrazides of the type $R_1CONZNR_2R_3$ (R_1 = CH_3, C_6H_5; Z = H, CH_3, C_6H_5CO, *p*-$CH_3C_6H_4SO_2$; R_2R_3 = C_6H_5, CH_3, C_6H_5CO, CH_3CO) have been determined with 254-nm light. All reaction products are the result of dissociative processes with the two primary processes being nitrogen–nitrogen and carbonyl carbon–nitrogen cleavage. The first of these processes yields amides and amines, while the second yields aldehydes and acids. The amount and direction of cleavage appear to depend on the relative dissociation energies of the bonds in the vicinity of the carbonyl group of hydrazides. Secondary products of the type R_1CONZR_2 and R_1COR_2 are observed and shown to arise *via* known photochemical processes of the initial photoproducts of the acid hydrazides.

Although the photochemistry of amides[2] has been well studied, the corresponding aza analogs, acid hydrazides, have received scant attention in the literature.[3] Generally, amides undergo photochemical reactions similar to those of ketones, namely α cleavage and Norrish type II cleavage[4] (Scheme I). The analogous α-amino ketones undergo, almost exclusively, elimination reactions.[5,6] However, cyclization in very high yields has been reported for α-*N*-alkylaminoacetophenones to produce 3-azetidinols[7] similar to the cyclobutanol formation of ketones.[8-11]

Scheme I
Photolytic Reactions of Amides

α cleavage $CH_3CH_2CH_2CONH_2 \xrightarrow{h\nu} CH_3CH_2CH_2NH_2 + CO$

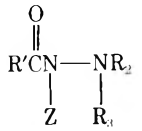
type II $CH_3CH_2CH_2CONH_2 \xrightarrow{h\nu} CH_2{=}CH_2 + CH_3CONH_2$

Considering the large volume of previous work on the ketones and amides, as well as their variety of photochemical reactions, it appeared reasonable to investigate the photochemistry of acylhydrazides as aza analogs of amides and diaza analogs of ketones to determine their comparative modes of reaction. Of particular interest was the potential for synthetic routes to diazetidinols *via* an internal cyclization of the hydrazides.

Results and Discussion

The results of the photolysis of the compounds reported in this study are summarized in Table I. Percentage yields are not corrected for unreacted starting material as they could not be assayed *via* gas chromatography. However, in the preparative runs, analyzed by column chromatography, the unreacted starting material was recovered, accounting for approximately 90–95% of the material balance. There-

Table I
Summary of Photolysis Products



Compd	R_1	Z	R_2	R_3	Primary N–N bond cleavage products	Primary CO–N cleavage products	Secondary products
3a	C_6H_5	C_6H_5CO	CH_3	CH_3	$C_6H_5CONH_2$ (7a) (14%) $(C_6H_5CO)_2NH$ (7b) (4.5%)[a] $(CH_3)_2NH$ (8a) (23%)[b]	C_6H_5CHO (4a) (8.1%) 3b (19.6%)[a]	7c (11%) $C_6H_5COCH_3$ (6) (trace)
3b	C_6H_5	H	CH_3	CH_3	7a (19%)	4a (5.4%)	7c (11%) 6a (trace)
3c	C_6H_5	p-$CH_3C_6H_4SO_2$	CH_3	CH_3	7a (10%)	4a (4.3%)	7c (5.2%) $C_6H_5CH_3$ (14%) 6a (trace)
3d	C_6H_5	H	$(CH_3)_2CH$	$(CH_3)_2CH$	7a (25%) $[(CH_3)_2CH]_2NH$ (8b) (21%)	4a (4.3%)	7f (20%)
3e	C_6H_5	CH_3	C_6H_5CO	CH_3	$C_6H_5CONHCH_3$ (7c) (30%)	4a (9.2%) $C_6H_5CO_2H$ (2.1%)	6 (2.9%)
3f	CH_3	CH_3	CH_3CO	CH_3	$CH_3CONHCH_3$ (7d) (2.6%)	CH_3CHO (4b) (1.2%)	$CH_3CON(CH_3)_2$ (9a) (3.0%)
3g	CH_3	$(CH_3)_2CH$	H	$(CH_3)_2CH$	$CH_3CONHCH(CH_3)_2$ (7e) (27%) $(CH_3)CHNH_2$ (8c) (11%)	4b (10%)	
3h	C_6H_5	H	C_6H_5CO	$(CH_3)_2CH$	7a (11%)	4a (8.3%) $C_6H_5CO_2H$ (9.9%)	
10a	C_6H_5	H	C_6H_5	C_6H_5	7a (24%) $(C_6H_5)_2NH$ (11) (37%)	4a (4.7%)	
10b	CH_3	H	C_6H_5	C_6H_5	11 (23%)[c]		
10c	$ClCH_2$	C_6H_5	H	C_6H_5		12 (52%)	

[a] Determined by column chromatography. [b] Determined by bubbling hydrogen chloride through the solution and isolating the amine hydrochloride. [c] Photolyzed 5.5 hr.

fore, the total yields listed may be considered as a good approximation to the percentage conversion.

An examination of the products obtained as well as their percentage yields in Table I reveals that three types of bond cleavage occur in the photochemical reaction of acid hydrazides: nitrogen–nitrogen (NN) bond cleavage, carbonyl carbon–nitrogen (CON) cleavage, and alkyl carbon–nitrogen (CN) cleavage. A detailed consideration of these reactions including comparison with ketones and amides is included in the following discussion.

Nitrogen–Nitrogen Bond Cleavage. Rupture of the nitrogen–nitrogen bond is evidenced by the presence of amines and amides as major products of the reaction. This mode of cleavage is a logical consequence of the low-energy requirements of the nitrogen–nitrogen bond (*i.e.*, a dissociation energy of 38 kcal/mol[12]). The carbonyl excitation energy of benzamide, analogous to the hydrazides studied, is 79 kcal/mol,[13] more than enough to induce NN cleavage. Dissipation of photoexcitation energy of the hydrazides may then occur by rupture of the bonds near the chromophore in order of their stability. Since the nitrogen–nitrogen bond is the least stable bond, the primary photoreaction then is the NN cleavage. A comparison of the NN cleavage products in Table I indicates the yields parallel the ability of the substituents to stabilize the radical produced. Compounds **3b,d** and **10a,b** particularly illustrate this trend. In particular, **10b** cleaving to give the relatively stable diphenylamino radical produced 23% NN cleavage in just 5.5 hr, while the alkyl hydrazides took much longer to produce a similar reaction yield. The results of Davidson and Lewis[3] also agree with this conclusion. A summary of the mode of formation of the photolysis is contained in Schemes II and III.

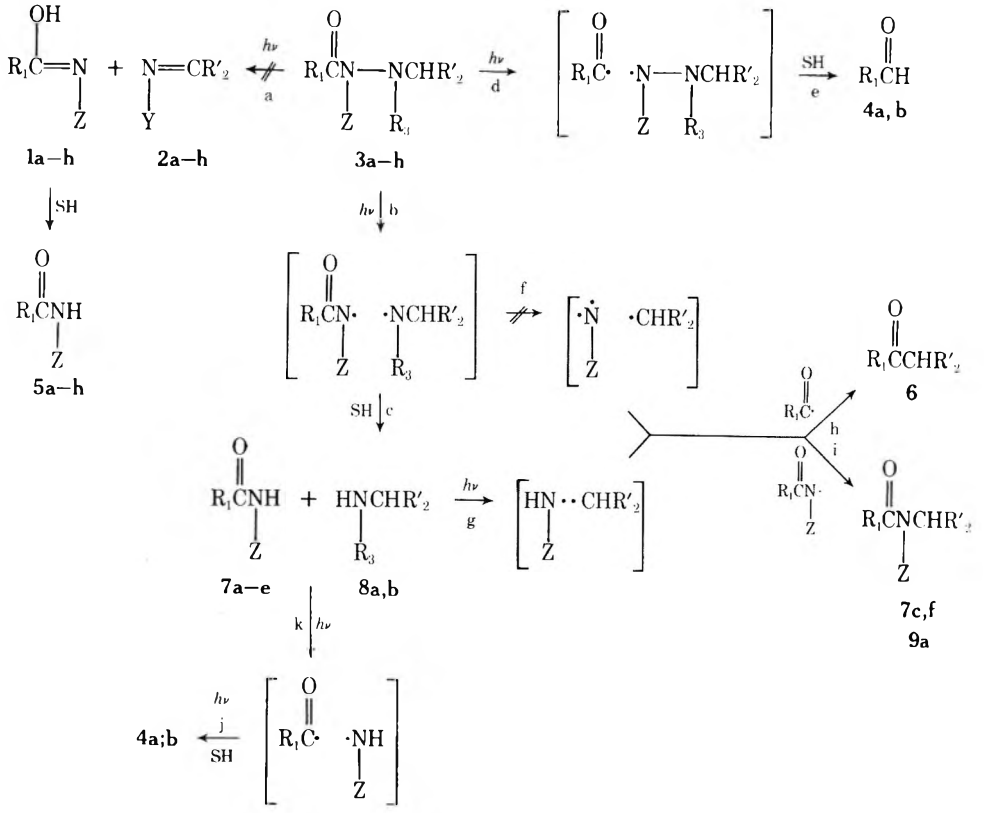
It is also apparent that substituents on the nitrogen α to the carbonyl also facilitate the NN cleavage, although a distinction between steric and electronic factors is not clear-cut. Compounds **3f** and **3g** indicate that bulky α substituents not only facilitate NN cleavage but also induce a greater reactivity in the photoreaction.

Compounds **3c** and **10c** are two notable exceptions to the predominance of NN cleavage in Table I. Their behavior, however, can be easily explained. Compound **3c** has a relatively weak nitrogen–sulfur bond (*i.e.*, approximately 45 kcal/mol[14]) which makes it nearly as susceptible to rupture as the nitrogen–nitrogen bond. In fact, a comparison of **3b** and **3c** shows that the combination of nitrogen–sulfur and NN cleavage in **3c** is essentially the same as the NN cleavage for **3b**. It is assumed that the formation of toluene from **3c** results from nitrogen–sulfur cleavage to give the tosyl radical which, in turn, loses sulfur dioxide to give the tolyl radical. The tolyl radical then abstracts a hydrogen atom from the solvent to give the toluene product. The lack of toluene product in the other benzoic acid hydrazides supports the contention that the tosyl group is the source of toluene.

The second exception is **10c** which gives azobenzene and hydrogen chloride as the only identifiable products. In this particular case, the ease of oxidation of N-substituted hydrazobenzenes[15] can account for the cleavage of the carbonyl–nitrogen bond, the driving force being the formation of the very stable azobenzene molecule. This reaction path is indicated in path b, Scheme III.

The above results indicate that acyl hydrazides differ considerably in their mode of reaction when compared to the ketones[10,11] and amides.[2] It is readily apparent that the NN cleavage is not the typical Norrish type II cleavage as

Scheme II
Photolysis of *N*-Alkyl Acid Hydrazides

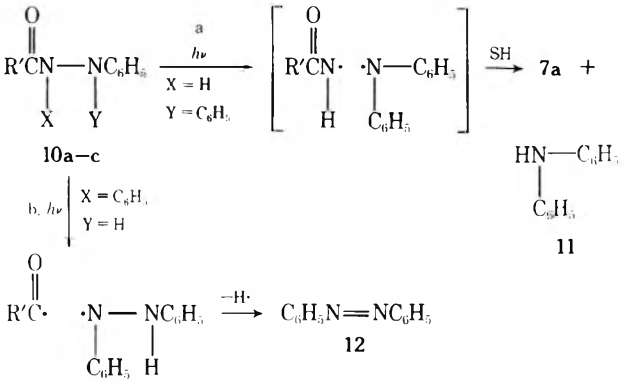


indicated in Scheme II, path a. Although the amides would be expected from such a cleavage, there is no evidence that the imine is formed in the reaction, either in this work or in that of Davidson and Lewis.[3] Therefore, paths b and c in Scheme II indicate a much better representation of the NN cleavage reaction.

Carbonyl Carbon–Nitrogen Cleavage. The second type of cleavage observed, namely the carbonyl carbon–nitrogen cleavage (CON), is evidenced by the presence of **4a** and **b.** Additionally, the benzoic acid found may be considered as a CON cleavage product, either formed by oxidation of **4a** during work-up procedure or from trace amounts of oxygen present in the nitrogen gas used for purging the reaction solutions.[16,17] The percentage yields of the aldehydes or benzoic acid must be considered as minimum yields since the acyl radicals formed can readily decarbonylate to give either benzene or methyl radicals leading to products that would not be detected using our method of assaying the reaction products.

The carbonyl carbon–nitrogen bond energy is greater than that of the nitrogen–nitrogen bond (*i.e.*, approximately 80 kcal/mol for benzoic hydrazides and 96 kcal/mol for acetic hydrazides[18]), and therefore less likely to rupture. As a first approximation, it appears that the amount of CON cleavage is related to the number of carbonyl groups in the molecule. Compounds **3b–d** and **10a** all have one benzoyl group and give approximately the same amount of CON cleavage products, about 5%. However, photolysis of the amide photoproducts alone, under the same conditions, gives an identical yield of CON cleavage product, about 5%, no matter what the nature of the N substituent. It would appear then that small yields of the CON cleavage products of about 5% are due to cleavage of the photoproduct amide rather than the direct cleavage of the acid hydrazide. Compound **3e** may be included in this group, since, with two carbonyl groups on different nitrogens, it yields 11% CON

Scheme III
Photolysis of *N*-Aryl Acid Hydrazides



scission products, approximately double that of a single carbonyl. It is known that photolysis of amides does indeed proceed with CON cleavage.[19-21] To effectively discuss the CON cleavage reaction then, one must consider that approximately 5% of such products arise from further photolysis of the amide photoproducts.

There are, however, several compounds, **3a,g,h** and **10c,** that exhibit a substantially greater degree of CON scission. This increase in CON cleavage arises from a general weakening of the CON bond through decreased resonance interaction of the nitrogen lone-pair electrons and the carbonyl group. Since **3a** exhibits the greatest amount of CON scission, 45%, consideration of its mode of reaction may be used to illustrate the concept of decreased resonance interactions as the primary cause of such cleavage. The 45% figure for CON cleavage is arrived at by the summation of the yield of photoproducts **3b, 7a,** and **7c.** Direct CON scission of **3a** gives **3b,** while **7a** and **7c** are produced by further reaction of **3b.** Appearance of **7a** and **7c** in the reaction

Table II
Photolysis Products of 3d as a Function of Added 8c[a,b]

Hydrazide/amine	7f/7a
No amine	0.48
7.35	0.54
2.45	0.55
1.33	0.56
1.05	0.58
0.61	0.61

[a] Molarity of hydrazide = 3.88×10^{-2}. [b] Photolyzed in 15-ml quartz tubes in a merry-go-round, without purging with nitrogen. It was found that purging reactions gave increased yields of photoproducts while unpurged solutions gave, in addition to lower yields, an increase in the amount of tars formed on the sides of the reaction vessel. This would be expected with a reaction involving radical intermediates.

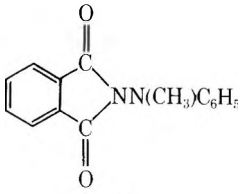
does not arise from **7b**, the NN cleavage product, since **7b** was unreactive under the conditions of photolysis.

Examination of a molecular model of **3a** reveals that the coplanarity of the carbonyls, nitrogen atom, and benzene rings, required for maximum resonance stabilization, cannot be achieved. In addition, coplanarity of the carbonyl system alone introduces unfavorable steric and electrostatic interactions with the benzene rings. It is fairly obvious that decreased resonance interaction will be the result of these steric and electrostatic effects. This would tend to weaken the CON bond and render it more susceptible to rupture in the photoexcited hydrazide.

A similar argument may be advanced for the other compounds, **3g,h** and **10c**, to rationalize the increased degree of scission observed for these substances. All have a substituent on the nitrogen α to the carbonyl which is either bulky or capable of resonance interaction with the lone-pair electrons on the nitrogen. Both types of groups would tend to weaken the CON bond *via* decreased resonance interaction and lead to increased susceptibility to cleavage in the photoreaction. An additional possibility for **10c** has already been presented above.

It appears that there are some similarities between ketones and hydrazides in this type of reaction since the trend in CON cleavage parallels the α cleavage of ketones. The greater the bulk of the α substituent, the greater the degree of α cleavage.[22] In addition, a number of amides containing supplementary chromophoric groups have exhibited CON cleavage.[2]

The high reactivity of **3a** appears to be in direct contrast with the results of Davidson and Lewis[3] who observed a lack of reactivity of compound **13**. This could either be due



13

to a solvent effect, or, since the five-numbered phthalimido group is planar, there is ample opportunity for resonance interaction of the nitrogen lone-pair electrons with both carbonyls and the benzene ring. The CON bond would thus be much more stable and less likely to cleave in the photoexcited hydrazide. In support of this, we observed only 4.5% NN cleavage in **3a** in 24 hr, while Davidson and Lewis observed no reaction in **13** in 6 hr. It would appear then that increased resonance interaction reduces the susceptibility toward photoreaction of hydrazides, while a decreased resonance interaction increases the photoreactivity.

Table III
Photolysis Function of 3d as a Function of Time[a,b]

Time, hr	% 7a	% 7f
1.4	9.8	0.0
2.8	11.5	2.9
5.2	19.1	3.8
6.9	14.8	4.5
12.0	14.6	7.2
24.0	12.0	10.8

[a] Molarity of acid hydrazide = 3.74×10^{-2}. [b] See footnote *b* in Table II.

Alkyl Carbon–Nitrogen Cleavage. A secondary product arising in the photochemical reaction is that of the *N*-alkylamides shown in Table I. The presence of such products may arise by paths f + i or g + i in Scheme II. That the latter path is involved, while the first does not appear to be operative, is supported by the following discussion.

Path g + i is evidenced by the data in Table II, which show the ratio of the *N*-alkylamide photoproducts of **3d** as a function of added **8b**. As the amount of added amine is increased (*i.e.*, lowering the hydrazine/amine ratio) the ratio of **7f/7a** increases. This result is indicative of the involvement of the amine in the formation of **7f**. It is well known that amines may cleave in the manner indicated by path g,[23] suggesting that at least a portion of **7f** arises *via* path g + i.

A consideration of the data in Table III shows the rate of appearance of the two amide products as a function of time. It may be seen that the primary NN cleavage product, **7a**, appears early in the reaction, before the appearance of *N*-isopropylbenzamide. This means that considerable NN cleavage is necessary for the production of the *N*-alkylamide product. Since the amine is a product of NN cleavage, this is indirect evidence of the pathway g + i. In addition, it appears that, late in the reaction, **7f** is formed at the expense of **7a**. This is indicative of path k + i and/or k. A reaction path such as f + i would be expected to have a constant **7f/7a** ratio since the radical generated by f would be in the vicinity of the benzamido radical. Thus a constant rate of NN cleavage coupled with a constant rate of path f should give a ratio that is relatively constant throughout the reaction. The constantly changing ratio as indicated by the data in Table III makes f + i an unlikely reaction pathway. Additionally, attempts to trap the nitrene intermediate that would be generated by path f were unsuccessful.

The yield of this secondary amide product appears to be related to the stability of the alkyl radical produced, the isopropylhydrazides giving higher yields than the methylhydrazides.

The appearance of **9a** from **3f** does not arise from alkyl–nitrogen cleavage but rather from the photolysis of **7d**, initially formed to give methyl radicals *via* carbonyl carbon–carbon cleavage which combine with the *N*-methylacetamido radicals formed by NN cleavage. Such photolytic reactions have been observed previously[24] and the photostability of *N*-alkyl bonds of amides is also documented.[25,26] This would also support path g + i.

Small amounts of **16** appeared in the photolysis of **3a,b,c,** and **e**. It would seem likely that its formation is due to diffusive encounters of benzoyl and methyl radicals since both are produced during the course of the photoreaction. Also, the greatest yield of **6** was observed with **3e**, which also exhibited a high percentage of CON cleavage.

Conclusions

From a consideration of the results in Table I and the above discussion it is clear that the photochemical processes of hydrazides in 254-nm light are exclusively dissociative processes. No rearrangement or cyclization products were detected in the compounds studied. It also appears that the amount of bond dissociation parallels the strengths of the bonds in the vicinity of the carbonyl group of hydrazides.

The weakest bond, the nitrogen–nitrogen bond, undergoes cleavage in most of the compounds, with greater amounts of cleavage occurring with substituents that either weaken the nitrogen–nitrogen bond and/or stabilize the incipient radicals. In one case, compound IV, with the presence of the relatively weak N–S bond, the nitrogen–nitrogen dissociation is reduced by the amount of N–S cleavage which occurs.

With the carbonyl carbon–nitrogen bond, the dissociation energy is presumably in the vicinity of energy of the radiation used for photolysis, approximately 78 kcal. Therefore, substituents which interfere with resonance interactions of the nitrogen lone pair and the carbonyl group lower the bond dissociation energy and thus increase the amount of carbonyl carbon–nitrogen bond cleavage.

The results of Davidson and Lewis[3] are consistent with the bond dissociation energy hypothesis. With compound 14 predominantly nitrogen–nitrogen bond cleavage occurs and with type 15 cleavage occurs at the weaker carbonyl carbon–carbon bond.

$C_6H_5CONHNR_1R_2$ $C_6H_5CH_2CONHNR_1R_2$

14 15

In addition to the primary dissociative process, secondary dissociative processes occur in the initial products to give *N*-alkylamides and acetophenone. These products may be rationalized on the basis of known photochemical processes of the initial photoproducts.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover (Unimelt) apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer Model 240 carbon–hydrogen–nitrogen analyzer.

Nuclear magnetic resonance spectra were obtained with Hitachi–Perkin-Elmer Models R-10 and R-24 spectrometers. Infrared spectra were obtained with a Beckman Model IR-10 recording spectrophotometer. Ultraviolet spectra were determined on a Cary 14 recording spectrophotometer.

Thin-layer chromatography (tlc) was carried out using Eastman or Brinkmann precoated silica gel or alimina plastic plates. Preparative thin-layer chromatography (plc) was run on Brinkmann precoated silica gel plates of 2 mm thickness. Tlc was used to examine the purity of products and plc was used for purifying samples whenever necessary. Vapor phase chromatography was conducted on a Gow-Mac Model 550 gas chromatograph equipped with a thermal conductivity detector and a Kontron Model 1100 recorder fitted with an electronic integrator. Quantitative data were obtained using the relative weight response technique[27] with an internal standard added after photolysis. For the benzoylhydrazides, benzophenone was the internal standard, and toluene was likewise used for the acetylhydrazides. Blanks were also run to ascertain that the observed products were the result of photolysis and not due to a thermal reaction during the gas chromatographic analysis. The quantitative values listed are the average of at least three determinations and are accurate to ±4% of the indicated value.

Photolysis Procedure. Photolyses were carried out in a Rayonet Photochemical Reactor at 253.7 nm using a 100-ml quartz tube for exploratory and quantitative runs and a 1500-ml quartz tube for preparative runs. Benzene solutions, 0.1–0.01 *M*, were purged by bubbling dry nitrogen into the solutions for at least 0.5 hr, and then photolyzed for 24 hr. Initially, the photolysis solutions were analyzed by column chromatography to characterize the products. All products isolated by column chromatography were identified by comparison of their melting point and infrared and nmr spectra with an authentic sample as well as a mixture melting point determination. Quantitation of products was conducted by gas chromatography. At the end of the photolysis, 10 ml of the solution was removed and analyzed for the presence of volatile materials using a 4 ft × 0.25 in. Carbowax column. The reminder of the photolysis solution was evaporated under reduced pressure into an oil or slurry, dissolved in 2–5 ml of benzene and transferred to a 10-ml flask. A known weight of the internal standard was introduced and enough benzene was added to make a total volume of 10.0 ml. These solutions were analyzed on a 4 ft × 0.25 in. DC200 on Chromosorb P column. Relative weight response values were determined with standard solutions and used in the analysis of the photolysis solutions.

***N,N*-Dibenzoyl-*N',N'*-dimethylhydrazine (3a)** was prepared by the method of Hinamann:[28] mp 152–153° (lit. 152–153°); λ_{max} (MeOH) 323 (ϵ 1800), 236 nm (15,000).

***N'*-Benzoyl-*N,N*-dimethylhydrazine (3b)** was prepared by the method of Hinmann:[28] mp 104–105° (lit. 106–107°); λ_{max} (MeOH) 214 nm (ϵ 9300).

***N,N*-Dimethyl-*N'*-(*p*-toluenesulfonyl)hydrazine (16)** was prepared by the method of Wawazonek and Meyer:[29] mp 80–81° (lit. 79–81°).

***N*-Benzoyl-*N',N'*-dimethyl-*N*-(*p*-toluenesulfonyl)hydrazine (3c).** A well-stirred suspension of 32.4 g (0.15 mol) of 16 in 300 ml of ether and 15.3 g (0.15 mol) of triethylene, cooled to 0°, was treated, dropwise, with 20.1 ml (0.19 mol) of benzoyl chloride. After the addition the mixture was stirred for 1 hr and then allowed to stand overnight. The white needles of triethylamine hydrochloride were filtered off and washed with ether. The filtrate was evaporated and the brown viscous residue recrystallized from methanol. Two crops gave 6.0 g (10.5%) of **3c**: mp 95–95.5°; ir (film) 1680, 1600, 1350, 1290, 1170, 1030, and 820 cm^{-1}; nmr ($CDCl_3$) δ 2.45 (s, 3 H), 3.00 (s, 6 H), 7.3–8.1 (m, 9 H); λ_{max} (MeOH) 233 nm (ϵ 21,900)

Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80; S, 10.07. Found: C, 60.71; H, 5.98; N, 8.60; S, 10.04.[30]

***N,N*-Diisopropylhydrazine (17)** was prepared by the method of Lemal, *et al.*:[31] bp 135–136° (lit. 130–132°).

***N'*-Benzoyl-*N,N*-diisopropylhydrazine (3d).** A solution of 31 g (0.22 mol) of benzoyl chloride in 60 ml of ether was cooled to 5° and 13 g (0.11 mol) of diisopropylhydrazine in 50 ml of ether was added dropwise, with stirring, over a period of 1 hr, keeping the temperature between 5 and 10°. After stirring an additional hour, the white crystals that separated were collected and recrystallized from ethanol–water and then carbon tetrachloride to yield 7.0 g (29%) of **3d**: mp 140–141°; ir (Nujol) 3260, 1625, 1130, 915, and 695 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (d, 12 H, J = 6 Hz), 3.20 (m, 2 H), 6.60 (s, 1 H), and 7.3–7.9 (m, 5 H); λ_{max} (MeOH) 222 nm (ϵ 11,200).

Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.71. Found: C, 70.67; H, 9.12; N, 12.52.

***N,N'*-Dibenzoyl-*N,N'*-dimethylhydrazine (3e)** was prepared by the method of Craig, *et al.*:[32] mp 84–87° (lit. 84–87°[33] and 88–89°[32]).

***N,N'*-Diacetyl-*N,N'*-dimethylhydrazine (3f)** was prepared by the method of Hinmann:[28] mp 60–62° (lit. 61–62°).

***N*-Acetyl-*N,N'*-diisopropylhydrazine (3g)** was prepared from *N,N'*-diisopropylhydrazine[34,35] by the method of Straub and Zeller:[36] bp 52–54° (2 mm) [lit. 88–89° (12 mm)].

***N,N'*-Dibenzoyl-*N*-isopropylhydrazine (3h)** was prepared from isopropylhydrazine by the method of Craig, *et al.*:[32] mp 163–164° (lit.[32,37] 161.5°); λ_{max} (MeOH) 222 nm (ϵ 15,000).

***N'*-Benzoyl-*N,N*-diphenylhydrazine (10a)** was prepared by the method of Fisher:[38] mp 192–193° (lit. 192°); λ_{max} (MeOH) 280 (ϵ 14,800), 226 nm (21,400).

***N'*-Acetyl-*N,N*-diphenylhydrazine (10b)** was prepared by the method of Gattermann, *et al.*:[39] mp 185–186° (lit. 184°); λ_{max} (MeOH) 280 (ϵ 12,200), 226 nm (9240).

***N*-(Chloroacetyl)-*N,N'*-diphenylhydrazine (10c)** was prepared by the method of Bauer:[40] mp 157–158° (lit. 163°); λ_{max} (MeOH) 225 nm (ϵ 19,000).

Anal. Calcd for $C_{14}H_{13}N_2OCl$: C, 64.48; H, 5.03; N, 10.75. Found: C, 64.51; H, 5.08; N, 10.67.

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Registry No.—**3a,** 30859-86-0; **3b,** 14674-46-5; **3c,** 53153-56-3; **3d,** 33721-50-5; **3e,** 1226-43-3; **3f,** 15857-21-3; **3g,** 53153-57-4; **3h,** 35787-02-1; **10a,** 970-31-0; **10b,** 6233-05-2; **10c,** 53153-58-5; **16,** 53153-59-6; **17,** 921-14-2; benzoyl chloride, 98-88-4.

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Synthesis and Properties of *N*-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)maleimide

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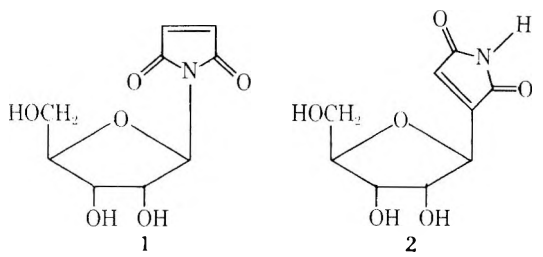
Reaction of silver maleimide with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride afforded *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)maleimide (**5**). The removal of the blocking acetyl groups to obtain the N-substituted analog of showdomycin was not possible owing to its instability. In water, **5** hydrolyzed to maleimide and 2,3,5-tri-*O*-acetyl-D-ribofuranose. In contrast, dissolution in methanol caused the maleimide ring to open, yielding the methyl ester of *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)maleamic acid (**6**). Compound **5** was found to be a good storage form of a reactive ribofuranose derivative. It underwent transglycosylation reactions readily in boiling nitromethane. In this manner, adenosine and cytidine were prepared using N^6-benzoyladenine and N^4-acetylcytosine, respectively. *N*-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)maleimide was also prepared; only in this case mercuric maleimide was the reactant of choice. In addition, the preparation of *N*-trimethylsilylmaleimide and N^4-adamantoylcytosine are described.

The preparation of *N*-β-D-ribofuranosylmaleimide (**1**) was undertaken because such a compound would be an N-substituted analog of the naturally occurring antibiotic, showdomycin (**2,** 2-β-D-ribofuranosylmaleimide, Chart I).[2] Since there is a structural similarity between **1** and **2,** it was thought that the N-substituted analog would be a biologically active substance, perhaps more so than showdomycin, but still maintain some of the biological selectivity of the latter. Recognizing that compound **1** could be a more powerful sulfhydryl reagent than **2,**[3] it was of interest to determine if the ribofuranose ring would confer specificity of binding to enzymes of nucleic acid metabolism and allow the compound to act, in part, as an N-substituted maleimide. Such compounds would have a potential use as antitumor and antimicrobial agents[4] and could conceivably function as "active-site-directed irreversible inhibitors."[5]

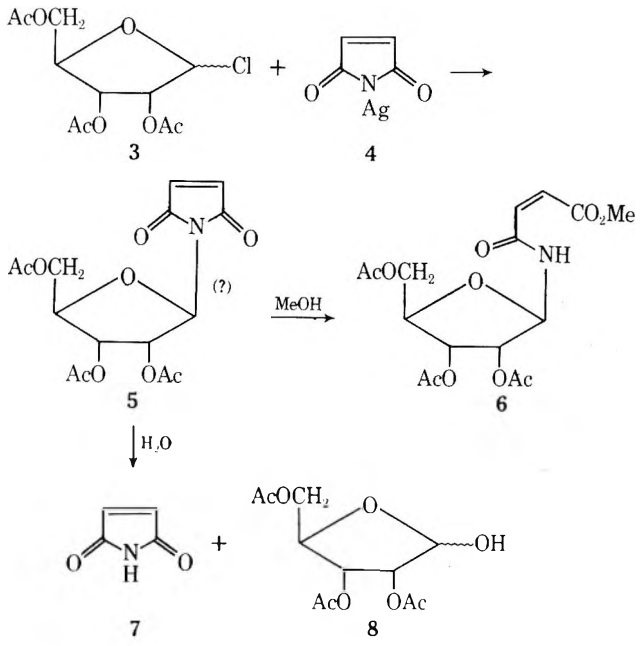
Chart I



1 2

The preparation of silver maleimide and its use in the formation of N-substituted aralkylmaleimides was recently reported.[6] Reaction of silver maleimide (**4**) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride (**3**) in hot benzene gave the blocked product, *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)maleimide (**5,** Scheme I). Unless great care is utilized in the preparation of the chloride **3,** and yields are maximized, the product **5** will be contaminated with unreacted tetra-*O*-acetyl-D-ribofuranose, an undesirable situation since purification by many of the standard procedures, as discussed below, is virtually impossible without degradation of

Scheme I

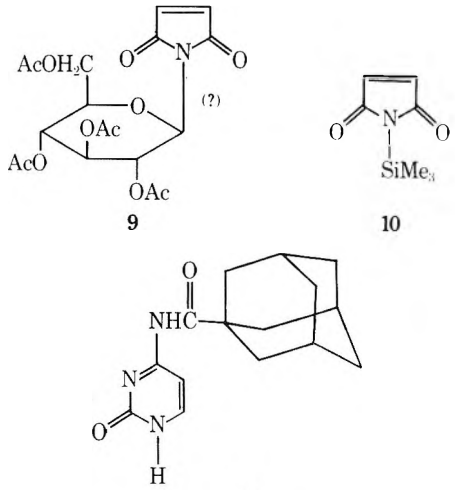


the product. For this reason, a modification of the procedure of Piskala and Šorm[7] was used in the preparation of **3**, which gave superior results over other preparations involving reaction of tetra-*O*-acetyl-D-ribofuranose with hydrogen chloride. Although **5** was not obtained in crystalline form, proof of its structure was confirmed by elemental analysis, uv, ir, and nmr spectra, and homogeneity was further demonstrated by tlc. The ir spectrum of **5** had peaks typical for an N-substituted maleimide at 5.81, 12.04, and 14.45 μ.[6] In contrast, the peaks typical of free maleimide at 3.03 and 14.75 μ were not observed and are a further indication of the purity of the product.[6] The nmr spectrum showed a clean doublet at δ 6.07 which was a good indication that only one anomer was present. Unfortunately, we have not been able to elucidate the anomeric configuration of **5**. The well-known and often quoted trans rule[8] would predict that the product was β; however, the optical rotation (+121°) indicated that the opposite was true and that the configuration was α. The latter would only be the case if Hudson's Isorotation rules were followed, but such an assumption is no longer valid with nucleoside-like compounds.[9] The anomeric coupling constant (J = 4 Hz) does not shed any additional light on this problem since a β-D configuration can only be implied by coupling constants below 3.5 Hz, but can only be unequivocally established at values less than 1.0 Hz.[10]

The problem of removing the blocking acetyl groups was recognized early in the synthetic design. The maleimide moiety should be unstable in a basic medium and there was a good probability that the *N*-glycosyl bond would be unstable in acid. Quite unexpectedly, **5** was found to be susceptible to hydrolysis simply by shaking in water. Although **5** was rather insoluble in water, the products of hydrolysis were soluble and the aqueous solution could be assayed for the appearance of maleimide either by gas chromatography or by uv. The half-life was estimated to be about 1 hr and the products of the hydrolysis, maleimide (**7**) and 2,3,5-tri-*O*-acetyl-D-ribofuranose (**8**), were isolated and identified. In contrast to this behavior in water, a solution of **5** in benzene or chloroform could be washed many times with water without noticeable degradation. Partial degradation was noticed on preparative tlc plates, but not on the analytical tlc plates used in this study. Vacuum distillation of **5** caused extensive decomposition. Maleimide crystals (mp 93–95°) sublimed and then a liquid substance distilled over, whose identity has not been established, but which is probably the elimination product.

Simultaneously with the preparation of **5**, the preparation of *N*-(2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl)-maleimide (**9**, Chart II) was undertaken. When 2,3,4,6-

Chart II



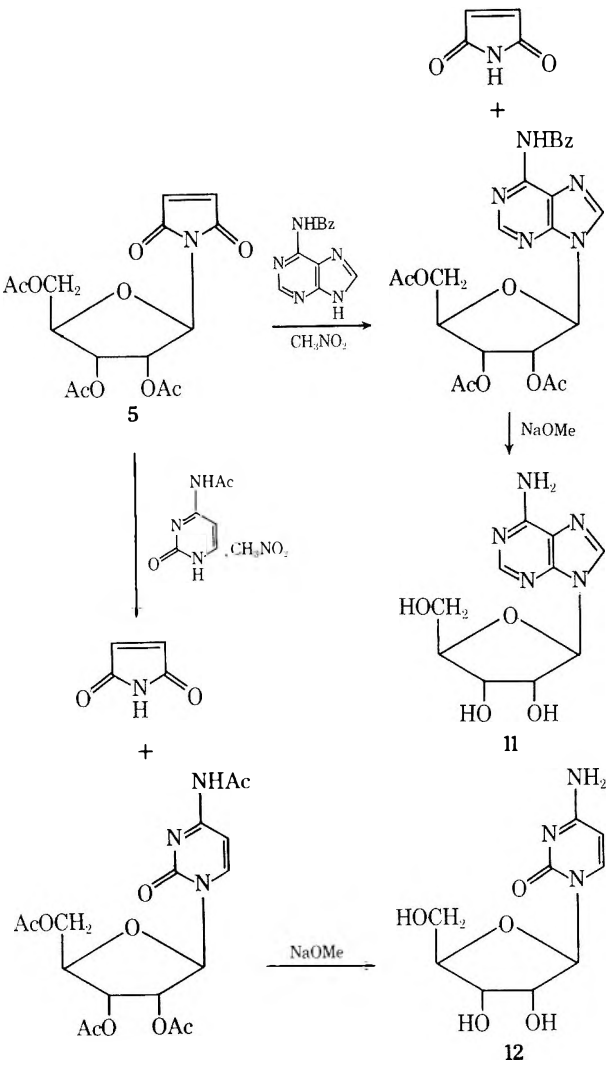
tetra-*O*-acetyl-α-D-glucopyranosyl bromide was reacted with silver maleimide in hot benzene, extensive decomposition occurred. At room temperature, no N substitution took place although a product was formed which may have been the O isomer.[6] However, it was not isolated or identified. Successful coupling was achieved by using mercuric maleimide[6] instead of silver maleimide, and a 36% yield of **9** was obtained following its purification by preparative tlc. Proof of structure was similar to that of **5**. In contrast to the ribosyl derivative **5**, the nmr spectrum of **9** appears to present a good argument concerning the anomeric configuration. A distinct doublet at δ 5.85 indicated that only one anomer was present and the low coupling constant (J = 4 Hz) is suggestive of an α configuration.[10-12] Compound **9** exhibited many of the properties of **5**, being slowly hydrolyzed in water to maleimide and 2,3,4,6-tetra-*O*-acetyl-D-glucose, which were isolated and identified by ir and nmr data. Compound **9** was very unstable on silicic acid columns and only the hydrolytic products were eluted.

Prior to the successful synthesis of either **5** or **9**, a number of coupling procedures were attempted based upon literature methods, which were recently reviewed by Zorbach.[13] The methods employed included the fusion of maleimide with the peracetylated sugar under acid catalysis, coupling of the gylcosyl halide with maleimide utilizing mercuric cyanide as the acid acceptor and nitromethane as the solvent, and the reaction of *N*-trimethylsilylmaleimide (**10**) with the glycosyl halides under various conditions. None of these reactions were successful, although in a few cases, traces of products could be detected on tlc plates.

As yet no method has been devised for the removal of the acetyl groups and another approach will probably have to be used for the synthesis of **1**. It may be advantageous not to have a 2′-acyloxy group because this group could be aiding the ionization of **5** in water by forming a 1,2-orthoacetate ion. A nonparticipating group may, therefore, help stabilize the *N*-glycosylic bond. Experiments along these lines are in progress.

Due to the interesting property of hydrolysis exhibited by **5**, it seemed of interest to attempt a series of transglycosylation reactions in order to form glycosides and nu-

Scheme II



cleosides. When **5** was dissolved in absolute methanol for about 3 hr, what was obtained was not the methyl glycoside, but instead *N*-(2,3,5-tri-*O*-acetyl-D-ribofuranosyl)-maleamic acid methyl ester (**6**). Proof of structure was derived from ir and nmr data in addition to elemental analysis. The reaction of **5** with methanol was exceptionally rapid in comparison to other N-substituted maleimides which are reported to undergo slow ring opening in alcohols[14] and some have even been crystallized from alcohols or alcohol-containing solvent mixtures.

When **5** was treated with N^6-benzoyladenine in refluxing nitromethane and the blocking groups were removed with sodium methoxide (Scheme II), adenosine (**11**) was obtained in 44% yield after purification on an ion-exchange column by the method of Dekker.[15] No α anomer was detected although it is known to give a separate peak preceding adenosine.[16] These results indicate that the formation of the orthoacetate ion could be an important part of the process, resulting in exclusive attack by the nucleophile to give only the β anomer. In a similar manner, cytidine (**12**) was prepared in a 25% yield, using N^4-acetylcytosine as the base. A change in solvent, such as to *N*,*N*-dimethylformamide, gave no reaction. The simplicity by which these transglycosylations can be carried out can be somewhat advantageous for synthetic purposes, especially since **5** can be stored for long periods without degradation if kept cold and dry. On the other hand, the nature of the nitrogenous base appears to be very important. Two cytosine derivatives, N^4-benzoylcytosine and N^4-adamantoylcytosine (**13**), and benzimidazole failed to form the desired nucleosides in the reaction mixture.

Experimental Section[17]

2,3,5-Tri-*O*-acetyl-D-ribofuranosyl Chloride (3). To a suspension of tetra-*O*-acetyl-β-D-ribofuranose (14.4 g, 45.3 mmol) in 250 ml of anhydrous ethyl ether was added 1.5 ml of acetic anhydride. The mixture was chilled in an ice bath and dry hydrogen chloride was passed through at such a rate so as to maintain a temperature of 14–18°. When the temperature dropped to 3° and did not rise again, even with vigorous addition of the gas, saturation of the solution was complete and the clear solution was stored in a glass-stoppered flask at 2–3° for 9 days. The solvent was removed by evaporation at 32° and the liquid residue was coevaporated with five 100-ml portions of toluene and then with two 80-ml portions of benzene, leaving a slightly yellow liquid which was used in the following step.

***N*-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)maleimide (5).** The entire sample of **3** was dissolved in 400 ml of dry benzene, 9.2 g of silver maleimide[6] was added, and the mixture was stirred at reflux for 5.5 hr. After cooling, the mixture was filtered using a "medium" porosity sintered-glass funnel, and the filtrate was evaporated to dryness. The residue was dissolved in 250 ml of carbon tetrachloride and stored at −19° for 3 days. A small amount of a precipitate was removed by filtration through a "very fine" porosity sintered-glass funnel and the solvent was evaporated (50°), leaving a viscous oil which was dissolved in 800 ml of benzene and washed four times with 800-ml portions of water and dried. Evaporation of the benzene, followed by repeated addition and evaporation of methylene chloride, afforded 13.1 g (81%) of a thick, colorless oil. A portion of this was transformed into a foam by placing it under high vacuum (0.02 mm) for 2 days: $[\alpha]^{25}D$ +121° (c 1.93, 1,2-dichloroethane); uv max (1,2-dichloroethane) 278 nm (ϵ 393); ir (film) 3.25 (C=CH), 5.75 (CH_3C=O), 5.81 (NC=O), 8.10 (CO, acetyl), 12.04, 14.45 μ (maleimide ring); nmr ($CDCl_3$) δ 6.60 (s, 2, olefinic H), 6.07 (d, 1, J = 4 Hz, anomeric H), 5.08 (t, 1, J = 4 Hz), 4.8–3.8 (m, 5 H) 2.10 (s, 9, acetyl H).

Anal. Calcd for $C_{15}H_{17}NO_9$: C, 50.71; H, 4.82; N, 3.94. Found: C, 50.33; H, 4.68; N, 3.72.

***N*-(2,3,4,6-Tetra-*O*-acetyl-D-glucopyranosyl)maleimide (9).** Mercuric maleimide[6] (0.64 g, 1.62 mmol) and 0.4 g of Celite-545 were suspended in 36 ml of dry benzene and traces of moisture were removed by distillation of 12 ml of the solvent. To this mixture was added 0.64 g (1.55 mmol) of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, and refluxing was continued for 48 hr. The cooled reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in 25 ml of methylene chloride and kept in a refrigerator overnight. A small amount of white precipitate was removed by filtration and the filtrate was washed with 30% aqueous potassium iodide solution (3 × 25 ml). Drying and evaporation of the solvent afforded 0.39 g of a light-amber gum. This was subjected to preparative tlc on two 20 × 20 cm, 2 mm thick F_{254} silica gel plates (E. Merck, Darmstadt) using 1:1 methylene chloride–ethyl ether. The uv absorbing band at R_f 0.48 was excised and extracted from the silica gel with the same solvent mixture, affording 0.21 g (36%) of a white glass following evaporation and high vacuum treatment; uv max (1,2-dichloroethane) 276 nm (ϵ 385); ir (film) 3.23 (-C=CH), 5.72 (C=O), acetyl), 5.83 (NHC=O), 12.08, 14.50 μ (maleimide ring); nmr ($CDCl_3$) δ 6.62 (s, 2, olefinic H), 5.85 (d, 1, J = 4 Hz), anomeric H), 5.20 (t, 1, J = 3 Hz), 5.0-3.6 (series of m, 5), 2.08 (s, 12, acetyl H).

Anal. Calcd for $C_{18}H_{21}NO_{11}$: C, 50.59; H, 4.95; N, 3.28. Found: C, 50.02; H, 5.17; N, 3.26.

Hydrolysis of 5. A small amount (0.42 g, 1.18 mmol) of **5** was shaken in 10 ml of water at 29°. The appearance of maleimide, which is soluble in water, was monitored by gas chromatography on a Hewlett-Packard Model 5700A flame ionization gas chromatograph, equipped with a 20 × ⅛ in. Chromosorb W-AW silicone rubber column. The temperature was 78° and the flow rate of carrier gas (nitrogen) was 27 ml/min. A calibration curve was prepared from known standard concentrations of maleimide in water, and a plot of the amount of maleimide *vs.* peak area was made. Aliquots removed from the aqueous portion of the hydrolysis mixture were injected onto the column and the appearance of maleimide was monitored. Compound **5** appeared to have a half-life of *ca.* 1 hr.

The hydrolysis was also followed qualitatively by tlc using 97:3 benzene–2-propanol and 1:1 methylene chloride–ethyl ether as solvent systems. At the end of 3 hr a homogeneous solution was ob-

tained. The solution was extracted with chloroform and the chloroform was washed with water, dried, and evaporated. Tlc data and the ir spectrum confirmed that the product was 2,3,5-tri-*O*-acetyl-D-ribofuranose when compared against an authentic sample obtained from hydrolysis of **3**. A sample of maleimide was isolated also and was identical with authentic maleimide, mp 93–95°.

Methanolysis of 5. A mixture of **5** (0.39 g) and anhydrous methanol[18] (10 ml) was stirred for 3.3 hr. The methanol was evaporated, leaving 0.41 g of a light-yellow oil. Tlc in 98:2 chloroform–methanol showed that **5** was absent and a new major compound had formed with several minor components. No free maleimide was detected. The oil was chromatographed on 30 g of silicic acid (Mallinckrodt, 100 mesh) packed in chloroform and 25-ml fractions were collected. Fractions 1–4 were eluted with chloroform, fractions 5–7 with 99:1 chloroform–methanol, and fractions 8–11 with 98:2 chloroform–methanol. The product was eluted in fraction 11. Evaporation of the solvents gave 0.21 g of **6** which was homogeneous by tlc. Coevaporation with ethyl ether caused the syrup to form a hard, glass-like foam, which was dried at 0.02 mm for 2 days: uv max (1,2-dichloroethane) 229 nm (ϵ 5,300); ir (film) 3.05 (NH), 5.75 (CH_3C=O), 5.82 (MeO-C=O), 6.12 (–NH-C(=O)– or –C=CC(=O)–), 6.5 μ (amide II); nmr ($CDCl_3$) δ 6.13 (m, 2, olefinic H),[19a] 6.02 (d, 1, J = 3 Hz anomeric H), 5.10 (t, 1, J = 4 Hz), 4.8–4.0 (series of m, 4 H), 3.76 (s, 3, OCH_3), 2.07, 2.05 (both s, 6, acetyl H), 1.83 (s, 3, acetyl H),[19b] 9.33 (s, 1, –NHCO).

Anal. Calcd for $C_{16}H_{21}NO_{10}$: C, 49.61; H, 5.46; N, 3.62. Found: C, 49.67; H, 5.45; N, 3.65.

Transribosylation. A. Preparation of Adenosine (11). A mixture of **5** (1.39 g) and N^6-benzoyladenine (0.96 g) in 90 ml of freshly distilled, dry nitromethane was heated at reflux for 17 hr. The orange-colored solution was evaporated, the residue was triturated with chloroform, and some unreacted N^6-benzoyladenine (0.22 g) was removed by filtration. Evaporation of the solvent gave 2.36 g of a thick syrup which was dissolved in 300 ml of methanol, 10 ml of 1*N* methanolic sodium methoxide was added, and the mixture was refluxed for 2 hr. The methanol was evaporated, the residue was dissolved in 250 ml of water, and the pH was adjusted to 6.4 with Bio-Rad AG50W-X8 (H^+) resin. The resin was removed by filtration and washed with water. The water was evaporated and the resulting syrup (1.53 g) was dissolved in 15 ml of water and applied to the top of a column (45 × 1.8 cm) of Bio-Rad AG1-X2 (OH^-, 200–400 mesh), packed in water. The column was eluted with 15% aqueous methanol and 20-ml fractions were collected.[15] The eluate was monitored at 254 nm and at fraction 120, the solvent was changed to 30% aqueous methanol. Tubes 165–280, which absorbed in the uv, were pooled and the solvents evaporated. Crystallization from water afforded adenosine (**11**), 0.46 g (44%), mp 239–241°. Admixture of an authentic sample of commercial adenosine (also recrystallized from water) gave no depression of melting point. The ir and nmr spectra were identical, as were the chromatographic mobilities by tlc (solvents: water; 86:14 1-butanol–water, v/v) and paper chromatography (solvents: 5% aqueous disodium hydrogen phosphate and 4:1:5 1-butanol–acetic acid–water, v/v, top layer).

B. Preparation of Cytidine (12). A mixture of 0.27 g (0.7 mmol) of **5** and 0.108 g of N^4-acetylcytosine in 15 ml of nitromethane was heated at reflux for 24 hr. Some unreacted N^4-acetylcytosine (51 mg) was filtered off when the mixture had cooled. Evaporation gave a thick syrup, which was dissolved in 7 ml of chloroform and some additional N^4-acetylcytosine was again removed by filtration. The solvent was evaporated, and the syrup was dissolved in 30 ml of methanol and treated with 1 ml of 1*N* methanolic sodium methoxide and kept at room temperature for 24 hr. The work-up was the same as for adenosine, except that the column (15 × 2 cm) was eluted with 20% aqueous methanol and 7-ml fractions were collected. Tubes 32–64, which contained the product, were pooled and evaporated. Cytidine (**12**) was crystallized from 8 ml of ethanol containing several drops of water, 40 mg (25%), mp 219–220°. Admixture with an authentic sample of commercial cytidine (also recrystallized from aqueous ethanol) gave no depression of melting point. The uv and ir spectra were identical, and chromatographic mobility by tlc and paper chromatography are the same.

***N*-Trimethylsilylmaleimide (10).** A mixture containing 9.7 g (0.10 mol) of maleimide, 31 ml (d 0.845 g ml^{-1}) of trimethylsilyl chloride, 34 ml of triethylamine,[20] and 300 ml of dry benzene was stirred at reflux for 24 hr under a nitrogen atmosphere. The reaction mixture was concentrated to 200 ml by distillation and triethylammonium chloride was removed by filtration after the mixture had cooled. The solvent was evaporated and the oil was distilled through a Vigreaux column at 55 mm. The product **10** was obtained as a clear, colorless oil, 12.4 g (71%): bp 118–122°, uv max (1,2-dichloroethane) 281 nm (ϵ 484); ir (CCl_4) 3.30 (C=CH), 5.85 (C=O), 14.27 μ (maleimide ring); nmr (CCl_4) δ 6.55 (s, 2. olefinic H), 0.27 (s, 9, methyl H).

Anal. Calcd for $C_7H_{11}NO_2Si$: C, 49.68; H, 6.55; N, 8.28. Found: C, 49.57; H, 6.59; N, 8.52.

N-Trimethylsilylmaleimide was quite stable for many months when stored in a desiccator. Upon contact with water, maleimide (**7**) was immediately generated.

***N*^{4}-Adamantoylcytosine (13).** Adamantoyl chloride (4.21 g, 21 mmol) was slowly added to a stirring suspension of cytosine (1.17 g, 11 mmol) in 100 ml of dry pyridine. The mixture was heated in oil bath to 78° and kept at this temperature for 3 hr. The clear solution was poured into 120 ml of ice–water, whereupon a gum separated. Chloroform (400 ml) was added and the mixture was stirred and chilled in an ice bath while 420 ml of 3*N* hydrochloric acid was slowly added, dropwise. The temperature was maintained below 15° throughout this operation. The chloroform layer was separated and washed with water (250 ml) and 5% aqueous sodium bicarbonate (300 ml) and dried. Evaporation of the solvent afforded a white solid which was tritruated with 40 ml of chloroform. Filtration gave 1.89 g and an additional 0.24 g was obtained by two similar treatments of the filtrate using *ca.* 15 ml of chloroform each time. The combined product was crystallized from 300 ml of absolute ethanol, 1.16 g of shiny platelets. A second crop, 0.16 g (total yield, 43%), was obtained, mp 347–350° dec: uv max (absolute ethanol) 245 (ϵ 16,940), 296 nm (ϵ 6,410), identical with N^4-acetylcytosine;[21] ir (KBr) 3.00, 3.08, 3.46, 5.86, 5.91, 5.96, 6.17, 6.35, 6.40 μ; nmr (trifluoroacetic acid) δ 10.10 (s, 1, –NHCO), 8.35 (d, 1, J = 7 Hz, C-5 H), 6.82 (d, 1, J = 7 Hz, C-6 H), 2.06, 1.86 (adamantane ring protons).

Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.81; H, 7.01; N, 15.37. Found: C, 65.60; H, 7.18; N, 15.07.

Registry No.—**3,** 40554-98-1; **5,** 53209-76-0; **6,** 53209-77-1; **9,** 53209-78-2; **10,** 53209-79-3; **11,** 58-61-7; **12,** 65-46-3; **13,** 53209-80-6; tetra-*O*-acetyl-β-D-ribofuranose, 13035-61-5; 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, 572-09-8; N^6-benzoyladenine, 4005-49-6; N^4-acetylcytosine, 14631-20-0; maleimide, 541-59-3.

References and Notes

(1) This work was supported by Grant No. CA 12205 from the National Cancer Institute, National Institutes of Health.
(2) The synthesis of showdomycin has been accomplished: L. Kalvoda, J. Farkas, and F. Šorm, *Tetrahedron Lett.*, 2297 (1970); G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, **38,** 1841 (1973).
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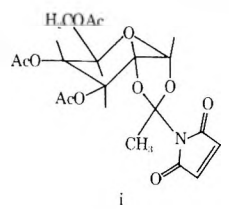
(12) One of the referees suggested that this could occur *via* an ortho imide intermediate (i), which could form the *O*-glycoside in the α configura-



i

tion. This in turn could undergo an O → N rearrangement to give **9.** Such intermediates and rearrangements have been previously proposed; *e.g.*, R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43,** 2214 (1965); K. A. Watanabe, D. Hollenberg, and S. S. Fox, *J. Carbohyd. Nucleosides, Nucleotides,* **1,** 1 (1974). Another possibility is prior formation

of the β-O-glycoside which is anomerized to the α-O-gylcoside under the influence of mercuric bromide. This could then rearrange to the N-substituted compound **9**. For an example, see G. Wagner and H. Frenzel, *Arch. Pharm.* (*Weinheim*), **299**, 536 (1966).

(13) W. W. Zorbach, *Synthesis*, 329 (1970).
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(16) M. Miyaki, A. Saito, and B. Shimizu, *Chem. Pharm. Bull.*, **18**, 2459 (1970).
(17) Melting points were determined on a Kofler micro hot stage and are corrected values. Nmr spectra were determined on a Varian T-60A spectrometer using TMS as the internal reference. Ir spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and uv spectra were obtained on a Beckman DK-2 spectrophotometer. Elemental analyses were performed by the Baron Consulting Co., Orange, Conn., or the Spang Microanalytical Laboratory, Ann Arbor, Mich. Moist organic solutions were dried over anhydrous magnesium sulfate. Evaporations were carried out on a rotary evaporator under reduced pressure and a bath temperature of about 40°, except where noted otherwise. Tic was performed on precoated silica gel F-254 plates (E. Merck, Darmstadt) of 0.25 mm thickness. Spots were first located with an ultraviolet lamp and the plates were then sprayed with a solution of 20% ethanolic sulfuric acid and heated in an oven at 140°.
(18) Reagent grade methanol was percolated through a column of molecular sieve 3A and stored over calcium hydride. Distillation under nitrogen through a column of Raschig rings gave anhydrous methanol which was stored over molecular sieve 3A.
(19) (a) It was expected that the olefinic protons would produce a typical AB quartet. When this region was swept over a 50 Hz width, some separation into two very broad peaks was accomplished. (b) Molecular models showed that the acetyl groups at C-2′ or C-5′ can interact with the double bond and, therefore, be influenced by an anisotropic effect, which probably accounts for the shift in one of the methyl peaks.
(20) Triethylamine was purified by distillation from phenylisocyanate just prior to use.
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Crystal and Molecular Structure of β-Peltatin A Methyl Ether

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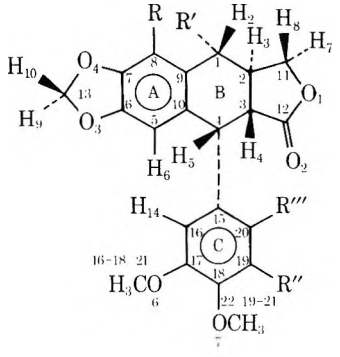
The crystal structure of β-peltatin A methyl ether ($C_{23}H_{24}O_8$), a natural antitumor agent, has been solved by direct methods with the aid of the combined figure of merit. The space group is $C222_1$. Cell dimensions are a = 23.670, b = 10.024, c = 17.611 Å, and Z = 8. The structure was refined to R = 0.046. The conformation is similar to that of the 5′-demethoxy compound except for the methoxyl groups, which are all rotated differently in the two compounds. Presumably the favored conformation of other antitumor lignans is similar except for methoxyl rotation.

β-Peltatin A methyl ether (I) and 5′-demethoxy-β-peltatin A methyl ether (II), both isolated from the Mexican plant *Bursera fagaroides* (Burseraceae),[1] are antitumor agents of the podophyllotoxin (III) class. An X-ray study on II[2] revealed its conformation in the crystalline state. We have now completed an X-ray study of the former, which shows some aspects of the conformations of the two substances to be similar and some different. This is the second X-ray study of an antitumor lignan; in addition, a derivative, 2′-bromopodophyllotoxin (IV), was recently studied[3] to check the absolute configuration of the compounds of this series.



	R	R′	R″	R‴
I	$O^5C^{14}H_3^{11-13}$	H^1	$O^8C^{23}H_3^{22-24}$	H^{15}
II	OCH_3	H	H	H
III	H	OH	OCH_3	H
IV	H	OH	OCH_3	Br

Experimental Section

Collection and Reduction of the Data. Oscillation and Weissenberg photographs of a needle 0.2 × 0.2 × 0.4 mm indicated space group $C222_1$. The cell parameters were found by least-squares fitting of the settings for the four angles of eight reflections on a Picker-FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 23.670 (9), b = 10.024 (4), c = 17.611 (8) Å, ρ_{calcd} = 1.37, ρ_{obsd} = 1.40 g/ml, and Z = 8. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, 2°/min scan rate, 10-sec background counts, attenuators when the count rate exceeded 10^4 counts/sec, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1889 independent reflections measured, $1630 > 3\sigma(I)$ were considered observed. Three standard reflections were monitored every 50 measurements; no decrease in the intensity of the standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Solution and Refinement. The structure was solved by direct methods using the MULTAN[4] program with 308 E's > 1.4. The correct solution had the highest *combined* figure of merit (C), defined as

$$C = \frac{\Sigma\alpha - \Sigma\alpha_{min}}{\Sigma\alpha_{max} - \Sigma\alpha_{min}} + \frac{(\psi_0)_{max} - \psi_0}{(\psi_0)_{max} - (\psi_0)_{min}} + \frac{R_{max} - R}{R_{max} - R_{min}}$$

where $\Sigma\alpha$ (absolute figure of merit), ψ_0, and R are the usual three indicators employed in the program. The correct solution was 11th in $\Sigma\alpha$, 27th in ψ_0, and 5th in Resid. All the nonhydrogen atoms were located from the E map. Two cycles of full matrix isotropic least-squares refinement of nonhydrogen atoms reduced R to 0.145, and then two anisotropic cycles to 0.094. A difference Fourier map showed all the hydrogens except H-16–H-18, whose positions were calculated. One more cycle of least-squares refinement in which nonhydrogen atoms were refined anisotropically and hydrogen atoms isotropically reduced R to 0.046. Refinement was terminated at this stage since the average ratio of shifts in parameters to standard deviations was less than 0.3. Unit weights were used and refinement was based on F_o with $\Sigma(F_o - F_c)^2$ minimized. The scattering factors used were those of Hanson, *et al.*[5] No correction was applied for extinction.

Table I
Fractional Coordinates and Estimated Standard Deviations

Atom	x/a	y/b	z/c
O-1	−0.2411 (2)	0.6094 (5)	0.2454 (3)
O-2	−0.1525 (2)	0.6941 (4)	0.2508 (3)
O-3	−0.0638 (2)	0.1530 (5)	0.5647 (3)
O-4	−0.1521 (2)	0.0825 (5)	0.6005 (2)
O-5	−0.2591 (2)	0.1926 (5)	0.5215 (2)
O-6	−0.0938 (2)	0.0379 (3)	0.2111 (2)
O-7	−0.0385 (2)	0.1902 (4)	0.0946 (2)
O-8	−0.0292 (2)	0.4520 (4)	0.1104 (2)
C-1	−0.2483 (3)	0.3599 (7)	0.4025 (4)
C-2	−0.2321 (2)	0.4267 (6)	0.3283 (3)
C-3	−0.1840 (2)	0.5207 (6)	0.3407 (3)
C-4	−0.1290 (2)	0.4449 (5)	0.3563 (3)
C-5	−0.0935 (3)	0.3028 (6)	0.4619 (3)
C-6	−0.1037 (3)	0.2139 (6)	0.5201 (3)
C-7	−0.1567 (3)	0.1731 (7)	0.5409 (3)
C-8	−0.2034 (3)	0.2211 (7)	0.5056 (4)
C-9	−0.1952 (2)	0.3111 (6)	0.4428 (3)
C-10	−0.1412 (3)	0.3494 (5)	0.4232 (3)
C-11	−0.2764 (3)	0.5152 (7)	0.2910 (4)
C-12	−0.1880 (3)	0.6190 (7)	0.2745 (4)
C-13	−0.0951 (4)	0.0774 (8)	0.6178 (4)
C-14	−0.2710 (4)	0.1129 (8)	0.5872 (4)
C-15	−0.1056 (2)	0.3749 (4)	0.2870 (3)
C-16	−0.1105 (2)	0.2360 (4)	0.2774 (3)
C-17	−0.0873 (2)	0.1774 (5)	0.2138 (3)
C-18	−0.0617 (2)	0.2482 (5)	0.1581 (3)
C-19	−0.0561 (2)	0.3885 (5)	0.1690 (3)
C-20	−0.0774 (2)	0.4459 (5)	0.2311 (3)
C-21	−0.0671 (9)	−0.0417 (10)	0.1680 (7)
C-22	−0.0747 (6)	0.1881 (12)	0.0338 (6)
C-23	−0.0259 (3)	0.5927 (7)	0.1143 (5)
H-1	−0.279 (2)	0.417 (4)	0.443 (2)
H-2	−0.276 (2)	0.292 (5)	0.386 (3)
H-3	−0.219 (2)	0.371 (4)	0.289 (2)
H-4	−0.194 (2)	0.575 (4)	0.389 (2)
H-5	−0.096 (2)	0.497 (5)	0.376 (2)
H-6	−0.050 (2)	0.315 (5)	0.449 (2)
H-7	−0.307 (2)	0.587 (5)	0.339 (3)
H-8	−0.314 (2)	0.496 (5)	0.252 (3)
H-9	−0.091 (2)	0.125 (6)	0.670 (3)
H-10	−0.068 (2)	0.021 (6)	0.645 (3)
H-11	−0.322 (2)	0.127 (5)	0.598 (3)
H-12	−0.272 (2)	0.166 (6)	0.637 (3)
H-13	−0.244 (2)	0.022 (6)	0.587 (3)
H-14	−0.137 (2)	0.192 (4)	0.314 (2)
H-15	−0.075 (2)	0.518 (5)	0.254 (3)
H-16	−0.038 (2)	−0.042 (5)	0.128 (3)
H-17	−0.045 (3)	−0.089 (6)	0.204 (4)
H-18	−0.021 (3)	−0.025 (8)	0.190 (4)
H-19	−0.111 (2)	0.128 (6)	0.052 (3)
H-20	−0.048 (2)	0.147 (6)	−0.002 (3)
H-21	−0.108 (2)	0.242 (7)	0.029 (4)
H-22	−0.068 (2)	0.637 (6)	0.102 (3)
H-23	−0.007 (2)	0.633 (5)	0.060 (3)
H-24	0.009 (2)	0.622 (6)	0.165 (3)

Results and Discussion

Table I shows the observed atomic coordinates. Figure 1 shows the bond lengths in I and, in parentheses, the corresponding bond lengths in II.[2] There appears to be some disordering of the C-21 methoxyl carbon. As can be seen in the ORTEP[6] drawing in Figure 2, this study confirms the constitution and relative configurations proposed for I.[1]

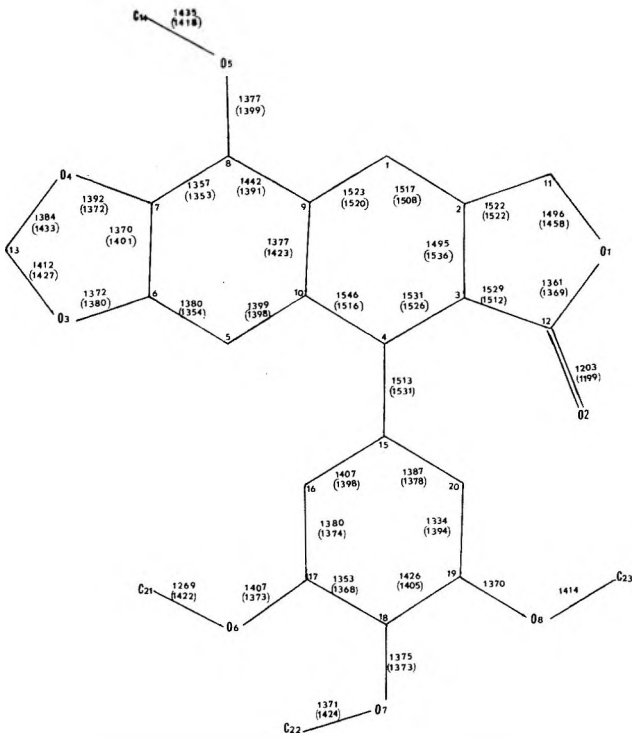


Figure 1. Bond lengths (picometers) in the molecule compared with bond lengths (picometers) in 5′-demethoxy-β-peltatin A methyl ether (in parentheses). The average σ values are 8 and 5 pm, respectively.

Figure 3 compares the conformations of I and II, after least-squares overlapping of the A rings *via* the BMFIT program of Nyburg.[7] The conformations are quite similar to one another—and presumably to the other antitumor lignans—except for the orientations of the methoxyl groups, which are rotated very differently. The angle between the aromatic rings is 81.7° in I and 88.8° in II; similar angles were observed in the two crystallographically independent molecules of the bromide IV,[3] as expected with the 2′-bromo group. The B ring is in the usual cyclohexene half-chair conformation, as evidenced by torsion angles, starting from the C-9–C-10 bond and proceeding clockwise around the ring, of −1.3, 13.7, −46.4, 71.1, −54.1 and 20.5° in I. The γ-lactone ring approximates an envelope conformation with C-2 at the point, opposite the ring from the C-12–O-1 partial double bond; the torsion angles in this ring, clockwise starting from the C-12–O-1 bond, are −3.6, −18.4, 32.1, −33.7, and 23.8°. The other five-membered ring is a nearly flat envelope with C-13 at the point; torsion angles clockwise from the C-6–C-7 bond are 0.3, 3.3, −5.8, 6.0, and 3.9°.

In the absence of ortho substituents on both sides, the methoxyl carbon in a methoxybenzene generally prefers to lie nearly in the plane of the benzene ring, permitting (with sp^2 hybridization of the ether oxygen) resonance interaction between the oxygen and the ring.[8] This is the situation in I for C-23 (torsion angle of 3.5° between the C-23–O-8–C-19 plane and plane of the adjacent aromatic ring), and in II for C-21 (torsion angle 4.3°) and C-22 (torsion angle 5.8°). Surprisingly, C-21 in I is not similarly found pointing away from its ortho substituent, but *toward* it, with a torsion angle of 15.2°. This is very likely the result of packing forces, since the 3- and 5-methoxyls in the 3,4,5-trimethoxyphenyl group of reserpine[9] adopt the usual conformation, and it can be seen from Figure 4 that the usual conformation is precluded since it would put the C-21 methyl group too close to C-13 and O-4 in an adjacent molecule: The C-22 methoxyl, flanked by two ortho methoxyls, expectedly

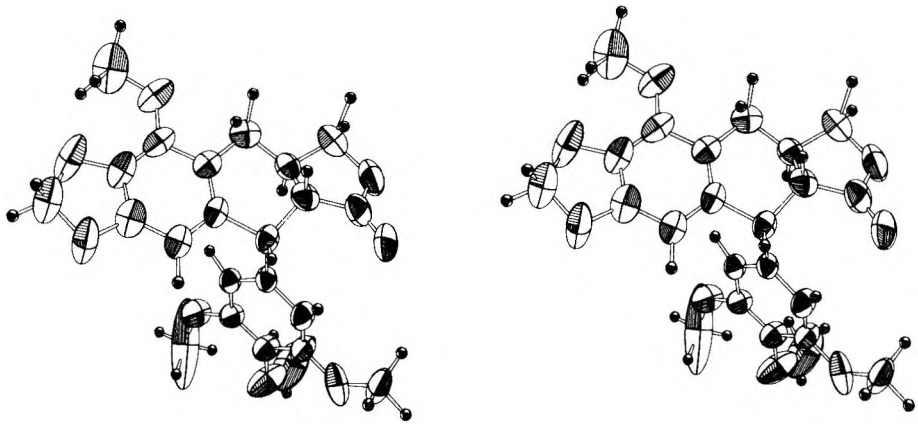


Figure 2. Stereoscopic view of β-peltatin A methyl ether. Hydrogen atoms are shown as spheres, and other atoms as 50% probability ellipsoids.

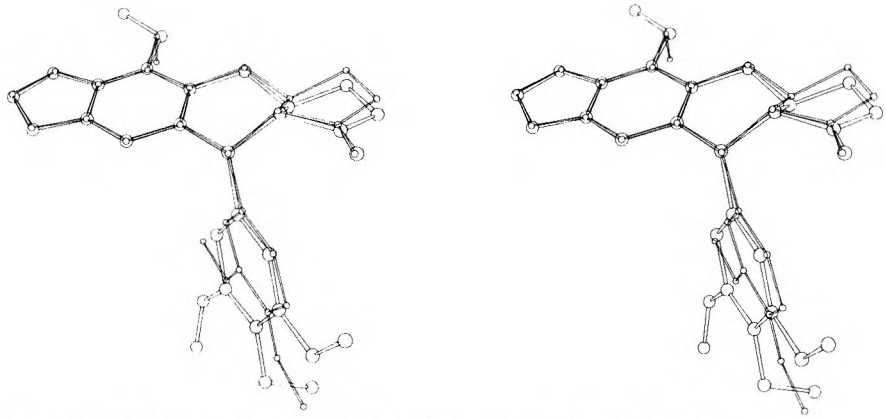


Figure 3. A stereoview comparing I and II (smaller atoms) after least-squares fitting of the A rings.

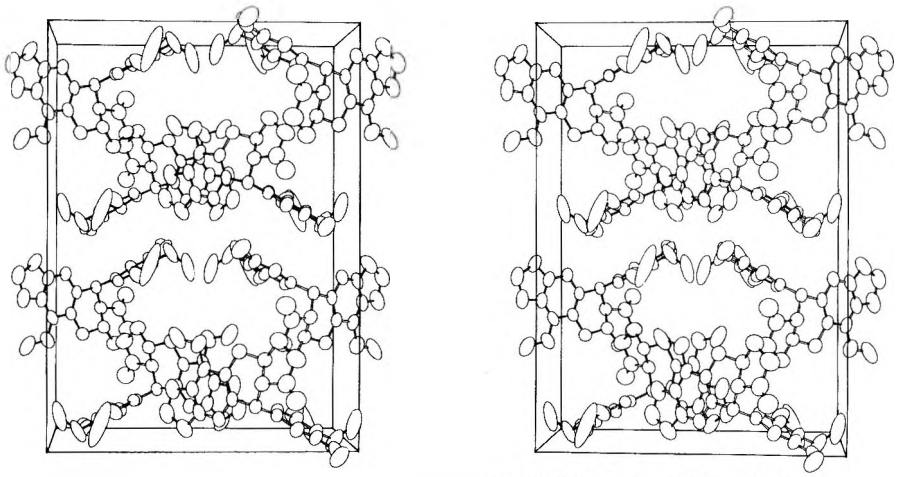


Figure 4. Stereoscopic view of a unit cell, *b* axis projection, with the *c* axis vertical and *a* axis horizontal.

has a torsion angle (87.6°) close to 90°.[9] The C-14 methoxyls in I and II provide a surprise: their torsion angles are 5.2 and 80.2°, respectively. The large difference is almost surely due to packing forces. Unfortunately, since packing in I appears to preclude the conformation adopted in II and *vice versa*, it does not seem possible at this time to say which conformation is preferred in the absence of packing forces.

The shortest intermolecular distance between hydrogens is H-19–H-10 of 2.24 Å. The shortest intermolecular distances between nonhydrogen atoms are O-6–C-11 (3.082 Å), O-6–C-13 (3.228 Å), O-3–C-23 (3.431 Å), O-4–O-2 (3.443 Å), O-5–C-7 (3.468 Å), and O-1–C-2 (3.492 Å).

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Registry No.—I, 23978-65-6.

Supplementary Materials Available. Tables of temperature factors, bond distances involving hydrogen, bond angles, least-squares planes, and structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all

of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-28.

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Narcotic Antagonists. V. Stereochemistry of Reactions at C-6 in 14-Hydroxynoroxymorphone Derivatives

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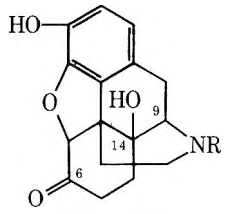
The epimeric products of the borohydride reduction and of the methyllithium reaction of the C-6 ketone of naloxone were isolated. The stereochemistry of the products was assigned on the basis of nmr evidence, which indicates that in each case the major product has the 6α-hydroxy orientation.

The retention of varying degrees of agonist character in virtually all of the presently known narcotic antagonists serves to limit their clinical utility. Striking exceptions are the structurally related compounds naloxone (Ia) and naltrexone (Ib) which exhibit minimal agonist activity. This

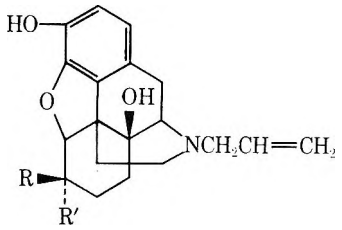


Ia, R = $CH_2CH{=}CH_2$
b, R = CH_2-cyclopropyl

has led to the clinical use of naloxone for the reversal of narcotic-induced effects and to the present clinical evaluation of naltrexone as a potential prophylactic agent in narcotic addiction.[1] In the course of their clinical evaluation, the metabolism of these compounds in man has been investigated and it showed that their principal transformation *in vivo* is the reduction of the 6-ketone group.[2] The report that naltrexone, unlike naloxone, gives rise to a reduced metabolite with the C-6 isomorphine configuration,[3] and that this metabolite may be responsible for its long duration of action in man,[4,5] has aroused our interest in the stereochemistry of reactions at that functional center since the epimeric relationship of their metabolites may have bearing on the difference in properties of the two drugs.

A structural feature common to both naloxone and naltrexone is the 14β-hydroxyl group which may influence the course of reaction at the C-6 position and give products with an orientation different from those obtained from the more common morphine and codeine derivatives containing a hydrogen at the C-14 position.

Sodium borohydride reduction of the C-6 carbonyl group of Ia has been previously reported on by Dayton and Blumberg,[6] and the product was identified as the 6-hydroxy compound IIa which was shown to be identical with the principal metabolite of naloxone obtained *in vivo*.[2] The orientation of the 6-hydroxy group in IIa was assigned



IIa, R = H; R' = OH
b, R = OH; R' = H

as α by analogy to reductions of the 6-ketone in other morphine derivatives. There have been a number of other reports on the sodium borohydride reduction of the 6-ketone in 14-hydroxy morphine and codeine derivatives in which the orientation of the products was similarly assigned by analogy to 14-hydrogen compounds. These reactions included reduction of 14-hydroxycodeinone by Sargent, *et al.*,[7] and Currie, *et al.*,[8] and the reduction of 14-hydroxydihydromorphinone by Weiss and Daum.[9] Conclusive evidence for the stereochemistry of reduction in the model 14-hydrogen series has only recently been provided by Sargent and Jacobson.[10] They compared the nmr spectra of codeine and isocodeine and noted differences in the chemical shift of the 14-proton. In isocodeine it was deshielded by the β-hydroxyl group at C-6 because of its 1,4-diaxial relationship and appeared at δ 3.08. In the spectrum of codeine, where the C-6α-hydroxyl group is equatorially oriented, the 14-hydrogen resonance was at δ 2.66. The above nmr evidence of the interaction of the C-6 and C-14 substituent suggests that the presence of a 14β-hydroxyl group makes such an analogy to the 14-hydrogen series suspect as far as the C-6 ketone reduction products are concerned, and therefore the assigned stereochemistry of IIa and the other reduced products cannot be considered secure.

Naloxone was reduced quantitatively with borohydride and gave a mixture which by tlc analysis consisted of two compounds. The less polar IIa was the major product and was estimated to be nine times greater than the yield of the lesser and more polar product IIb. Preparative tlc permitted the isolation of a small quantity of each of the two components of the mixture. Oxidation of either IIa or IIb re-

generated naloxone confirming the epimeric nature of the two reduction products. The relationship between the two isomeric compounds was further established by chemical inversion of the major product IIa to the minor one IIb. Treatment of the 6α-hydroxy epimer of IIa with toluenesulfonyl chloride gave the tritosyl derivative at positions 3, 6 and 14 (III). This compound, when allowed to react with tetrabutylammonium acetate, and then 5% ethanolic potassium hydroxide,[11] gave the epimeric 6β-hydroxy compound IIb in low yield. A better source of IIb was attained by a separation of the mixture of C-6 epimers using high-pressure liquid chromatography. The compounds IIa and IIb isolated by this technique were indistinguishable from those obtained by the previous procedures.

Spectral data were used to assign the absolute configurations in IIa and IIb. The infrared spectra of both compounds showed no carbonyl absorption and only subtle differences between the spectra in the fingerprint region were apparent. The nmr spectra of the two compounds proved to be more informative. Product IIa showed a peak at δ 4.62 which was assigned to the 5β hydrogen and a broad resonance at δ 4.2–4.4 attributed to the 6β hydrogen. Compound IIb had a peak at δ 4.52 corresponding to the 5β hydrogen and a new broad absorption in the region δ 3.3–3.6, which we assign to the 6α hydrogen. These values were compared with the nmr data reported for dihydrocodeine and dihydroisocodeine[12] (Table I). The greater downfield

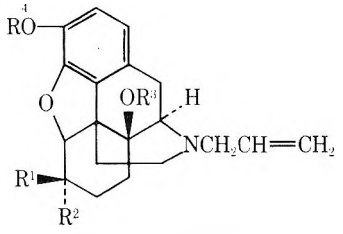
Table I[a]

Compd	5β-H	6α-H	6β-H
IIa[b]	4.62		4.2–4.4
IIb[b]	4.52	3.3–3.6	
Dihydrocodeine[c]	4.58		4.0–4.2
Dihydroisocodeine[c]	4.37	3.4–3.6	

[a] Spectra are reported in δ values. [b] Spectra were run in $CDCl_3$ using TMS as internal standard. [c] Spectra were obtained using cyclohexane as internal standard.

shift of the 5β hydrogen in IIb relative to that in dihydroisocodeine is a reflection of the difference in the angular relationship to the 6β hydroxyl because of the steric influence of the 14β hydroxyl. Also, the greater deshielding of the 6β hydrogen in IIa relative to dihydrocodeine is the result of the presence of the cis 14β-hydroxyl group.

Further support for the above stereochemical assignments was obtained from the nmr spectra of the acetate derivatives of IIa and IIb. The position of the 6-hydrogen absorption in 3,6-diacetates IVa and IVb is unchanged from



IVa, R^1 = H; R^2 = OAc; R^3 = H; R^4 = Ac
b, R^1 = OAc; R^2 = R^3 = H; R^4 = Ac
c, R^1 = H; R^2 = OAc; R^3 = R^4 = Ac
d, R^1 = OAc; R^2 = H; R^3 = R^4 = Ac

that in IIa and IIb. However, its position is shifted downfield to δ 4.5–4.8 (superimposed on the C-5 hydrogen) in 3,6,14-triacetate IVc. This effect is not noted in triacetate IVd, where the C-6-hydrogen absorption is unchanged. The downfield shift may be ascribed to a deshielding effect by the 14-acetate group in IVc, since it is cis to the 6β hydrogen. This situation does not exist in IVd where the 6α hydrogen is trans to the 14-acetate group. The new absorption at δ 4.35 in IVc and IVd is attributed to the 9α hydrogen, which has shifted downfield due to esterification of the 14β-hydroxyl group.

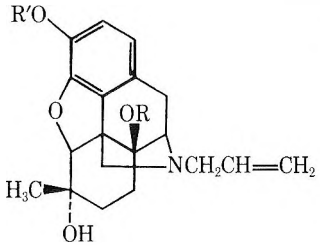
The position of acetate group absorption in IVa and IVb also confirms our assignments. In 3,6-diacetate IVa, the 6-acetate exhibits a peak at δ 1.80, while the 3-acetate absorbs at δ 2.28. In IVb, however, the position of absorption of the 6-acetate has shifted downfield to δ 2.08, while that of the 3-acetate is unchanged. This shift is a result of the 14-hydroxyl group interacting with the cis 6-acetate of IVb and it is absent in IVa where the groups are trans to one another.

The above data provide evidence that the stereochemistry of the borohydride reduction of the 6-keto group is only mildly affected by the presence of a 14β-hydroxyl function, in that it leads to the generation of a small amount of the 6β-hydroxy product, which is absent in the reduction of the 14-hydrogen series.[8,9]

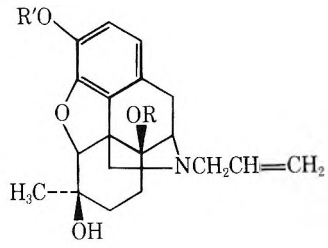
To examine the effect of the 14β-hydroxyl group on other sterically demanding reactions at the C-6 ketone group, we studied the C-6 methylation of naloxone, Ia. Reaction of Ia with methyllithium provided the 6β-methyl derivative Va, but the yield was moderate compared to the same reaction in the 14-hydrogen series.[13,14] When the reaction was carried out on a larger scale a small amount of the 6α-methyl isomer VIa was also isolated; the ratio of Va to VIa was 20:1. In an effort to improve the overall yield of the 6-methyl isomers, we reacted naloxone 3,14-diacetate[15] with methyllithium. In addition to naloxone and Va, compound Vb, the product of deacetylation at the more reactive position 3, was also isolated.

The stereochemistry of the isomeric 6-methyl derivatives was assigned using the nmr data which are presented in Table II. It is evident that changes at position 6 or 14 have

Table II[a]



Va, R = R′ = H
b, R = Ac; R′ = H
c, R = H; R′ = Ac



VIa, R = R′ = H
b, R = H; R′ = Ac
c, R = R′ = Ac

Compd	5-H	6Me	14-OAc(Me)	3-OAc(Me)
VIa	4.32	1.27		
Va	4.36	1.38		
VIb	4.34	1.23		2.29
Vc	4.35	1.30		2.31
VIc	4.38	1.21	2.15	2.31
Vb	4.34	1.30	2.06	

[a] Spectra were run in $CDCl_3$ using TMS as internal standard and are reported in δ values.

little effect on the C-5 proton. In VIa the C-6 methyl absorbs at δ 1.27 *vs.* δ 1.38 in Va. This agrees with the deshielding effect noted in the borohydride reduction products, IIa and IIb, *i.e.*, the methyl group cis to the 14-hydroxyl function absorbs at a lower frequency than the one

trans to it. A similar situation is observed in 3-acetate derivatives Vc and VIb. When comparing 14-acetate derivatives Vb and VIc, a deshielding is recorded for the 14-acetate methyl cis to the 6-hydroxyl group VIc, relative to that in Vb where a trans relationship exists. This data for the relative positions of these absorptions in the epimeric products correlate well with values observed in IIa and IIb and also with those in the report by Sargent and Jacobson who compare the nmr spectra of 6-methylcodeine and 6-methylisocodeine.[10] The latter comparison appears to be valid despite the relative flexibility of ring C in the dihydrocodeine *vs.* codeine structure. It should be noted that the 3-acetate of VIc does not influence the position of absorption of the 14-acetate group.[15]

The present work provides a secure stereochemical identification of the major and minor epimeric products of the borohydride reduction and the methyllithium reaction of the C-6 ketone in the 14β-hydroxy morphinone series. The major product in each case reflects predominant approach of the reagent from the β side yielding the 6α-hydroxy epimer in each case. This disproportionate preference for β side attack, despite the presence of the 14β-hydroxyl group, suggests that in the chair conformation of ring C,[12] α approach at C-6 is greatly hindered and the products of the reactions reflect steric approach control.

Experimental Section[16]

***N*-Allyl-7,8-dihydro-14-hydroxynormorphine (IIa) and *N*-Allyl-7,8-dihydro-14-hydroxynorisomorphine (IIb) by Sodium Borohydride Reduction of Naloxone.** Naloxone (63 mg, 0.2 mmol) was dissolved in ethanol (10 ml) and sodium borohydride (40 mg, 0.8 mmol) was added. The reaction was stirred at room temperature for 3 hr. Excess sodium borohydride was destroyed by the addition of a saturated solution of ammonium chloride, and the pH of the reaction was adjusted to 8. The aqueous phase was extracted with chloroform (3×), and the combined organic extracts were dried, filtered, and evaporated *in vacuo* to give 60 mg of an oil which solidified on standing. This was shown to be a mixture of IIa and IIb by tlc.

Separation was effected on silica gel (0.5-mm plate thickness) using ethyl acetate:ethanol:ammonia (90:10:3) as the solvent system (freshly prepared). About 10 mg was applied to each plate. After elution about 50 mg of IIa and 6 mg of IIb were isolated. Both compounds solidified on standing or could be precipitated from ether:petroleum ether, mp IIb = 85–88°. IIa: ir (KBr) λ_{max} 3400 (broad), 2960, 1640, 1505, 1465, 1325, 1120, 1050, 980, 915 cm^{-1}; nmr ($CDCl_3$) δ 6.3–6.6 (2 H, arom), 4.9–5.3 (m, 4 H, on addition of D_2O one peak disappears), 4.62 (d, J = 4, 1 H), 4.2–4.4 (broad, 1 H). IIb: ir (KBr) λ_{max} 3400 (broad), 2955, 1625, 1505, 1450, 1370, 1325, 1120, 1055, 985, 920 cm^{-1}; nmr ($CDCl_3$) δ 6.3–6.6 (2 H, arom), 4.9–5.3 (m, 4 H, on addition of D_2O one peak disappears), 4.52 (d, J = 6, 1 H), 3.3–3.6 (broad, 1 H).

3,6,14-Tritosylate of 6-Hydroxy Derivatives IIa and IIb (III). The mixture (70 mg; 0.2 mmol) obtained from sodium borohydride reduction of naloxone was dissolved in pyridine (3 ml) and *p*-toluenesulfonyl chloride (172 mg; 0.9 mmol) was added. The solution was allowed to stand at room temperature overnight, after which time the pyridine was evaporated *in vacuo*. The residue was dissolved in chloroform and extracted with an aqueous solution at pH 8. The organic phase was dried, filtered, and evaporated *in vacuo* to give about 170 mg of oily III, which did not solidify: ir (KBr) λ_{max} 2960, 1600, 1490, 1415, 1375, 1195, 1180, 820, 660, 575, 555 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.5 and 7.6–8.0 (m, 12 H), 6.3–6.7 (m, 2 H), 4.8–5.6 (m, 3 H), 4.43 (d, J = 4, 1 H), 2.48 (broad singlet, 9 H, on expanded scale this peak is comprised of three sharp peaks).

Reaction of Tosylate III with Tetrabutylammonium Acetate. Compound III (144 mg, 0.3 mmol) was dissolved in *N*-methylpyrollidone (3 ml) and then tetrabutylammonium acetate (120 mg; 0.4 mmol) was added. The reaction was heated at 140° for 3 hr, after which period the cooled reaction was diluted with a saturated sodium chloride solution, and extracted with chloroform (2×). The organic extracts were dried, filtered, and evaporated *in vacuo*. Since all of the solvent was not removed by evaporation the residue was passed through a dry column of silica gel (about 20 gm). The silica gel was deactivated as described by Loev.[17] The solvent system was ethyl acetate:ethanol (9:1). The desired product was collected in the first few fractions, while the *N*-methylpyrollidone remained on the column. The tosylate obtained was dissolved in 5% potassium hydroxide in ethanol (20 ml) and heated under reflux for 2 hr. The reaction was diluted with water and acidified. The aqueous phase was extracted with chloroform, which was discarded. The pH of the aqueous phase was then adjusted to 8 and then was extracted with chloroform:2-propanol (3:1). The combined organic extracts were dried, filtered, and evaporated *in vacuo*. The oil obtained was purified by preparative tlc as described above to isolate 12 mg of IIb, which was identical with IIb isolated directly from the sodium borohydride reduction of naloxone (*via* tlc and ir).

***N*-Allyl-7,8-dihydro-14-hydroxynormorphine 3,6-Diacetate (IVa).** Compound IIa (9 mg) was dissolved in pyridine (1 ml) and 2 drops of acetic anhydride were added. The solution was allowed to stand overnight at room temperature after which time it was evaporated *in vacuo*. Thin-layer chromatography of the oil obtained showed only one compound present. The oil could not be induced to solidify. The ir spectrum (KBr) showed two carbonyl absorptions (1770 and 1740 cm^{-1}) corresponding to the 3- and 6-acetates, respectively; nmr ($CDCl_3$) δ 6.6–6.9 (2 H, arom), 4.9–5.7 (m, 3 H), 4.75 (1 H, corresponds to H^5), 4.32 (1 H, corresponds to H^6), 2.28 (s, 3 H), 1.80 (s, 3 H).

***N*-Allyl-7,8-dihydro-14-hydroxynorisomorphine 3,6-Diacetate (IVb).** Acetylation of IIb (9 mg), as described above for IIa, gave an oil after evaporation of the solvent. An ir spectrum showed two peaks corresponding to the acetate absorptions; nmr ($CDCl_3$) δ 6.6–6.9 (2 H, arom), 4.9–5.8 (m, 3 H), 4.68 (1 H, corresponds to H^5), 3.3–3.6 (corresponds to H^6, upfield portion is superimposed on other methylene absorptions), 2.26 (s, 3 H), 2.08 (s, 3 H).

***N*-Allyl-7,8-dihydro-14-hydroxynormorphine 3,6,14-Triacetate (IVc).** Diacetate IVa (10 mg) was dissolved in a minimum amount of acetic anhydride and heated on a steam bath for 15 min. The solvent was removed *in vacuo* to give IVc as an oil. An ir spectrum showed bands at 1770 cm^{-1} (3-acetate) and a broad band at 1740 cm^{-1} (6- and 14-acetates); nmr ($CDCl_3$) δ 6.6–6.8 (2 H, arom), 4.9–5.7 (m, 3 H), 4.5–4.8 (m, 2 H, corresponds to H^5 and H^6), 4.35 (d, J = 6, 1 H), 2.26 (s, 3 H), 2.13 (s, 3 H, corresponds to 14 OAc methyl), 1.80 (s, 3 H).

***N*-Allyl-7,8-dihydro-14-hydroxynorisomorphine 3,6,14-Triacetate (IVd).** Acetylation of IVb (10 mg) was carried out as described above for IVc. An ir spectrum showed carbonyl peaks corresponding to the three acetate groups; nmr ($CDCl_3$) δ 6.6–6.8 (2 H arom), 4.9–5.7 (m, 3 H), 4.63 (1 H, corresponds to H^5), 4.35 (d, J = 6, 1 H), 3.3–3.6 (corresponds to H^6, upfield portion is superimposed on other methylene absorptions), 2.26 (s, 3 H), 2.23 (s, 3 H), 2.08 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine (Va).** Naloxone (150 mg; 0.45 mmol) was dissolved in anhydrous diethyl ether (30 ml) in a three-neck 100-ml round-bottom flask equipped with a condenser and a rubber septum. The flask was cooled in ice and a positive pressure of nitrogen was maintained while methyllithium (3 ml, 1.85 *M* solution) was added *via* a syringe through the septum. The milky white reaction mixture was allowed to stir for 18 hr at room temperature after which time the pH was adjusted to 8 with a saturated ammonium chloride solution. The ether phase was separated, and the aqueous phase was extracted with chloroform (2×). The combined organic extracts were dried, filtered, and evaporated *in vacuo* to give 144 mg of a mixture of naloxone and Va. 6-Methyl derivative Va was isolated by preparative tlc on silica gel (0.5 mm thickness) using ethyl acetate:ethanol:ammonia (90:10:3) as the solvent system. Compound Va (50 mg) was eluted with chloroform:methanol. It is a low melting amorphous solid that precipitated from ether:petroleum ether.

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 14-Acetate (Vb).** The 3,14-diacetate of naloxone[15] was reacted as described for naloxone. Diacetate (137 mg) yielded 125 mg of a mixture consisting of naloxone, Va, and Vb. Using the chromatographic procedure employed above, 15 mg of Vb was isolated as an oil which could not be induced to solidify.

Isolation of 6-Methyl Epimers Va and VIa. Naloxone (3.014 g, 9.2 mmol) was dissolved in anhydrous dioxane (200 ml) and reacted with methyllithium (10 ml, 2.2 *M* CH_3Li) in a manner analogous to that described above. Three grams were isolated after neutralization and extraction. The product was purified by dry column chromatography using silica gel that was suitably treated.[17] A loading ratio of 600:1 was used with a column 2 ft × 1.75 in. The solvent employed was ethyl acetate:ethanol:ammonia (90:10:2). The less polar naloxone was collected prior to a mixture of Va

and VIa (1.5 g). The mixture obtained in this manner was further purified by dry column chromatography using a loading ratio of 100:1. The column was run, using 500-mg samples of the mixture. A portion of compounds VIa and Va isolated by the above technique was then purified by tlc on silica gel (0.5-mm plate thickness) to obtain samples for spectra. Both epimers were amorphous solids that precipitated from ether:petroleum ether: mp Va 101–104° and VIa 92–96°. Va: ir (KBr) λ_{max} 3350 (broad), 1640, 1620, 1505, 1460, 1165, 1100, 950, 905, 790 cm^{-1}; nmr ($CDCl_3$) δ 6.4–6.7 (2 H, arom), 4.9–5.7 (m, 4 H, on addition of D_2O one peak disappears), 4.32 (s, 1 H), 1.27 (s, 3 H). VIa: ir (KBr) λ_{max} 3400 (broad), 1645, 1620, 1505, 1460, 1149, 1097, 940, 802 cm^{-1}; nmr ($CDCl_3$) δ 6.3–6.6 (2 H, arom), 4.9–5.7 (m, 4 H, on addition of D_2O one peak disappears), 4.36 (s, 1 H), 1.38 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynorisomorphine 3-Acetate (VIb).** Compound VIa (8 mg, 0.023 mmol) was dissolved in pyridine (1 ml) and acetic anhydride (4 μl, 0.04 mmol) was added. The solution was allowed to stand overnight at room temperature after which time the solvent was evaporated *in vacuo*. Thin-layer chromatography showed only one compound present in the residue. An ir spectrum (KBr) of the oil showed an absorption at 1770 cm^{-1} corresponding to the 3-acetate group; nmr ($CDCl_3$) δ 6.5–6.8 (2 H, arom), 5.9 (broad, 1 H, disappears on addition of D_2O), 5.0–5.6 (m, 3 H), 4.34 (s, 1 H), 2.29 (s, 3 H), 1.23 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 3-Acetate (Vc).** Acetylation of Va (25 mg) was carried out as for VIb. An ir spectrum of the oil obtained verified the presence of the 3-OAc (1775 cm^{-1}); nmr ($CDCl_3$) δ 6.5–6.8 (2 H, arom), 4.9–5.4 (m, 3 H), 4.35 (s, 1 H), 3.88 (broad, disappears on addition of D_2O) 3.39 (broad, disappears on addition of D_2O), 2.31 (s, 3 H), 1.30 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynorisomorphine 3,14-Diacetate (VIc).** Compound VIa (14 mg) was dissolved in a minimum amount of acetic anhydride and heated under reflux for 30 min. The solvent was removed *in vacuo* to give 15 mg of VIc as an oil. An ir spectrum (KBr) showed peaks at 1770 and 1735 cm^{-1} corresponding to the 3- and 14-acetate groups, respectively; nmr ($CDCl_3$) δ 6.4–6.7 (2 H, arom), 4.9–5.7 (m, 4 H, one peak disappears on addition of D_2O), 4.38 (s, 1 H), 4.35 (H^9, superimposed on H^5), 2.31 (s, 3 H), 2.15 (s, 3 H), 1.21 (s, 3 H).

***N*-Allyl-6-methyl-7,8-dihydro-14-hydroxynormorphine 14-Acetate (Vb).** Compound Va, isolated from the reaction of naloxone 3,14-diacetate with methyllithium, was purified by tlc on silica gel using the system previously described to give Vb. An ir spectrum (KBr) contained a carbonyl absorption at 1745 cm^{-1}. The oil could not be induced to crystallize; nmr ($CDCl_3$) δ 6.4–6.6 (2 H, arom), 4.9–5.6 (m, allyl group), 4.34 (s, 1 H), 4.18 (d, J = 6, 1 H), 2.06 (s, 3 H), 1.30 (s, 3 H).

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Registry No.—IIa, 20410-95-1; IIb, 53154-12-4; III, 53154-13-5; IVa, 53154-14-6; IVb, 53154-15-7; IVc, 53154-16-8; IVd, 53154-17-9; Va, 53154-18-0; Vb, 53154-19-1; Vc, 53154-20-4; VIa, 53154-21-5; VIb, 53154-22-6; VIc, 53154-23-7; *p*-toluenesulfonyl chloride, 98-59-9; naloxone, 465-65-6; naloxone 3,14-diacetate, 50510-01-5.

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(16) All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Ir spectra were obtained on a Beckman IR-9. Nmr spectra were recorded on a Varian EM-360 spectrophotometer; TMS was used as the internal standard and coupling constants are in hertz. Naloxone hydrochloride was obtained from Endo Laboratories. The free base was made by precipitating naloxone from an aqueous solution of its HCl salt by the addition of 10% NH_4OH. The free naloxone was washed with distilled water and dried *in vacuo* at 58° for 24 hr. Methyllithium was purchased from Alfa Inorganics. Silica gel for column chromatography was obtained from W. R. Grace and Co. Silica gel for tlc was obtained from Brinkmann Instruments, Inc. (GF-254, Type 60). Drying involved use of anhydrous sodium sulfate.
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Stereochemistry of Nucleophilic Addition Reactions. The Addition of Diethyl Malonate to Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate. Equilibration of 1-*tert*-Butyl-3-carboxymethylcyclohexane-4-carboxylic Acids

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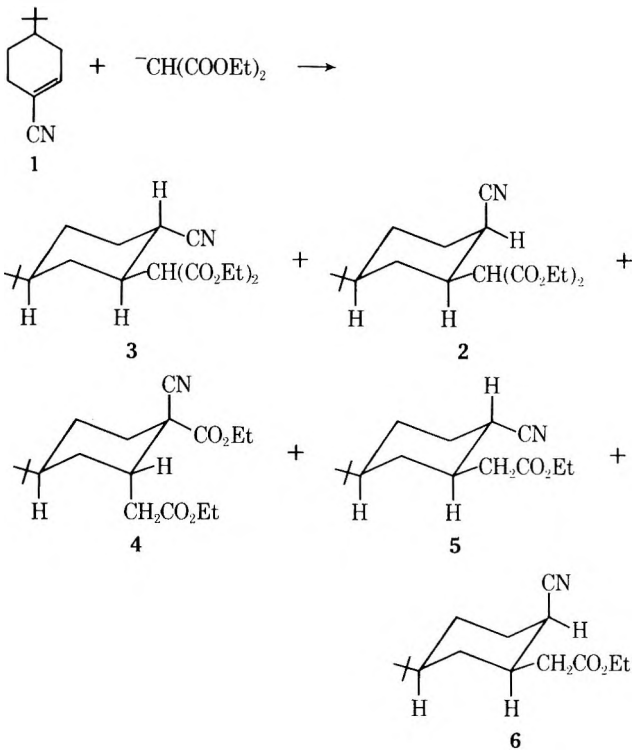
The Michael addition of diethyl malonate to ethyl 4-*tert*-butylcyclohexene-1-carboxylate gives three of the four possible malonate adducts and the corresponding acetates. The effect of solvent upon the stereochemistry of the addition has been investigated. Under conditions of kinetic control the main product is the *r*-1,*c*-3,*c*-4 isomer (**10**) while under thermodynamic control conditions the *r*-1,*c*-3,*t*-4 isomer predominates. No product of abnormal addition is observed. Equilibration of these adducts with base proceeds mainly by reversal and re-addition. The regioselectivity of the protonation of the intermediate anion is discussed in terms of current theories and the results reconcile the various theories. The equilibrations of the dicarboxylic acids **14**, **15**, **16** and **20** have been studied. $\Delta G°$ for **15** $\rightleftharpoons$ **16** is smaller than expected, and for **14** $\rightleftharpoons$ **20** less of the diaxial epimer is formed than would be predicted on the basis of $\Delta G°(CO_2H)$. Possible explanations are proposed for these observations.

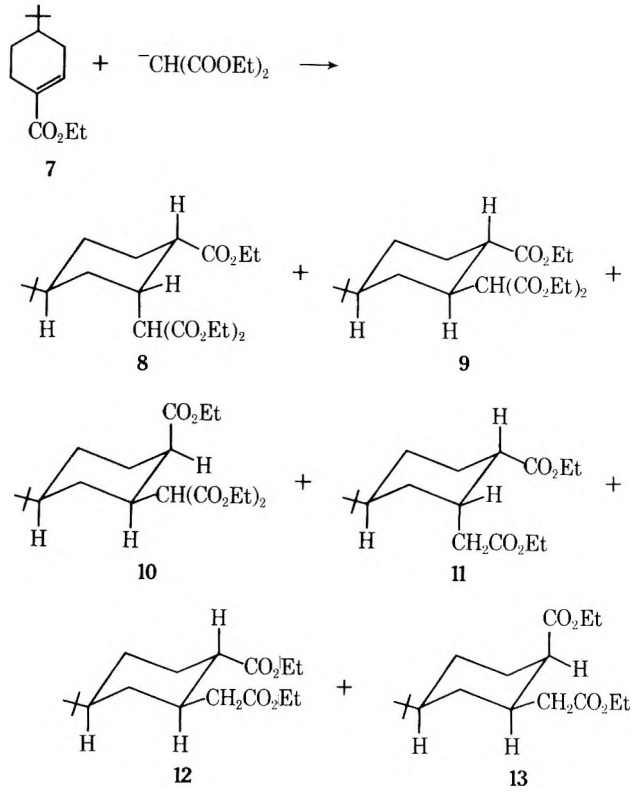
The stereochemistry of some nucleophilic additions to activated olefins of rigid conformation has been reported. Under conditions of kinetic control, the diethyl malonate anion in ethanol solution adds to 4-*tert*-butyl-1-cyanocyclohexene (**1**) to give the addition product with the malonate group equatorial and the cyanide group axial as the

main product (2), together with the (e)-malonate (e)-nitrile (3) as the minor product.[1] Under conditions of thermodynamic control, the latter was the main product. No axial malonate could be detected, but small amounts of the product of "abnormal" Michael addition, ethyl *r*-1-*tert*-butyl-*t*-3-carbethoxymethyl-c-4-cyano-*t*-4-cyclohexanecarboxylate (4), were obtained, which resulted from the rearrangement of the initially formed axial malonate anion intermediate. The two acetates, **5** and **6**, were also obtained in a nonprotic solvent, but the main product was that of "abnormal" addition. On the other hand, the addition of thiophenoxide ion to the above unsaturated nitrile in ethanol gave both possible products containing an axial thiophenoxy group, the main product under both conditions of kinetic and thermodynamic control being the (a)-thiophenoxy-(e)-cyano conformer.[2] In tetrahydrofuran solution, some of the (e)-thiophenoxy-(a)-cyano conformer is also formed.



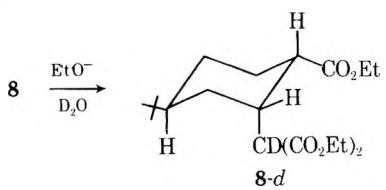
The preferred equatorial approach of the bulky malonate was attributed[1] to large diaxial nonbonded interactions in the transition state for axial addition, which transition state was assumed to resemble the intermediate. With smaller nucleophiles such as PhS^- and Cl^- such 1,3-diaxial repulsions would be much less important, and axial approach of the nucleophile would be favored because of almost continuous overlap between the developing σ bond and the conjugated system in the formation of the transition state leading to axial product.[2]

The question arose as to whether or not replacement of the relatively small, linear nitrile group by the relatively larger, nonlinear carbethoxy group would lead to the same results in the Michael addition. Ethyl 4-*tert*-butylcyclohexene-1-carboxylate (**7**) was readily synthesized by hydrolysis of the nitrile (**1**) with 40% sulfuric acid followed by esterification of the acid with ethanol and acid. Indeed, addition of diethyl malonate to the ester (**7**) proved not to be entirely analogous to the addition to the nitrile (**1**). Six products were identified: three malonates (**8**, **9**, and **10**) and the corresponding acetates (**11**, **12**, and **13**). Five of the six products were isolated by preparative gas chromatography (the sixth, **11**, was present in insufficient quantities for isolation; it was identified by its synthesis from the known dicarboxylic acid and comparison of glc retention times). That **8**, **9**, and **10** were indeed malonates was demonstrated by nmr spectroscopy and mass spectrometry. The nmr spectrum of each isomer showed a distinctive malonate proton signal,[3] a very sharp doublet around δ 3.7, $J \simeq 12$ Hz [**8**, δ 3.65 (J = 12 Hz); **9**, δ 3.70 (J = 13 Hz); **10**, δ 3.76 (J = 11 Hz)].



The mass spectrum of each compound showed a strong peak at *m/e* 160. For **8** and **9** it is the base peak; for **10**, it has a relative intensity of 67% and is the second most intense peak in the spectrum. Williams and coworkers[4] showed that monosubstituted malonic esters undergo the McLafferty rearrangement to give a peak due to $EtOOCH{=}C(OH)OEt \cdot^+$ at *m/e* 160 which is generally the base peak for the spectrum.

It was not possible to demonstrate chemically that **9** and **10** were malonates. Attempts to alkylate or deuterate (both under basic conditions) these isomers met with unqualified failure. Conditions employed fell into two categories: not sufficiently strong to effect any change, or strong enough to cause reversal of the Michael addition. Isomer **8** was deuterated under conditions which did not succeed with **9** and **10**. Compound **8**-*d* did not show a malonate proton in the



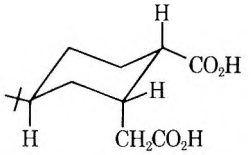
nmr spectrum and did show a prominent peak at *m/e* 161 (84%) and a much smaller peak at 160 (28%).

The configurations of **8**, **9**, and **10** were determined by conversion to known dicarboxylic acids, **14**–**16**.[1] The acetates **11**, **12**, and **13** were synthesized by esterification of the corresponding dicarboxylic acids for comparison with material previously obtained from preparative gas chromatography. The acetates could also be synthesized by decarbethoxylation of the malonates in a sealed tube over 10%

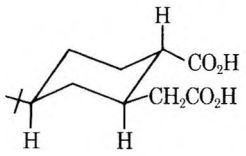
Table I
Michael Additions in Ethanol and Toluene

Olefin	Solvent	T, °C	Base	Main product
Nitrile (1)	EtOH	R.T.	EtO^-	*r*-1, *c*-3, *c*-4 (2)
	EtOH	80	EtO^-	*r*-1, *c*-3, *t*-4 (3)
	toluene	110	Na	Abnormal prod (4)
Ester (7)	EtOH	R.T.	EtO^-	*r*-1, *c*-3, *c*-4 (10)
	EtOH	80	EtO^-	*r*-1, *c*-3, *t*-4 (9)
	toluene	110	Na	*r*-1, *c*-3, *c*-4 (9)

palladium on charcoal at elevated temperatures (10 + 10% Pd–C → 13 + 12). The reaction was complicated by the occurrence of equilibration as well as decarbethoxylation, but the latter reaction was faster, and if the reaction was run for an appropriately short time, virtually stereospecific decarbethoxylation could be observed.



14



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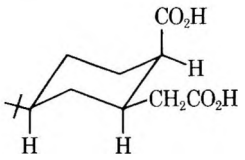
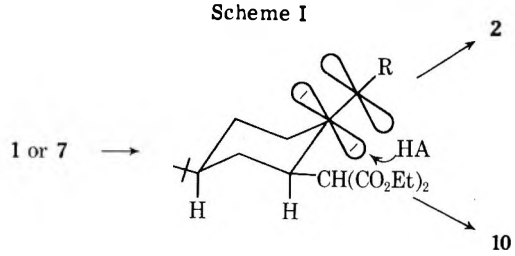


16

Solvent plays a major role in determining the stereochemistry of the addition of malonate anion to **1**. The Michael addition to the ester (**7**) did not follow entirely the same pattern. The results are summarized in Table I. The reactions of the two olefins are entirely analogous under kinetic control conditions, *i.e.*, in ethanol at room temperature using sodium ethoxide as the base. Both olefins gave the *r*-1,*c*-3,*c*-4 isomer as the predominant product (Scheme I). Protonation occurs from the equatorial direc-

Scheme I



tion in both cases, despite the disparity in size of the nitrile and carboethoxy groups. Even with a bulky equatorial substituent at C-3, attack leading to equatorial proton is the "least hindered" giving the thermodynamically less stable product. The substituent at C-4 is axial, in complete accord with Zimmerman's theory[5] that protonation occurs preferentially from the least hindered (usually equatorial) side.

Under thermodynamic control conditions (sodium ethoxide–ethanol under reflux) both the nitrile (**1**) and the ester (**7**) give the thermodynamically more stable diequatorial products **3** and **9**, respectively, again in accord with Zimmerman's theory.[5]

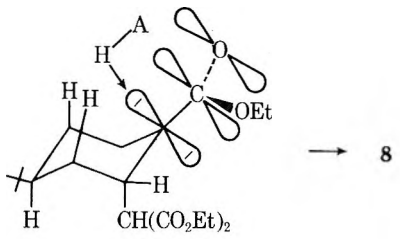
The reactions of the ester (**7**) and the nitrile (**1**) with diethyl sodiomalonate in aprotic solvent are not at all similar. In toluene or dioxane **1** gave mainly the rearranged product (**4**), while the ester (**7**) gave no detectable amount of a rearranged product, and the products of the Michael addition

Table II
Michael Addition to the Ester (7) in Various Solvents

Solvent	T, °C	Time, hr	Molar ratios of 8	9	10	Overall yield, %
Ethanol	R.T.	96		33	67	45
Ethanol	80	48	17	72	11	65
Toluene	110	48	1	39	60	25
Diethyl carbonate	Reflux	12	19	64	17	16

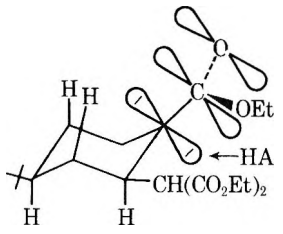
to the ester in aprotic solvents were the same as those in protic solvent, except that the product ratios changed and that higher temperatures were often needed to effect the addition; also the yields were relatively low. The results are summarized in Table II.

The formation of isomer **8** is the result of the less favored[1] axial addition of malonate to the olefin. With an axial substituent at C-3, the entering proton donor finds axial approach past the syn-diaxial hydrogens less hindered than equatorial approach. This result is in complete agreement with the views of Malhotra and Johnson[6] in the sense that in **17** an axial group (not, however, formed as a result of $A^{(1,3)}$ strain) is adjacent to the carbanionic center, and it would sterically hinder the approach of a proton from that side.



17

Thus, the results of one Michael addition seem to reconcile the views of Zimmerman,[5] Bordwell,[7] and Johnson.[6] When the malonate group at C-3 is equatorial, considerable $A^{(1,3)}$ strain undoubtedly exists in the intermediate **18**, but this strain cannot be relieved by chair–chair interconversion, since the presence of the *tert*-butyl group at C-1 effectively freezes the conformation. Despite the $A^{(1,3)}$ strain, then, protonation occurs from the equatorial direction (**18**), which is still the least hindered direction, in accord with Zimmerman's theory. When the malonate is in an axial configuration, protonation occurs from the axial direction (**17**) which is now the least hindered. Aspects of the argument used by Bordwell will be discussed in a future paper. Suffice it to say here that the bending away of the vicinal groups in **18** would force the malonate moiety at C-3 up and block approach from the axial direction.



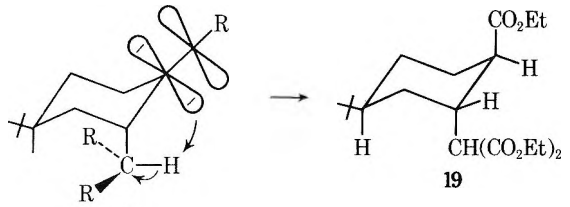
18

The question remains as to why no rearranged product is formed in the addition of diethyl malonate to the ester (**7**). One possible explanation is that the malonate groups at C-3 is in a configuration that sterically prohibits the necessary intramolecular attack (*vide infra*). Alternate explanations can be found in the literature. There are no examples

Table III
Equilibrations of the Dicarboxylic Acids

Compd	Catalyst	T, °C	K_{eq}	ΔG°, kcal/mol ±0.01	ΔH°, kcal/mol	ΔS°, eu	ΔG°_{25}, kcal/mol
15	12 *N* HCl	240	0.89	+0.11			
15	10% Pd–C	240	0.97	+0.03			
15	5% NaOH	240	2.3	−0.84			
15 or 16	None	153	1.05	−0.04			
15 or 16	None	203	0.95	+0.05			
15 or 16	None	252	0.87	+0.135	−0.84 ± 0.06	−1.9 ± 0.3	−0.2 ± 0.1
14	12 *N* HCl	178	11.5	−2.18			
14	12 *N* HCl	198	9.0	−2.05			
14	12 *N* HCl	217	7.7	−1.98	−4.4 ± 0.1	−4.8 ± 0.1	−2.9 ± 0.2
14	12 *N* HCl	240	8.1	−2.13			
14	10% Pd–C	240	10.2	−2.28			
14	5% NaOH	240	49	−3.88			
12 or 13	10% Pd–C	249	4.88	−1.6			

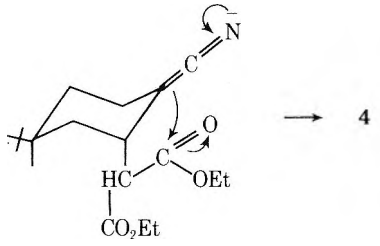
of an abnormal Michael addition occurring in the addition of diethyl malonate to an α,β-unsaturated ester, although many such reactions are known when diethyl methylmalonate is the Michael donor.[8] Several theories have been proposed to explain this observation. One is that the greater acid strength of the abnormal products is the driving force for the rearrangement. When diethyl malonate is the donor, both normal and abnormal products would have the same acidity, and hence no driving force for migration would be present.[9] Another possible explanation suggested that the malonate proton migrates more readily than the carbethoxyl group. When a C-monosubstituted malonate is the Michael donor a carbethoxyl group migrates more readily than an alkyl group.[10] This cannot apply to our reactions, since proton migration from the malonate moiety would lead to **19**, which is not observed. Furthermore, it is



17a **19**

highly unlikely that the malonate would be in a rotational conformation that would permit such an intramolecular proton migration, since such a conformation would be one in which at least one of the carbethoxyl groups would have to be oriented under the cyclohexane ring (**17a**), which would be unstable relative to that rotational conformation in which the malonate hydrogen atom protrudes under the cyclohexane ring.

A more plausible explanation in the present case would consider the steric requirements of the transition state involved in the rearrangement process. Abramovitch and Struble[1] have supported the Holden–Lapworth mechanism, which requires a cyclobutanone-type transition state.

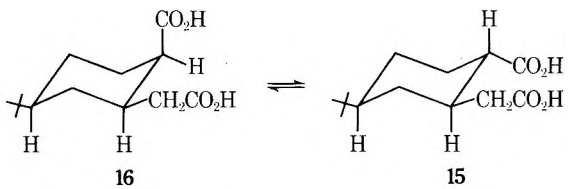


The steric requirements for this transition state may be rigid so that in the case of **17** the cyclobutanone ring cannot form. Thus, it is conceivable that steric interaction between the carbethoxyl group and the C-3 equatorial proton [*i.e.*, $A^{(1,3)}$ strain] causes some ring deformation that precludes formation of the cyclobutanone transition state.

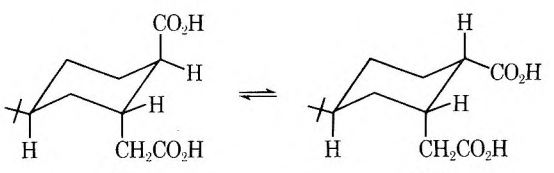
Equilibrations of the malonates **8**, **9**, and **10** under thermodynamic control conditions should lead to a mixture of the epimeric malonates, *e.g.*, **9** ⇌ **10**, **8** ⇌ **19**. Equilibration of either **9** or **10** gave a mixture of all three malonate adducts, in the ratio expected for thermodynamic control conditions: **8:9:10 = 6:78:16**. Quantities of the olefin (**7**) were also present in the reaction mixture after equilibration. This, together with the formation of some of the axial adduct (**8**), suggests that reversal and subsequent readdition may well be an important reaction path (the product of axial addition could only arise this way), and that an actual equilibration of **9** and **10** *via* the C_4 carbanion could be only a minor pathway.

Attempted equilibration of **8** under thermodynamic control conditions gave unchanged **8**, *i.e.*, neither reversal nor equilibration occurred. This could be accounted for if the malonate proton is more acidic and/or more accessible than the proton at C-4. This is supported by the observation that **8** is the only one of the three malonates in which H–D exchange of the malonic ester proton was possible (*vide supra*).

Equilibration of the *r*-1-*tert*-Butyl-3-carboxymethylcyclohexane-4-carboxylic acids. The equilibrations of the dicarboxylic acids **14**, **15**, and **16** with 12 *N* hydrochloric acid, 5% sodium hydroxide, or 10% palladium on charcoal have been studied. The results are summarized in Table III.



16 **15**



20 **14**

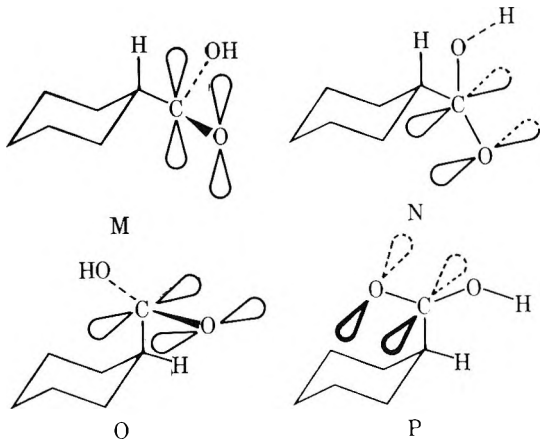


Figure 1. Cyclohexyl carboxyl group conformations.

The normal $\Delta G°$ value for a carboxyl group is in the range −1.15 to −1.6 kcal/mol at 25°,[11] and indeed we confirmed a value of $\Delta G°$ = −1.56 kcal/mol for 4-*tert*-butylcyclohexanecarboxylic acid at 258° (*cf.* $\Delta G°_{25}$ = −1.4 ± 0.1 kcal/mol, $\Delta H°$ = −1.63 ± 0.05 kcal/mol, and $\Delta S°$ = −0.8 eu[12]). Tichý and Sicher[13] reported $\Delta G°$ = −1.89 for the carboxylate anion at 180°, while Eliel[12] reported a preferred $\Delta G°_{25}$ value of −2.2 kcal/mol.

The equilibrium of **15** ⇌ **16** has a $\Delta G°$ much *smaller* than the normal value for the carboxyl group (−0.2 *vs. ca.* −1.4 kcal/mol at 25°). At 25° the equatorial isomer is very slightly favored, and at higher temperatures there is actually a preference for the axial epimer.

Tichý and Sicher[13] found a *larger* than normal $\Delta G°$ for the equilibrium of the *r*-1-*tert*-butyl-*c*-3-methyl-4-cyclohexanecarboxylate ion ($\Delta G°$ = −3.5 kcal/mol at 180°). They ascribed this to a steric effect of the methyl group preventing the axial COO^- from achieving its preferred rotational conformation (see Figure 1). They suggested that the preferred rotational conformation for an equatorial carboxyl was the "perpendicular" one (*e.g.*, N, Figure 1), while the preferred rotational conformation for the axial carboxyl was the "tangential" one (*e.g.*, O, Figure 1). pK_a data supported this assignment. van Bekkum, Verkade, and Wepster[14] concurred with this view, while Dunitz and Strickler[15] disagreed. The latter determined the structure of *trans*-1,4-cyclohexanedicarboxylic acid by X-ray analysis and found that the equatorial carboxyls prefer the rotational conformation in which they are syn planar with the ring, *i.e.*, M, Figure 1. Calculations indicated that an axial carboxyl would also prefer the syn-planar configuration, *i.e.*, O, Figure 1. They believed that it was unlikely that the same conformational requirements would hold for the more symmetrical carboxylate anion.

The major difference between our systems, and that of Tichý and Sicher is that ours involves the vicinal interaction of two polar groups (carboxyl and carboxymethyl and the corresponding anions) while theirs involves the interaction of a polar and a nonpolar group (carboxylate and methyl). Since their results are in the opposite direction to ours, one might conclude that polar interactions are very important in the free dicarboxylic acids and the dicarboxylate anions. The methyl esters **12** and **13**, on the other hand, behave normally when equilibrated at 249° with 10% palladium on charcoal ($-\Delta G°$ = −1.6 kcal/mol at 249°, compared with a literature[11] value of −1.1 kcal/mol at 25°) see (see Table III).

The results of the equilibrations **15** ⇌ **16** (Table III) indicate that for both the free acids *and* the carboxylate anion the axial epimer is stabilized more than usual relative to the equatorial epimer (or the equatorial isomer is unusually destabilized). Solvation may be ruled out as an important factor in the free acid equilibrations, since the same values are obtained whether or not the equilibration is carried out in a solvent and $\Delta S°$ is relatively small and negative (−1.9 eu). If solvation were important, a positive $\Delta S°$ would have been expected, assuming the more stable isomer were more highly solvated than the less stable one. This would be expected for an equatorial substituent since it is less hindered than an axial one. Solvation may play some role in the carboxylate anion equilibrations. Evaluation of this possibility is prevented by lack of data on equilibrations at various temperatures. Intramolecular hydrogen bonding may play a role in stabilizing **16** relative to **15**, but this effect cannot obtain in the dicarboxylate anion. In the latter case dipolar repulsion between the two carboxylate functions, as well as solvation, may be important.

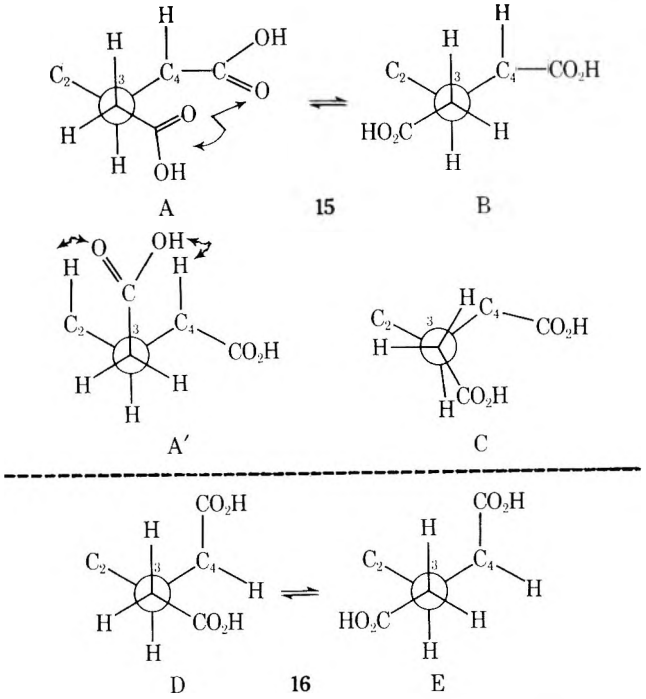


Figure 2. Rotational conformations of the carboxymethylene group in **15** and **16**.

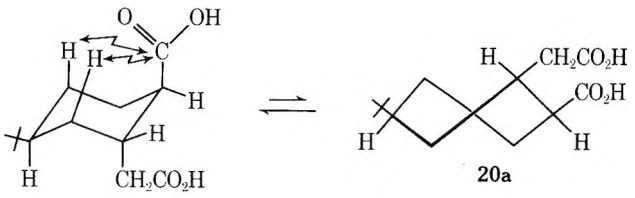
The results of the dicarboxylic acid equilibrations may perhaps be explained by a consideration of the possible rotational conformations available to the carboxymethyl group. In Figure 2, Newman projections are shown looking down the C-3-carboxymethylene bond, assuming (probably incorrectly) a perfect chair conformation for the cyclohexane ring. The expected ring flattering should, if anything, accentuate the arguments.

In **15** there are two possible reasonable staggered rotational conformations of the carboxymethylene group, *i.e.*, A and B (Figure 2). In A there would be considerable dipolar and steric interaction between the two eclipsed carboxyl groups [an $A^{(1,4)}$ interaction]. Consequently, **15** will prefer the conformation B. A certain percentage may exist in the eclipsed conformation C, but this would be energetically less favored than B, as would A′, which would essentially have an exocyclic axial carboxyl group.

The epimeric dicarboxylic acid, **16**, does not have the same conformational problems as does **15**, as far as the exocyclic carboxyl is concerned. There will be no steric or dipolar interactions between the carboxyl groups in either rotamer D or E. Hence, two approximately energetically equal rotational conformations are available to **16**, while only one is available to **15**. This may account for the appar-

ent increased stability of **16**, as well as the more negative entropy found (−1.9 eu) for this equilibration compared with $\Delta S°$ = −0.8 eu for the equilibrium between *cis*- and *trans*-4-*tert*-butylcyclohexane carboxylic acid.[12] $\Delta H°$ for the latter process is −1.63 kcal/mol, while $\Delta H°$ for the equilibration **15** ⇌ **16** is −0.84 kcal/mol. The smaller $\Delta H°$ in this case reflects the lower activation energy required to go from equatorial to axial compared with the C-3 unsubstituted compound. Unfortunately, the nmr spectra do not permit a distinction to be made between the carboxymethylene protons in the various proposed conformations.

The equilibration of the *r*-1,*t*-3,*t*-4-dicarboxylic acid (**14**) is quite different from that of the isomeric compounds **15** and **16**. Much smaller amounts of the diaxial epimer (**20**) are formed than would be expected, the apparent $\Delta G°_{25}$ for the carboxyl being −2.9 kcal/mol (as compared with a literature value[11] of −1.1 to −1.6 kcal/mol for a carboxyl with no vicinal group). In other words, far less of the diaxial epimer is present at equilibrium than would be expected on the basis of the equilibrium constant for the C-3 unsubstituted compound. A lower $-\Delta S°_{25}$ is found for this reaction (−4.85 eu) as compared with −1.9 eu for the equilibrium **15** ⇌ **16** and −0.8 eu for the C-3 unsubstituted compound. This would suggest that the diaxial form (**20**) has more degrees of freedom than the epimer (**14**), which would be possible if **20** were to exist to some extent in the flexible form **20a**. This is likely, since the presence of two relatively large axial groups can cause the ring to equilibrate to the flexible form in order to avoid large syn-axial interactions.[16] However, **20a** would still be a much higher energy



20 **20a**

form than **14**. ΔH for the equilibrium **14** ⇌ **20** (−4.45 kcal/mol) is unusually high compared to that for the equilibrium **15** ⇌ **16** (−0.84 kcal/mol), and for the C-3 unsubstituted compound (−1.63 kcal/mol), and could be a reflection of the high energy difference between the chair and the flexible forms.

Experimental Section

4-*tert*-Butylcyclohexene-1-carboxylic Acid. 4-*tert*-Butyl-1-cyanocyclohexene (50 g) was treated with 40% sulfuric acid (500 ml) and the mixture was boiled under reflux until crystals had formed on the surface of the sulfuric acid and an oil (the nitrile) was no longer present. The mixture was cooled, diluted with water (1000 ml), and filtered. The crystalline acid (41 g, 75%) had mp 189–191° (from acetone) (lit.[17] 182–185° from acetic acid–water): ir (KBr) 3500–2500 (COOH), 1675 (C=O), 1645 cm^{-1} (C=C).

Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate. 4-*tert*-Butylcyclohexene-1-carboxylic acid (70 g) was dissolved in absolute ethanol (500 ml). Sulfuric acid (30 ml) was added, and the mixture was boiled under reflux for 5 hr. The solution was cooled, diluted with water (500 ml), and extracted with ether (4 × 200 ml). The combined ether extracts were washed with 5% sodium hydroxide (3 × 200 ml) and brine (3 × 200 ml), dried ($MgSO_4$), and evaporated. The residual oil was distilled to give the ester (64 g, 70%), bp 80–82° (0.1 mm): ir (neat) 1705 (C=O), 1645 cm^{-1} (C=C); nmr (CCl_4) δ 6.85 (s, br, 1, vinyl **H**), 4.10 (q, 2, $COOCH_2CH_3$), 1.25 (t, 3, $COOCH_2CH_3$), 0.90 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.41; H, 10.54.

Addition of Diethyl Malonate to Ethyl 4-*tert*-Butylcyclohexene-1-carboxylate. Thermodynamic Control Conditions. Sodium (3.6 g, 0.156 mol) was dissolved in absolute ethanol (50 ml). Diethyl malonate (37 g, 0.23 mol, freshly distilled) and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (16.4 g, 0.078 mol) were added. The solution was boiled under reflux for 24 hr. It was then cooled, acidified with glacial acetic acid, basified with 5% sodium hydroxide, and extracted with ether (3 × 100 ml). The combined ether extracts were extracted with 5% sodium hydroxide (3 × 100 ml), and brine (3 × 100 ml), dried ($MgSO_4$), and evaporated. The residual oil was fractionally distilled. The first fraction contained diethyl malonate, bp 45° (0.2 mm). The second fraction contained unreacted olefin (8 g), bp 75–85° (0.2 mm). The third fraction contained mixed malonate esters (9.5 g, 65% conversion), bp 142–155° (0.2 mm). Glc analysis (25% Apiezon on 60–100 mesh Chromosorb W, 6 ft × 3/16 in., program 210–250° at 2°/min, 60 ml/min flow rate of helium carrier gas) indicated the presence of five compounds which were subsequently shown to be three malonate adducts and two acetates (*vide infra*). The malonate adducts were present in the ratio **8:9:10** = 17:72:11, corrected for relative molar response factors, using benzanilide as internal standard. The components were separated by preparative gas chromatography using a 25% Apiezon M on 60–100 mesh Chromosorb W, 2 × 3 ft × 3/4 in. biwall column at 250° and a 300 ml/min helium carrier gas flow rate. The properties of the individual compounds are given below.

Diethyl *r*-1-*tert*-Butyl-*t*-4-carbethoxy-*c*-3-cyclohexylmalonate (9). The diequatorial ester (**9**) was obtained (3.2 g, 20%) by preparative gas chromatography as described above. It crystallized with difficulty from light petroleum (bp 30–60°), mp 30–31.5°: ir (neat) 1760, 1735 cm^{-1} (ester C=O); nmr (acetone-d_6) δ 4.15 (m, 6, $COOCH_2CH_3$), 3.70 (d, 1, J = 13 Hz, $-CH(COOEt)_2$), 3.00 (m, 1, C-3-H), 2.52 (br s, 1, C-4-H), 1.25 (m, 9, $COOCH_2CH_3$), 0.8p (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 370 (0.3), 324 (9), 278 (9), 266 (22), 240 (18), 239 (11), 222 (12), 221 (18), 211 (30), 166 (17), 165 (28), 161 (50), 160 (100), 153 (12), 137 (23), 133 (13), 57 (18).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.91; H, 9.28.

***r*-1-*tert*-Butyl-*c*-3-(carboxymethyl)cyclohexane-*t*-4-carboxylic Acid (15).** The ester (**9**) (0.5 g, 1.35 mol) was hydrolyzed with boiling 3 *N* hydrochloric acid (15 ml) for 3 days. On cooling the crystals of the dicarboxylic acid (**15**) (0.19 g, 58%) were collected and recrystallized from ether–light petroleum (bp 30–60°), mp 181–182.5° (lit.[1] 181–182°); infrared spectrum identical with that of authentic material.[1]

***r*-1-*tert*-Butyl-*c*-3-(carbethoxymethyl)-*t*-4-carbethoxycyclohexane (12).** The *r*-1,*c*-3,*t*-4 acetate (**12**) (0.35 g, 1.5%) was collected by preparative gas chromatography of the thermodynamic control reaction mixture under the conditions described above, colorless liquid, bp 106–110° (0.1 mm): ir (neat) 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.06 (q, 4, J = 8 Hz, $COOCH_2CH_3$), 1.23 (t, 6, J = 8 Hz, $COOCH_2CH_3$), 0.85 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H , 10.13. Found: C, 68.20; H, 10.12.

The *r*-1,*c*-3,*t*-4 acid (**9**) (50 mg, 0.2 mmol) in absolute ethanol (3 ml) and concentrated sulfuric acid (2 drops) was boiled under reflux for 5 hr. The solution was cooled, diluted with water (3 ml), and extracted with ether (3 × 3 ml). The combined extracts were washed with 5% NaOH (2 × 3 ml) and brine (2 × 3 ml), dried ($MgSO_4$), and evaporated to give 12 (40 mg, 66%), identical with the compound obtained above.

***r*-1,*c*-3,*t*-4 Acetate (12) by Decarbethoxylation of 9.** Malonate (**9**) (0.426 g, 1.15 mmol) and 10% palladium on charcoal (0.348 g) were sealed in a tube and heated at 210° for 3 days. The contents of the tube were suspended in ether and filtered. The filtrate was evaporated to give a colorless oil (0.343 g, 92%), glc analysis (20% SE 30 on Chromosorb W, 60–100 mesh, 6 ft × 3/16 in., program 200–240°/2°/min, 60 ml/min He carrier gas) of which indicated the presence of a mixture of two acetates. The acetates were separated by column chromatography on silica gel (100 g) and eluted with light petroleum (bp 30–60°)–benzene (1:9 v/v). Fractions rich in the *r*-1,*c*-3,*t*-4 acetate were further pruified by preparative glc under the conditions described above. The *r*-1,*c*-3,*t*-4 acetate thus collected (0.155 g, 20%) had an ir spectrum and glc retention time identical with those of the *r*-1,*c*-3,*t*-4 acetate obtained above.

Diethyl *r*-1-*tert*-Butyl-*t*-4-carbethoxy-*t*-3-cyclohexylmalonate (8) was obtained in very small amounts (200 mg) from the thermodynamic control reaction mixture by preparative gas chromatography. The malonate (**8**) is a colorless liquid, bp 140–144° (0.2 mm): ir (neat) 1750, 1730 cm^{-1} (ester C=O); nmr (acetone-d_6) δ 4.15 (m, 6. $COOCH_2CH_3$), 3.65 (d, 1, J = 12 Hz, $CH(COOEt)_2$), 2.80 (m, 1, C-3-H), 2.20 (m, 1, C-4-H), 1.25 (m, 9, $COOCH_2CH_3$), 0.89 (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 370 (19), 327 (7), 326 (34), 325 (5), 314 (4), 311 (6),

300 (4), 298 (4), 278 (9), 267 (7), 258 (6), 257 (4), 240 (8), 223 (6), 222 (6), 221 (5), 212 (6), 211 (32), 210 (42), 200 (4), 195 (7), 194 (4), 193 (5), 173 (12), 168 (6), 167 (6), 166 (11), 162 (5), 161 (52), 160 (100), 137 (13), 133 (7), 121 (7), 107 (7), 94 (9), 81 (11), 79 (11), 57 (26), 41 (17).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.38; H, 9.27.

***r*-1-*tert*-Butyl-*t*-3-(carboxymethyl)cyclohexane-*t*-4-carboxylic Acid (14).** 8 (0.188 g, 0.5 mmol) and 3 *N* HCl (5 ml) were boiled under reflux for 3 days. The white solid was filtered and recrystallized from ether–light petreoleum (bp 30–60°) to give the acid (34 mg, 36%), mp 193–194° (lit.[1] 190–192°); ir spectrum identical with that of authentic material.[1]

***r*-1-*tert*-Butyl-*t*-4-carbethoxy-*t*-3-(carbethoxymethyl)cyclohexane (11)** was prepared in 25% yield by the esterification of the corresponding dicarboxylic acid as described for the *r*-1,*c*-3,*t*-4 isomer. Insufficient amounts of acetate were present in the malonate reaction mixture to allow preparative glc isolation of this compound: colorless liquid, bp 88–92° (0.007 mm); ir (neat) 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.00 (q, 4, J = 8 Hz, $COOCH_2CH_3$), 1.17 (t, 6, J = 8 Hz, $COOCH_2CH_3$), 0.79 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.31; H, 10.16.

Diethyl *r*-1-*tert*-butyl-*c*-4-carbethoxy-*c*-3-cyclohexylmalonate (10) (200 mg) was obtained from the thermodynamic control reaction mixture by preparative gas chromatography as described above: mp 50.5–51.5° (from light petroleum, bp 30–60°); ir (KBr) 1730 cm^{-1} (C=O); nmr (acetone-d_6), δ 4.20 (m, 6, $COOCH_2CH_3$), 3.76 (d, 1, J = 11 Hz, $CH(COOEt)_2$), 3.05 (m, 1, C-3–H), 2.55 (m, 1, C-4–H), 1.25 (m, 9, $COOCH_3CH_3$), 0.85 (s, 9, *tert*-butyl); mass spectrum (70 eV) *m/e* (rel intensity) 326 (2), 325 (10), 324 (4), 312 (8), 280 (3), 240 (9), 223 (5), 222 (15), 221 (30), 211 (15), 210 (10), 208 (6), 207 (5), 205 (6), 195 (6), 193 (11), 161 (50), 160 (68), 155 (8), 153 (12), 149 (9), 148 (9), 139 (8), 137 (30), 135 (28), 133 (18), 121 (21), 115 (18), 93 (29), 91 (18), 87 (14), 83 (12), 81 (35), 79 (37), 69 (20), 67 (30), 57 (100).

Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.38; H, 9.27.

***r*-1-*tert*-Butyl-*c*-3-(carboxymethyl)cyclohexane-*c*-4-carboxylic Acid (16).** 10 (1.00 g, 2.7 mmol) and 3 *N* HCl (20 ml) were boiled under reflux for 3 days. The mixture was cooled and extracted with ether (2 × 30 ml). The residual solid (0.13 g, 20%) had mp 203–205° [from ether–light petroleum (bp 30–60°)] (lit.[1] 210–212°): ir (KBr) 3300–2500 (OH), 1725 cm^{-1} (C=O), identical with that of a previously obtained sample.[1] On heating with acetic anhydride for 4 hr it gave *cis*-4-*tert*-butyl-*cis*-hexahydrohomophthalic anhydride (70%): mp 104–105° (lit.[1] 113–115°); ir (KBr) 1810, 1765 cm^{-1} (cyclic anhydride C=O), identical with that of an authentic sample.[1]

***r*-1-*tert*-Butyl-*c*-4-carbethoxy-*c*-3-(carbethoxymethyl)cyclohexane (13).** The *r*-1,*c*-3,*c*-4 acetate (0.35 g, 1.5%), collected by preparative glc of the thermodynamic control reaction mixture the conditions described above, was a colorless liquid: bp 106–110° (0.1 mm); ir (neat) 1740 cm^{-1} (C=O); nmr (CCl_4) δ 4.00 (q, 4, J = 8 Hz, $COOCH_2CH_3$), 1.20 (t, 6, J = 8 Hz, $COOCH_2CH_3$), 0.85 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.01. Found: C, 68.16; H, 10.13.

It was also prepared (30% yield) by esterification of the *r*-1,*c*-3,*c*-4-dicarboxylic acid as described for the *r*-1,*c*-3,*t*-4 isomer and was identical with the cis,cis acetate obtained by preparative glc above.

***r*-1,*c*-3,*c*-4 Acetate (13) by Decarbethoxylation of 10.** This was prepared (90% yield) by decarbethoxylation of the *r*-1,*c*-3,*c*-4 malonate (10) as described for the *r*-1,*c*-3,*t*-4 acetate.

The Michael Addition. (a) In Toluene. Sodium (3 g, 0.13 mol) was dispersed in hot xylene, and the xylene was decanted and replaced with toluene (70 ml). Diethyl malonate (31 g, 0.19 mol) was added. When all the sodium had disappeared, the olefin (7) (27.3 g, 0.13 mol) was added, as was absolute ethanol (5 drops). The mixture was boiled under reflux for 48 hr, acidified with glacial acetic acid, and basified with 5% NaOH, and the organic layer was separated. The aqueous layer was extracted with ether (2 × 100 ml), the organic extracts were combined, washed with 5% NaOH (2 × 100 ml), brine (2 × 100 ml), and then dried ($MgSO_4$). The solution was evaporated and the residual oil was fractionally distilled. The fraction bp 142–145° (0.2 mm) contained a mixture of the malonate esters (12.01 g, 25%), **8:9:10** = 1:39:60 [by glc and corrected for relative molar response factors (benzanilide, internal standard) as described above]. The mixture was partially separated into its components by preparative gas chromatography.

(b) In Ethanol under Kinetic Control Conditions. Sodium (14.2 g, 0.61 mol) was dissolved in absolute ethanol (400 ml). Diethyl malonate (149 g, 0.93 mol) and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (65 g, 0.31 mol) were added and the mixture was stirred at room temperature for 4 days. Fractional distillation of the organic materials isolated gave a mixture of the isomeric malonate esters **9:10** = 33:67 [analyzed by glc and corrected for relative molar response factors (benzanilide as internal standard) as described above] (50 g, 45%), bp 140–144° (0.2 mm).

(c) In Diethyl Carbonate. Diethyl malonate (74.3 g, 0.465 mol) was added to a solution of sodium (7.53 g, 0.310 mol) in absolute ethanol (310 ml). The ethanol was distilled and replaced by diethyl carbonate (200 ml) and ethyl 4-*tert*-butylcyclohexene-1-carboxylate (32.5 g, 0.155 mol) was added. The solution was boiled under reflux for 12 hr and worked up as described above for the reaction in toluene.

Fractional distillation of the organic-soluble residue gave a mixture of malonate adducts, bp 110–124° (0.007 mm) (7.95 g, 16%), in which the ratio of **8:9:10** was 19:64:17 [analyzed by glc and corrected for relative molar response factors (benzanilide as internal standard) as previously described].

Attempted H–D Exchange in 10 at Room Temperature. The *r*-1,*c*-3,*c*-4 malonate (10) (0.396 g, 1.08 mmol) was dissolved in absolute ethanol (2 ml). A solution of sodium ethoxide [from sodium (0.087 g, 3.7 mmol) in absolute ethanol (4 ml)] was added. The solution was stirred at room temperature for 30 min. The solvent was evaporated under reduced pressure, D_2O (2 ml) was added, and the mixture was stirred at room temperature for 10 min. The mixture was then extracted with carbon tetrachloride (3 × 5 ml), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Glc analysis [20% SE 30 on Chromosorb W (60–100 mesh), 6 ft × 3/16 in., program 200–240°/2°/min; 60 ml/min He carrier gas] indicated that ethyl 4-*tert*-butylcyclohexene-1-carboxylate (7) was the only product formed.

H–D Exchange of the *r*-1,*t*-3,*t*-4 Malonate (8) in Ethanol at Room Temperature. 8 (40 mg, 0.11 mmol) was added to a solution of sodium (30 mg, 0.13 mmol) in ethanol (3 ml). The solution was stirred for 40 min at room temperature, the solvent was evaporated *in vacuo*, and D_2O (1 ml) was added. After 20 min the solution was extracted with carbon tetrachloride (3 × 5 ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated. Glc analysis indicated the presence of one compound, whose retention time was identical with that of starting material (20 min). Its nmr spectrum was identical with that obtained from starting material except that the doublet at δ 3.65 [$CH(COOEt)_2$] was now a very broad, weak absorption: mass spectrum (70 eV) *m/e* (rel intensity) 371 (1), 370 (1), 369 (1), 355 (5), 341 (2), 327 (4), 326 (16), 325 (19), 324 (5), 298 (5), 297 (5), 283 (6), 281 (5), 279 (19), 271 (5), 270 (5), 269 (8), 268 (13), 251 (8), 241 (5), 240 (8), 227 (5), 223 (11), 222 (12), 221 (14), 211 (23), 173 (28), 162 (25), 161 (84), 160 (28), 137 (28), 81 (31), 79 (44), 57 (100).

"Equilibration" of Diethyl *r*-1-*tert*-butyl-*t*-4-carbethoxy-*c*-3-cyclohexylmalonate (9). 9 (0.25 g, 0.68 mmol) was dissolved in a solution of sodium (31 mg, 1.35 mmol) and diethyl malonate (322 mg, 2.03 mmol) in absolute ethanol (3 ml). The mixture was boiled under reflux for 19 hr. The reaction was worked up as described in the H–D exchange studies. Glc analysis indicated the presence of the three malonates **8, 9,** and **10** in the ratio 6:78:16. The identity of the three malonates was confirmed by comparison of their infrared spectra with those of authentic materials. Similar results were obtained on "equilibration" of **10 (8:9:10** = 7:78:15).

Equilibration of the *r*-1,*t*-3,*t*-4-Dicarboxylic Acid (14). The following general procedure was used to equlibrate the *r*-1,*t*-3,*t*-4-dicarboxylic acid (14). Samples of the pure acid (18–22 mg) were placed in Pyrex test tubes (10 × 75 mm). An excess of concentrated HCl (0.2 ml) was added to each sample and the tubes were sealed. The sealed tubes were heated in an oven for 16 hr. Runs were carried out at three temperatures: 178 ± 2, 198 ± 2, and 217 ± 2°. The tubes were cooled and opened, and the HCl was removed under vacuum. The contents of each tube were dissolved in absolute methanol (3 ml). Sulfuric acid (1 drop) was added, and the solution was boiled under reflux for 5 hr. It was then diluted with water (5 ml) and extracted with ether (3 × 5 ml), and the ether extracts were then dried ($MgSO_4$) and evaporated. The residual oil (10 mg) was analyzed by glc (20% SE 30 on Gas-Chrom Q, 60–100 mesh; 6 ft × 3/16 in.; program 165–210°/2°/min; 60 ml/min He carrier gas). Two peaks were observed, the smaller and first eluting being due to the *r*-1,*t*-3,*c*-4 isomer, which had a re-

tention time of 24.8 min. The second peak (retention time, 26.3 min) was due to the *r*-1,*t*-3,*t*-4-ester (11) identical with the material previously obtained[1]). No side products were formed. Esterification runs on individual acids indicated these to be essentially quantitative.

The results, which are the averages of two runs, are summarized in Table IV.

Table IV
Equilibration of the *r*-1,*t*-3,*t*-4-Dicarboxylic Acid with 12 *N* Hydrochloric Acid

T, °K	*r*-1, *t*-3, *t*-4 : *r*-1, *t*-3, *c*-4	K_{eq}
451 ± 2	92 : 8 (±1%)	11.5 ± 0.2
471 ± 2	90 : 10 (±1%)	9.0 ± 0.2
490 ± 2	88.5 : 11.5 (±1%)	7.7 ± 0.2

$\Delta H°$ and $\Delta S°$ were determined graphically using the following equations.

$$\Delta H° = \frac{-R[\ln K_2 - \ln K_1]}{(1/T_2) - (1/T_1)}$$

$$\Delta S° = \frac{RT_2 \ln K_2 - RT_1 \ln K_1}{T_2 - T_1}$$

$$\Delta H° = -4.3 \pm 0.1 \text{ kcal/mol}$$

$$\Delta S° = 4.8_5 \pm 0.02 \text{ eu}$$

$$\Delta G°_{25} = \Delta H° - T\Delta S° = -2.9 \pm 0.1 \text{ kcal/mol}$$

Equilibration of Dicarboxylic Acids 15 and 16. (a) With 5% Aqueous Sodium Hydroxide (*cf.* **ref 18).** Each of the pure acids (0.014–0.018 g) was placed in a Pyrex tube and treated with an excess of 5% NaOH solution (0.3 ml): the tubes were sealed and heated at 240 ± 4° for 24 hr. The solutions were acidified and evaporated to dryness, the residue was esterified with diazomethane,[1] and the esters were analyzed by glc as described above.

(b) With 12 *N* HCl. This was carried out as described above for the equilibration of **14.** The infrared spectrum of the crude reaction mixture indicated the lack of formation of any cyclic or other acid anhydride, as also did glc. The crude acids were methylated with diazomethane [as under (a) above] and analyzed.

(c) With 10% Palladium on Charcoal (*cf.* **ref 19).** Each of the pure acids (0.02–0.03 g) was mixed with 10% Pd–C (0.007 g) and heated in a sealed tube at 240 ± 4° for 29 hr. The products were extracted with ether (2 (2 ml) and centrifuged, and the solution was decanted (procedure repeated twice). Again no anhydride was formed. Methylation with diazomethane was followed by quantitative glc analysis.

In none of the above cases were any by-products formed nor was any evidence found that one conformer was being selectively consumed. The results are summarized in Table III.

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Registry No.—**1,** 7370-14-1; **7,** 23022-33-5; **8,** 53154-24-8; **9,** 23191-42-6; **10,** 23191-41-5; **11,** 53154-25-9; **12,** 53154-26-0; **13,** 53154-27-1; **14,** 18680-01-8; **15,** 18679-93-1; **16,** 18679-94-2; 4-*tert*-butylcyclohexene-1-carboxylic acid, 31845-19-9; diethyl malonate, 105-53-3.

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The Direct Acylamination of Quinoline, Isoquinoline, Benzimidazole, Pyridazine, and Pyrimidine 1-Oxides. A Novel 1,5-Sigmatropic Shift[1]

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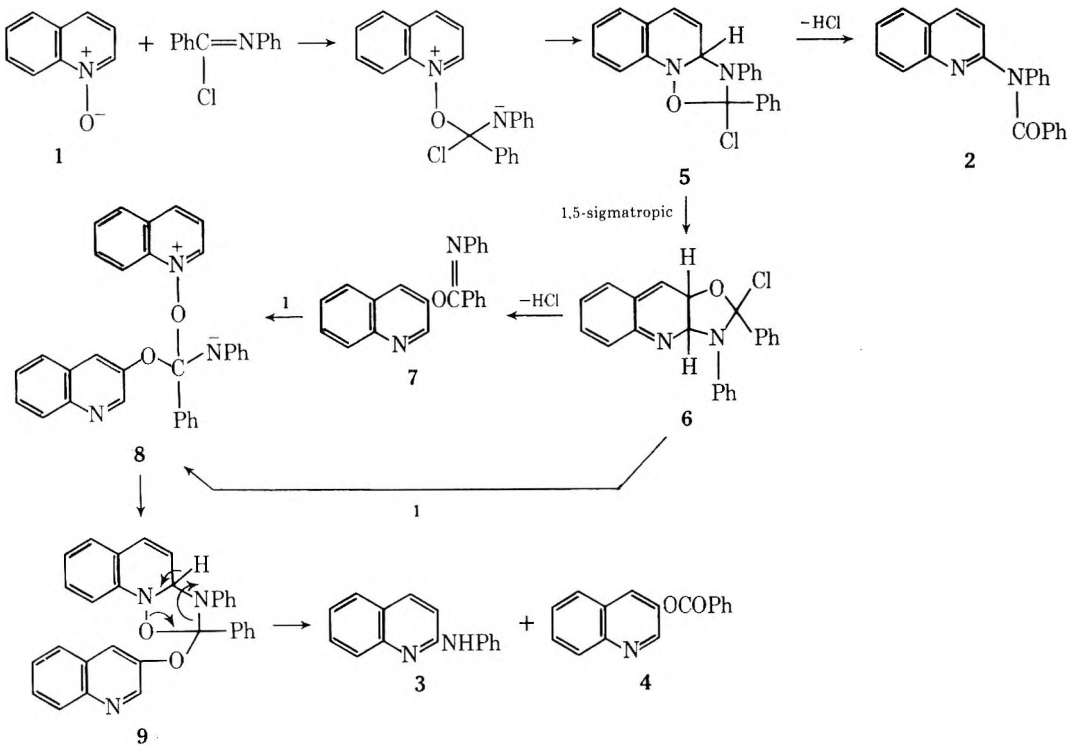
The direct acylamination of pyridine 1-oxides using an *N*-phenylbenzimidoyl chloride or the corresponding nitrilium salt has been extended to the title heteroaromatic *N*-oxides. With quinoline 1-oxide it is proposed that a novel 1,5-sigmatropic shift in the 1,2-dihydro intermediate eventually led to 3-quinolyl benzoate and to 2-anilinoquinoline. 2,6-Lutidine similarly gave 3-(2,6-dimethylpyridyl)-*N*-phenylbenzimidate. The possible mechanisms of the formation of these products are discussed.

The direct acylamination of pyridine 1-oxides using imidoyl halides or nitrilium salts has recently been reported.[2] The main by-products formed when *N*-phenylbenzimidoyl chloride was used were the corresponding 3-chloropyridine derivative and benzanilide. The present paper describes the extensions of this work to other heterocyclic systems.

Acylamination of 6-methyl- and 4,6-dimethylpyrimidine 1-oxides with *N*-phenylbenzimidoyl chloride gave low to moderate yields of the expected 2-*N*-benzoylanilino derivative together with some of the debenzoylated secondary amine (no attempt was made to optimize yields in these reactions; we believe that much higher yields of products are possible). In addition to being a synthetically useful approach to substituted 2-acylaminated pyrimidines this reaction could, in principle, be used to differentiate between isomeric unsymmetrically substituted pyrimidine 1-

Scheme I



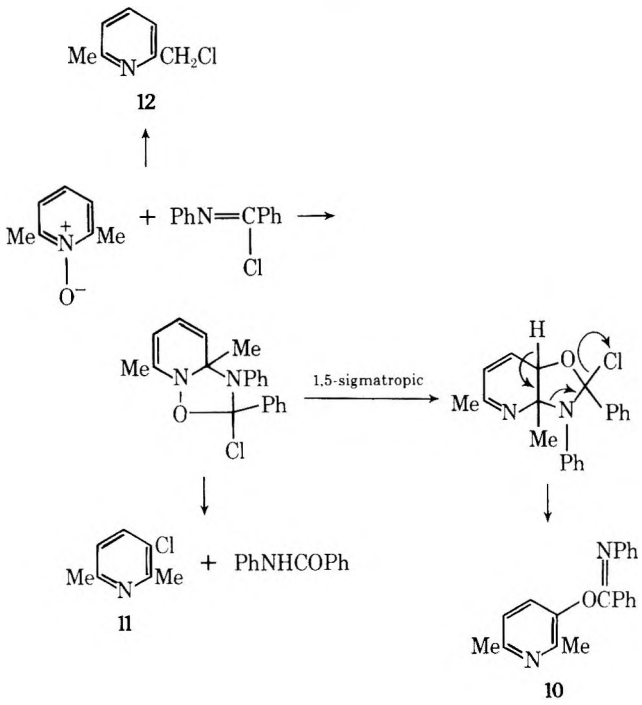
oxides and would thus complement the nmr technique for doing so. For example, 4-methylpyrimidine 1-oxide might be expected to give a mixture of both 2- and 6-acylaminated products, while 6-methylpyrimidine 1-oxide can only give the 2-acylaminated product.

Pyridazine 1-oxide gave 3-*N*-benzoylanilinopyridazine which, in contrast to the other tertiary amides, proved to be rather stable to hydrolysis by hot aqueous acid. Isoquinoline 1-oxide and *N*-phenylbenzimidoyl chloride gives the expected 1-acylaminated product together with a moderate yield of 4-chloroisoquinoline and of benzanilide.

The proposed mechanism[2] for the acylamination indicates that the reaction only depends on the presence in the substrate molecule of a nitrone function, and not on the substrate being a six-membered heteroaromatic *N*-oxide. Thus, benzimidazole *N*-oxides should behave similarly and, indeed, 2-*N*-benzoylanilino-1-benzylbenzimidazole could be prepared in high yield from 1-benzylbenzimidazole 3-oxide and *N*-phenylbenzimidoyl chloride. The amide underwent hydrolysis to the secondary amine on standing in a stoppered vial for some time. The results of these acylaminations are summarized in Table I. A possible explanation of the wide variation in product yields under comparable conditions is that the lower the basicity of the *N*-oxide function the slower the initial addition to the imidoyl chloride and the lower the yield of desired product. Some support for this comes from the fact that no acylamination product could be obtained from 4-nitropyridine 1-oxide.[2a] This suggests that longer reaction times may be beneficial in these cases.

The reaction of anhydrous quinoline 1-oxide (1) with *N*-phenylbenzimidoyl chloride led to some unexpected results. In addition to 2-*N*-benzoylanilinoquinoline (2) and benzanilide there were obtained about equal amounts of 2-anilinoquinoline (3) (35.8%) and 3-quinolyl benzoate (4) (33.5%) under completely anhydrous conditions and prior to hydrolysis. That 3 was not being formed from 2 under the reaction conditions was established by showing that 2 was stable under these conditions and that 2, 3, and 4 were being formed simultaneously right from the beginning

Scheme II



(course of the reaction followed with time by gas chromatographic analysis).

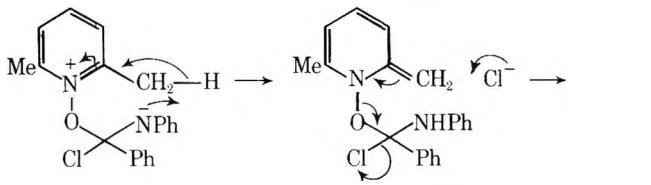
Since the reaction was carried out in the complete absence of air or any other source of oxygen both oxygen atoms in 4 must come from quinoline 1-oxide. A possible mechanism of the formation of 4 and the simultaneous generation of 3 is outlined in Scheme I. The key feature of this proposal is a 1,5-sigmatropic shift of the initial 1,2-dihydroquinoline intermediate (5) to give a 2,3-dihydro derivative (5). Aromatization of the latter would give 3-quinolyl *N*-phenylbenzimidate (7). This could conceivably react with more *N*-oxide to give an adduct (8) which would then undergo intramolecular cyclization to 9 that would aromat-

Table I
Reaction of Various Heteroaromatic *N*-Oxides with *N*-Phenylbenzimidoyl Chloride

N-Oxide	Registry No.	Products	Registry No.	% Yield[a]
6-Methylpyrimidine 1-oxide	33342-83-5	2-*N*-Benzoylanilino-4-methylpyrimidine	53112-25-7	1.5
		2-Anilino-4-methylpyrimidine	53112-26-8	11.5
		Benzanilide		33
4,6-Dimethylpyrimidine 1-oxide	14161-42-3	2-*N*-Benzoylanilino-4,6-dimethylpyrimidine	53112-27-9	22
		2-Anilino-4,6-dimethylpyrimidine	53112-28-0	9
		Benzanilide		29
Pyridazine 1-oxide[c]	1457-42-7	3-*N*-Benzoylanilinopyridazine	53112-29-1	18
		Benzanilide		5.3
1-Benzylbenzimidazole 3-oxide	27430-55-3	2-*N*-Benzoylanilino-1-benzylbenzimidazole	24068-32-4	92
Isoquinoline 1-oxide	1532-72-5	1-*N*-Benzoylanilinoisoquinoline	53112-30-4	55[b]
		4-Chloroisoquinoline		23[b]
		Benzanilide	1532-91-8	42[b]

[a] Isolated yields. [b] Gas chromatographic yields. [c] With *N*-phenylbenzonitrilium hexachloroantimonate.

ize to give 3 and 4. Alternatively, 6 could react with 1 directly to give 8. The latter appears to be the more likely possibility, for when authentic imidate 7 was prepared from the sodium salt of 3-hydroxyquinoline and *N*-phenylbenzimidoyl chloride and treated with 1 or 1-hydrochloride no 3 or 4 were formed. On the other hand, formation of 7 is not unreasonable. Indeed, we have found that in the pyridine 1-oxide series if the 2 and 6 positions are blocked by methyl groups so that aromatization of the 1,2-dihydro intermediate is not possible then the 1,5-sigmatropic shift occurs readily and gives *O*-(2,6-dimethyl-3-pyridyl)-*N*-phenylbenzimidate (10) (37%), together with some 3-chloro-2,6-lutidine (11) (21%),[4] 2-chloromethyl-6-methylpyridine (12) (12%), and benzanilide (45%) (Scheme II). Similar results were obtained contemporaneously by Parham and Sloan[3] who extended the work to 2,4-dimethylquinoline. The formation of the 3-chloro compound (11) and benzanilide can be explained by the mechanism proposed earlier.[2a] The side chain chlorinated compound probably arises by intramolecular hydrogen abstraction by the intermediate anion followed by intra- or intermolecular nucleophilic addition of chloride ion (only inter- shown). This is mechanistically

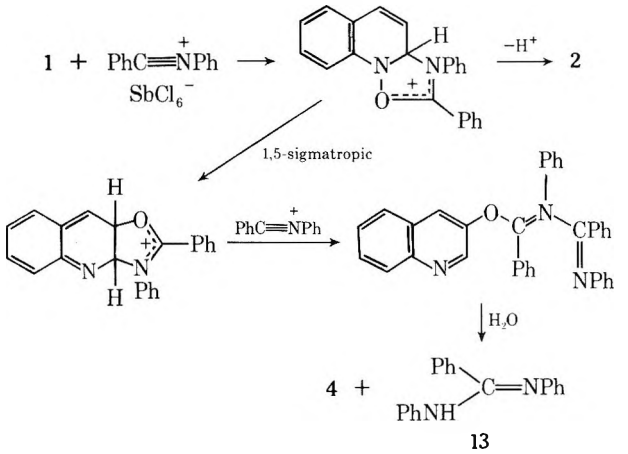


12 + PhNHCOPh + Cl^-

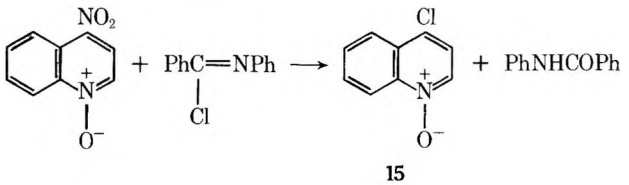
similar to the side-chain chlorination of 2-picoline 1-oxides by tosyl chloride.[5]

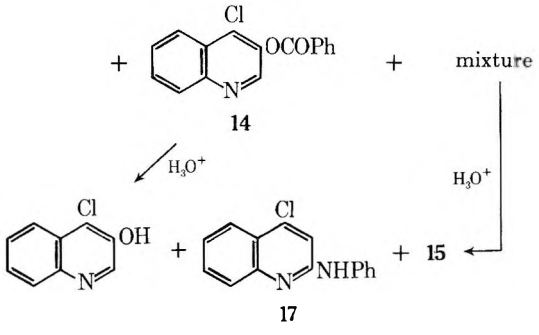
When quinoline 1-oxide was treated with *N*-phenylbenzonitrilium hexachloroantimonate a vigorous reaction occurred which was not as clean as the one in which the imidoyl chloride was used. Quenching the mixture with water gave 2 (5%), benzanilide (25%), 4 (20%), and *N,N'*-diphenylbenzamidine (13) (10%). No 3 was detected. A possible route to these products is outlined in Scheme III, though 13 could conceivably arise from benzanilide and nitrilium salt (which would not, however, explain the absence of 3).

Scheme III



The reaction of 4-nitroquinoline 1-oxide with *N*-phenylbenzimidoyl chloride gave a number of products only four of which have been characterized: benzanilide, 4-chloro-3-quinolyl benzoate (14),[6] 4-chloroquinoline 1-oxide (15), and an oily mixture which could not be resolved but which, on boiling with 4 *N* HCl, gave 15, 4-chloro-3-hydroxyquino-





line (**16**) (also obtained by hydrolysis of **14**), and 2-anilino-4-chloroquinoline (**17**), together with tars. The structure of **14** was deduced from its spectral properties (ester C=O stretch at 1745 cm^{-1} and strong band at 1255 cm^{-1}; $^{35}M^{\cdot+}$ *m/e* 283, $^{37}M^{\cdot+}$ *m/e* 285; *m/e* 105 (100) ($PhCO^+$), nmr δ 8.81, s, H_2), its hydrolysis to 4-chloro-3-hydroxyquinoline (ν_{OH} in ir, no C=O), and on the reasonable assumption that the chlorine substituent is introduced by nucleophilic displacement of the 4-nitro group either in the parent *N*-oxide or, more likely, in the initial *O*-acylated product. 2-Anilino-4-chloroquinoline (**17**) is a known compound[7] and had the expected spectral properties.

It is interesting to note that the formation of 3-substituted pyridyl or quinolyl esters in the reaction between pyridine or quinoline 1-oxide and 2-bromopyridine or 2-bromoquinoline[8] may be explained[9] by invoking a 1,5-sigmatropic shift similar to that postulated above.

Experimental Section

Reactants and solvents were purified prior to use either by recrystallization or distillation. Solvents were dried and distilled prior to use. Thus, all halocarbon solvents were boiled under reflux for 12 hr over phosphorus pentoxide and then distilled. Anhydrous diethyl ether was used directly from freshly opened cans. Tetrahydrofuran was purified by distillation from calcium hydride and then from lithium aluminum hydride. Light petroleum refers to that fraction with a boiling range of 60–110°, unless specified otherwise.

All nuclear magnetic resonance spectra were determined using a Varian Associates model HA-100 spectrometer. Mass spectra were recorded on a C.E.C. Model 21-104 spectrometer, usually at an ionizing voltage of 70 eV. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer. Solid compounds were run as KBr discs while liquids were run as liquid films. Each spectrum was calibrated using polystyrene as a reference at 1944 and 906 cm^{-1}. Melting points are uncorrected. Gas chromatographic analyses were carried out using a Varian Associates Model 200 with helium as the carrier gas. They were performed using dual columns (7 ft × 3/16 in.) packed with 20% SE-30 on Gas-Chrom Q (60–100 mesh), using the internal standard technique. In all cases, each peak was identified by collecting the compound as it eluted from the chromatograph and comparing its infrared spectrum with that of an authentic sample. The per cent yields are based on starting imidoyl chloride.

Reaction of 6-Methylpyrimidine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. 6-Methylpyrimidine 1-oxide (0.70 g, 6.4 mmol) was azeotroped with dry (Na) benzene (10 ml) and then dissolved in chlorobenzene (10 ml). The solution was added dropwise with stirring at room temperature to a solution of *N*-phenylbenzimidoyl chloride (0.71 g, 3.3 mmol) in chlorobenzene (10 ml). It was boiled under reflux for 8 hr, cooled, and concentrated, and the residue was chromatographed on a column of silica gel (100 g) to give benzanilide (0.22 g, 33%); ir (KBr) identical with that of an authentic sample.

The second fraction, eluted with $CHCl_3$, was 2-anilino-4-methylpyrimidine (0.070 g, 11.5%): mp 92–93.5° (ethanol) [lit.[10] mp 92–93°]; ir (KBr) 3250, 3180 cm^{-1} (NH); nmr ($CDCl_3$) δ 8.22 (d, 1 H, $J_{5,6}$ = 5.3 Hz, H-6), 7.62 (d of d, 2 H, J_o = 7.5 Hz, J_m = 1.5 Hz, phenyl-*o*-H), 7.7–7.6 (br s, 1 H, exchangeable with D_2O, N-H), 6.97 (t of d, 1 H, $J_{o,m} = J_{m,p}$ = 7.5 Hz, $J_{o',m}$ = 1.5 Hz, phenyl-*m*-H), 7.27 (t of t, 1 H, $J_{m,p}$ = 7.5 Hz, $J_{o,p}$ = 1.5 Hz, phenyl-*p*-H), 6.52 (d, 1 H, $J_{5,6}$ = 5.3 Hz, H-5), 2.33 (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 186 (7), 185 (55, $M^{\cdot+}$), 184 (100).

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99. Found: C, 71.09; H, 6.12.

The third fraction consisted mainly of **2-*N*-benzoylanilino-4-methylpyrimidine** (0.14 g, 15%). Crystallization from aqueous ethanol gave the analytical sample (0.012 g, 1.3%): mp 141.5–142°; ir (KBr) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.34 (d, 1 H, $J_{5,6}$ = 5 Hz, H-6), 7.6–7.1 (m, 10 H, aromatic-H), 6.80 (d, 1 H, $J_{5,6}$ = 5 Hz, H-5), 2.26 (s, 3 H, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 289 (3, $M^{\cdot+}$), 105 (100).

Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23. Found: C, 74.56; H, 5.30.

Reaction of 4,6-Dimethylpyrimidine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. A solution of 4,6-dimethylpyrimidine 1-oxide (1.04 g, 8.36 mmol) in chlorobenzene (20 ml) was added to freshly prepared and distilled *N*-phenylbenzimidoyl chloride (0.90 g, 4.18 mmol). The solution was boiled under reflux for 10 hr. The solvent was distilled and the black residue was chromatographed on a column of silica gel (100 g). The first fraction eluted (chloroform) was benzanilide (0.24 g, 29%). The second fraction was a mixture containing mainly 2-anilino-4,6-dimethylpyrimidine (0.14 g), mp 71–73°. Fractional crystallization from aqueous ethanol gave benzanilide (0.006 g, 0.7%) and 2-anilino-4,6-dimethylpyrimidine (0.074 g, 9%): mp 91–92° [lit.[11] mp 96–97°]; ir (KBr) 3250 and 3180 cm^{-1}; nmr ($CDCl_3$) δ 7.64 (d of d, 2 H, J_o = 8.0 Hz, J_m = 1.3 Hz, phenyl-*o*-H), 7.24 (m, 3 H, N-H and phenyl-*m*-H), 6.94 (t of t, 1 H, J_o = 7.5 Hz, J_m = 1.3 Hz, phenyl-*p*-H), 6.43 (s, 1 H, H-5), 2.31 (s, 6 H, 4- and 6-CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 199 (3), 198 (6), 197 (24).

The next fraction, also eluted with chloroform, was **2-*N*-benzoylanilino-4,6-dimethylpyrimidine** (0.42 g, 22%): mp 174–175° (aqueous EtOH); ir (KBr) 1670 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.82 (d of d, 2 H, J_o = 7 Hz, J_m = 3 Hz, benzoyl-o-H), 7.64–7.36 (m, 8 H, phenyl-H and benzoyl-*m*-and *p*-H), 6.95 (s, 1 H, H-5), 2.27 (s, 6 H, 4- and 6-CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 303 (4, $M^{\cdot+}$), 105 (100).

Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.22; H, 5.65. Found: C, 75.18; H, 5.81.

Reaction of Pyridazine 1-Oxide with *N*-Phenylbenzonitrilium Hexachloroantimonate. A solution of pyridazine *N*-oxide (1.72 g, 17.7 mmol) in ethylene chloride was added over a period of 10 min to a suspension of *N*-phenylbenzonitrilium hexachloroantimonate (5.25 g, 8.9 mmol) in ethylene chloride (50 ml) (drybox). All the salt dissolved during the addition of the *N*-oxide. The solution was boiled under reflux for 17 hr. After cooling to room temperature, the solution was stirred with water (25 ml) for 10 min to form insoluble antimony compounds and then filtered. The organic layer was dried, concentrated, and chromatographed on a column of silica gel (100 g). Chloroform elution gave benzanilide (0.094 g, 5.3%). Further elution with chloroform gave **3-*N*-benzoylanilinopyridazine** (0.44 g, 18%): mp 149–150° (aqueous acetone); ir (KBr) 1640 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 8.89 (d of d, 1 H, $J_{5,6}$ = 5 Hz, $J_{4,6}$ = 2 Hz, H-6), 7.65–7.00 (m, 12 H, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 274 (1, $M^+ - 1$), 105 (100).

Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76. Found: C, 74.35; H, 4.92.

1-Benzylbenzimidazole 3-Oxide.[12] *o*-Nitro-*N*-benzylformanilide (20 g, 0.078 mol) was added to ethanol (200 ml) and ethanolic ammonia (100 ml, saturated at 0°). Hydrogen sulfide was passed through the solution which was stirred at room temperature for 2 hr. The mixture was then stirred overnight. The brown solution was concentrated to 100 ml, cooled, and filtered to remove precipitated sulfur. Evaporation of the filtrate, addition of acetone, and chilling gave the crude product (9.45 g). Crystallization from acetone gave 1- benzylbenzimidazole 3-oxide monohydrate (2.0 g, 11.4%): mp 158–159° [lit.[12] mp 47–50° for the trihydrate]; ir (KBr) 1204 (N^+–O^-), 716 cm^{-1} (monosubstituted phenyl); nmr ($CDCl_3$) δ 8.63 (s, 1 H, H-2), 7.94 (m, 1 H, H-4), 7.5–7.1 (m, 8 H, aromatic H), 5.29 (s, 2 H, $PhCH_2$), 3.70 (br s, *ca.* 1.5 H, H_2O of hydrate); mass spectrum (70 eV) *m/e* rel intensity) 224 (2.4), 223 (1.2), 209 (5.6), 208 (10), 119 (1), 92 (11), 91 (100), 90 (5), 77 (7), 73 (9), 71 (5), 69 (6), 65 (19), 63 (9), 57 (9), 55 (9), 51 (7), 44 (22), 43 (10), 41 (12), 40 (44), and 39 (15).

The sample for analysis had mp 78.5–79.5° before drying, mp 161.5–163° after drying for 1 hr at 50° (0.005 mm), and mp 149–151° after drying for 12 hr at 50° (0.005 mm).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39. Found: C, 74.96; H, 5.56.

Reaction of 1-Benzylbenzimidazole 3-Oxide with *N*-Phenylbenzimidoyl Chloride. 1-Benzylbenzimidazole 3-oxide (1.21 g, 5.0 mmol) was dried by azeotroping it with chloroform (2 × 10 ml). A solution of *N*-phenylbenzimidoyl chloride (0.54 g, 2.5 mmol) in chloroform (10 ml) was added, and the solution was boiled under reflux for 22 hr. The solution was evaporated to dryness and the residue dissolved in ethanol. Decolorization, addition of water, and seeding gave **2-*N*-benzoylanilino-1-benzylbenzimidazole** (0.90 g, 92%): mp 151.5–153.5° (from EtOH); ir (KBr) 1690 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 7.64 (m, 1 H, H-4), 7.5–6.9 (m, 18 H, aromatic-H), 5.21 (s, 2 H, Ph CH_2).

Anal. Calcd for $C_{26}H_{21}N_3O$: C, 80.37; H, 5.23; N, 10.42. Found: C, 80.41; H, 5.54; N, 10.37.

2-Anilino-1-benzylbenzimidazole. (a) 2-*N*-Benzoylanilino-1-benzylbenzimidazole (0.029 g, 0.072 mmol) was boiled under reflux in 5% NaOH (3 ml) for 13 hr. After cooling to room temperature,

the solution was filtered and the solid obtained was boiled under reflux with another portion of 5% aqueous NaOH (3 ml) for 48 hr. The solid obtained (0.039 g) consisted mainly of sodium silicate plus the desired compound. It was boiled with chloroform and filtered. The filtrate was evaporated to give 2-anilino-1-benzylbenzimidazole (0.004 g, 18.5%), mp 183–184.5°; ir (KBr) identical with that of sample obtained as under (b) below.

(b) 1-Benzylbenzimidazole 3-oxide (0.242 g, 0.001 mol) was dried by azeotroping it with chloroform (2 × 5 ml) and dissolving in chloroform (3 ml). The solution was stirred at room temperature and phenyl isocyanate (0.12 g, 0.001 mol) was added slowly through a syringe. The reaction mixture set to a solid after the addition was complete. The solid (0.30 g, mp 184.5–189°) was recrystallized twice from chloroform to give **2-anilino-1-benzylbenzimidazole** (0.27 g, 90%): mp 188–190°; ir (KBr) 3200 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.56 (m, 1 H, H-4), 7.40–6.80 (m, 13 H, aromatic-H), 5.14 (s, 2 H, PhCH_2); mass spectrum (70 eV) *m/e* (rel intensity) 299 (3, M·+), 207 (6, M − benzyl).

Anal. Calcd for $C_{20}H_{17}N_3 \cdot \frac{1}{2}H_2O$: C, 77.81; H, 5.81; N, 13.62. Found: 77.70; H, 5.75; N, 13.14.

Reaction of Isoquinoline 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of isoquinoline *N*-oxide (2.08 g, 14.4 mmol) and distilled *N*-phenylbenzimidoyl chloride (2.76 g, 13 mmol) in 1,2-dichloroethane (30 ml) was boiled under reflux for 6 hr. The cooled solution was washed with 10% sodium carbonate solution (2 × 30 ml), the solvent evaporated from the organic phase, and the residue chromatographed on silica gel (250 g, 4 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as eluent.

Eluting first was a red oil which was distilled to give 4-chloroisoquinoline (0.33 g, 18%): bp 90° (0.5 mm) [lit.[13] bp 100–104° (1 mm)]; nmr ($CDCl_3$) δ 8.94 (s, 1 H, H-1), 8.43 (s, 1 H, H-3), 8.10–7.28 (m, 4 H, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 165 (31), 164 (10), 163 (100).

The second compound eluted was benzanilide (1.0 g, 39%).

The third product was recrystallized from light petroleum–acetone to give 1-(*N*-**benzoylanilino)isoquinoline** (1.6 g, 47%): mp 175–176°; ir (KBr) 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.24 (d, 1 H, $J_{3,4}$ = 6 Hz, H-3), 8.13 (br d, 1 H, $J_{7,8}$ = 6 Hz, H-8), 7.82–6.94 (m, 14 H, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 324 (8, M·+), 105 (100).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.48; H, 4.94. Found: C, 81.29; H, 5.19.

Analytical Run. A solution of isoquinoline *N*-oxide (3.62 g, 25 mmol) and *N*-phenylbenzimidoyl chloride (5.1814 g) in 1,2-dichloroethane (65 ml) was boiled under reflux for 6 hr. The mixture was cooled to room temperature, then was transferred to a 100-ml volumetric flask and made up to volume with 1,2-dichloroethane. Exactly 4 ml of this solution was added to *n*-octadecane (0.05681 g, 2.24×10^{-4} mol) and the mixture washed with 10% potassium carbonate solution (2 × 5 ml), the aqueous phases were extracted with 1,2-dichloroethane (3 ml), the combined organic phases dried ($CaCl_2$) and analyzed by gas chromatography. The results are given in Table I.

1-(*N*-Benzoylanilino) isoquinoline. A solution of 1-anilinoisoquinoline[14] (1 g, 4.5 mmol) and benzoyl chloride (0.65 g, 4.6 mmol) in dry pyridine (5 ml) was boiled under reflux for 2 hr, poured into water (25 ml), and cooled to 0°. The insoluble crystalline material was filtered, then recrystallized from aqueous ethanol to give 1-(*N*-benzoylanilino) isoquinoline (0.44 g, 30%), mp 175–177°, whose infrared spectrum was indentical with that of the compound obtained as described above.

Reaction of Quinoline 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. (a) A solution of freshly distilled quinoline 1-oxide (2.42 g, 17 mmol) and 1,2-dichloroethane (50 ml) was added to freshly distilled *N*-phenylbenzimidoyl chloride (2.86 g, 13.3 mmol). An immediate exothermic reaction ensued. The mixture was boiled under reflux for 8 hr after which it was cooled and the solvent evaporated *in vacuo*. The residue (*ca.* 5.0 g) was dissolved in chloroform (30 ml), stirred with sodium bicarbonate for 1 hr, then chromatographed on silica gel (500 g) using a mixture of light petroleum–acetone (9:1 v/v) as eluent. Four main products were obtained. Eluting first was benzanilide (0.28 g, 12%).

Eluting second and overlapping slightly with benzanilide was 3-quinolyl benzoate (2.18 g, 33%): mp 59–60° (ethanol); ir (KBr) 1740 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.81 (d, 1 H, $J_{2,4}$ = 2.5 Hz, H-2), 8.28–8.04 (m, 3 H), 7.99 (d, 1 H, $J_{2,4}$ = 2.5 Hz, H-4), 7.8–7.54 (m, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 249 (4, M·+), 105 (100); identical with a sample prepared by benzoylation of 3-hydroxyquinoline in pyridine.

Eluting third with slight overlap with 3-quinolyl benzoate was **2-(*N*-benzoylanilino)quinoline** (1.28 g, 30%): mp 116–117° (ethanol); ir (KBr) 1645 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.95 (d, 1 H, $J_{3,4}$ = 9 Hz, H-4), 7.78–6.99 (m, 15 H); mass spectrum (70 eV) *m/e* (rel intensity) 324 (9, M·+), 105 (100).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.48; H, 4.94. Found: C, 81.60; H, 5.27.

The final product to elute was 2-anilinoquinoline (1.96 g, 33%): mp 101–102° (petroleum ether, bp 30–60°) [lit.[15] mp 98°]; ir (KBr) 3420 cm^{-1} (NH); nmr ($CDCl_3$) δ 7. 86–6.90 (m, aromatic protons), 6.82 (d, 1 H, $J_{3,4}$ = 9 Hz, H-3); mass spectrum (70 eV) *m/e* (rel intensity) 221 (8.9), 220 (59, M·+), 219 (100).

As the solvent polarity was increased (increasing the per cent of acetone) traces (<1%) of two other products were isolated. The first was found to be 3-hydroxyquinoline, mp 198–200° [lit.[16] mp 198°]. Its infrared spectrum was identical with that of an authentic sample. The second product was 2-hydroxyquinoline, mp 197–199° [lit.[17] mp 199–200°]. Its infrared spectrum was identical with that of an authentic sample.

(b) A mixture of quinoline 1-oxide (1.27 g, 8.8 mmol), *N*-phenylbenzimidoyl chloride (1.72 g, 8.0 mmol), and 1,2-dichloroethane (15 ml) was boiled under reflux for 6 hr. The solvent was removed *in vacuo*, 6 *N* HCl (10 ml) was added to the residue, and the resulting solution was boiled under reflux for 4 hr. On cooling, benzoic acid (0.69 g, 70%) precipitated. The filtrate was extracted with chloroform (3 × 10 ml). The organic extracts and the aqueous phase were then analyzed separately.

The organic phase was dried ($MgSO_4$), filtered, and the solvent removed. The residue was chromatographed on silica gel (100 g) using a light petroleum–acetone mixture (9:1 v/v) as solvent to yield benzanilide (0.36 g, 23%) and 2-anilinoquinoline (0.91 g, 50%).

The aqueous phase was cooled to 0°, and slowly neutralized with 20% NaOH solution. At pH 7, 3-hydroxyquinoline (0.34 g, 29%), mp 197–200° [lit.[16] mp 198°], precipitated.

3-Quinolyl *N*-Phenylbenzimidate. A solution of 3-hydroxyquinoline[16] (1.10 g, 7.6 mmol) in ethanol (10 ml) and a solution of *N*-phenylbenzimidoyl chloride (1.64 g, 7.6 mmol) in anhydrous ether (5 ml) were added in quick succession to a solution of sodium (0.18 g, 7.8 mmol) in ethanol (50 ml). The solution was stirred at room temperature for 12 hr, then the solvent was removed *in vacuo*. The residual oil was shaken with water (10 ml) and the water decanted. The oil was dissolved in ethanol, boiled with activated charcoal, filtered, and cooled to give **3-quinolyl *N*-phenylbenzimidate** (0.86 g, 35%): mp 114–115°; ir (KBr) 1660 cm^{-1} (C=N); mass spectrum (70eV) *m/e* (rel intensity) 324 (0.6, M·+), 180 (100).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.48; H, 4.94. Found: C, 81.28; H, 5.07.

Attempted Reaction of 3-Quinolyl *N*-Phenylbenzimidate with Quinoline 1-Oxide and Hydrogen Chloride. A solution of 3-quinolyl *N*-phenylbenzimidate (0.041 g, 0.126 mmol) and quinoline 1-oxide (0.055 g, 0.378 mmol) in 1,2-dichloroethane (10 ml) was boiled under reflux for 4 hr. After this period, thin-layer chromatography showed only starting materials to be present. A saturated solution of hydrogen chloride in 1,2-dichloroethane (3 ml) was added and the mixture boiled under reflux for 20 hr. At the end of this time thin-layer chromatography showed that other than starting material a trace amount of a third compound to be present. The mixture was stirred with anhydrous sodium carbonate (3 g) for 1 hr, the filtered solution was concentrated, and the products were separated by preparative thin-layer chromatography on silica gel (25 g, 40 × 20 × 0.085 cm) using pentane–acetone (9:1 v/v) as eluent. Three compounds were isolated after the preparative plate had been developed three times. The compound with highest R_f value was identified by its infrared spectrum as 3-quinolyl *N*-phenylbenzimidate (0.03 g, 75%). The second compound was isolated in such small amounts that only a mass spectrum could be obtained. The mass spectrum of this compound was very similar to that of 2-(*N*-benzoylanilino)quinoline. The final compound isolated was identified by its infrared spectrum as quinoline 1-oxide (0.037 g, 67%). No 2-anilinoquinoline or 3-quinolyl benzoate were detected.

Reaction of Quinoline 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Analytical Run. A solution of quinoline 1-oxide (6.335 g, 44 mmol) in 1,2-dichloroethane (25 ml) was added to *N*-phenylbenzimidoyl chloride (8.5801 g, 40 mmol) in 1,2-dichloroethane (25 ml) and the mixture was boiled under reflux for 6 hr. The solution was cooled to room temperature, the volume was measured and found to be 63.8 ml. Exactly 3 ml of this solution was added to *N*-

(*p*-tolyl)benzamide (0.1238 g, 5.87 × 10^{-4} mol) (internal standard), the solution was stirred for 3 hr with anhydrous sodium bicarbonate and then analyzed by gas chromatography.

2-(*N*-Benzoylanilino)quinoline. To a solution of 2-anilinoquinoline[15] (0.55 g, 2.5 mmol) in pyridine (3 ml) was added benzoyl chloride (0.36 g, 2.5 mmol) and the mixture boiled under reflux for 1 hr, cooled to room temperature, and water (20 ml) added. The precipitate was filtered and recrystallized from ethanol to give 2-(*N*-benzoylanilino)quinoline (0.53 g, 63%), mp 116–117°.

Reaction of Quinoline 1-Oxide with *N*-Phenylbenzonitrilium Hexachloroantimonate. Preparative Run. To a stirred suspension of *N*-phenylbenzonitrilium hexachloroantimonate (10.30 g, 0.02 mol) in 1,2-dichloroethane (20 ml) was added quinoline 1-oxide (3.2 g, 0.022 mol) in 1,2-dichloroethane (10 ml). An immediate exothermic reaction occurred and the nitrilium salt was consumed. The mixture was stirred at room temperature overnight and poured into a 10% aqueous sodium carbonate, the inorganic salts were filtered, the organic layer was separated, the aqueous solution was extracted with 1,2-dichloroethane (20 ml), and the solvent was evaporated. Half the residue was chromatographed on silica gel (200 g) using light petroleum–acetone (9:1 v/v) as eluent. The first product to elute was a small amount of a solid which, after recrystallization from ethanol, was shown to be *N,N'*-diphenylbenzamidine hydrochloride, mp 285–290° dec [lit.[18] mp 300°]. Its infrared spectrum was identical with that of an authentic sample.

Eluting second was an oil composed of at least two compounds. This oil was dissolved in anhydrous ether and dry hydrogen chloride was bubbled into solution until a precipitate began to form. The mixture was allowed to stand for 2 min then filtered. The precipitate was identified as *N,N'*-diphenylbenzamidine hydrochloride (0.16 g, 5%), mp 285–290° dec by comparison of its infrared spectrum with that of an authentic sample.

The above ether filtrate was washed with 10% sodium carbonate solution (2 × 20 ml), the organic phase was dried ($MgSO_4$) and filtered, and the ether was evaporated. The residue was recrystallized from light petroleum to yield 3-quinolyl benzoate (0.40 g, 16%), mp 59–60°, identical in all respects with an authentic sample.

The final product obtained was benzanilide (0.38 g, 19%).

The second half of the residue obtained from the reaction of quinoline 1-oxide with *N*-phenylbenzonitrilium hexachloroantimonate was added to 6 *N* HCl (10 ml) and boiled under reflux for 6 hr. The mixture was brought to pH 9 with sodium carbonate and extracted with chloroform (3 × 10 ml), the solvent was evaporated, and the residue was chromatographed on silca gel (200 g) using light petroleum–acetone (9:1 v/v) as eluent.

Eluting first was *N,N'*-diphenylbenzamidine (0.19 g, 7%), identified by comparison of its infrared spectrum with that of an authentic sample. The second product to be obtained was 2-anilinoquinoline (0.09 g, 4%), mp 101–102° (light petroleum, bp 30–60°). The final product obtained was 3-hydroxyquinoline (0.2 g, 14%).

Analytical Run. A solution of quinoline 1-oxide (0.638 g, 0.44 mmol) in 1,2-dichloroethane (5 ml) was added to a stirred suspension of *N*-phenylbenzonitrilium hexachloroantimonate (2.183 g, 0.42 mmol) in 1,2-dichloroethane (15 ml) and the resulting mixture was stirred at room temperature for 12 hr. The mixture was poured into 20% sodium carbonate solution (100 ml), the inorganic salts were filtered, the organic phase was separated, and the aqueous phase was washed with 1,2-dichloroethane (10 ml). The combined organic phases were dried ($MgSO_4$), filtered, concentrated to approximately one-half of their original volume, then analyzed by gas chromatography.

Reaction of 4-Nitroquinoline 1-Oxide with *N*-Phenylbenzimidoyl Chloride. A solution of 4-nitroquinoline 1-oxide (4.75 g, 0.025 mol) in 1,2-dichloroethane (30 ml) and *N*-phenylbenzimidoyl chloride (4.27 g, 0.02 mol) in 1,2-dichloroethane (20 ml) was heated under reflux for 6 hr. A portion (20 ml) of this solution (59 ml) was extracted with 10% sodium carbonate (2 × 15 ml), the solvent evaporated, and the residue chromatographed on silica gel (200 g, 4 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as eluent. Eluting first was benzanilide (1.15 g, 29%). An oily mixture containing several products was then obtained which could not be solved further by this method. Overlapping somewhat with this mixture was then eluted **4-chloro-3-quinolyl benzoate:** mp 115–116° (benzene–light petroleum); ir (KBr) 3075 (aromatic C-H), 1745 (ester C=O), 1600, 1495, 1450 (aromatic ring stretching), 1255, 1245 (C-O), 1275, 1225, 1215, 1185, 1145, 1140, 1080, 1060, 1025, 935, 915, 820, 755, 705 (monosubstituted aromatic), and 685 cm^{-1}; nmr ($CDCl_3$) δ 8.81 (s, 1 H, H-2), 8.56 (d, 1 H, $J_{7,8}$ = 8 Hz, H-8), 8.30–7.25 (m, 8H, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 285 (0.43), 284 (0.26), 283 (1.2), 181 (0.33), 105 (100).

Anal. Calcd for $C_{16}H_{10}ClNO_2$: C, 67.73; H, 3.55. Found: C, 68.13; H, 3.79.

The final product to elute was 4-chloroquinoline 1-oxide (0.068 g, 2%): mp 132–135° [lit.[19] mp 133–135°]; ir (KBr) 1300 cm^{-1} (N-O); nmr ($CDCl_3$) δ 8.86–8.73 (m, 1 H, H-8), 8.43 (d, 1 H, $J_{2,3}$ = 7 Hz, H-2), 8.25–8.15 (m, 1 H, H-5), 7.92–7.64 (m, 2H, H-6,7), 7.37 (d, 1 H, $J_{2,3}$ = 7 Hz, H-3).

The oily mixture was boiled under reflux for 4 hr with 4 *N* HCl (15 ml), and then basified with sodium carbonate. It was extracted with chloroform (3 × 10 ml), the chloroform was evaporated, and the residue was chromatographed on silica gel (150 g, 3 ft × 1.5 in.) using light petroleum–acetone (9:1 v/v) as eluent. Three products were obtained. Eluting first was 2-anilino-4-chloroquinoline (0.2 g, 4%): mp 161–162° (light petroleum) [lit.[7] mp 161°]; ir (KBr) 3285, 3220, 3180, 3145 cm^{-1} (NH); mass spectrum (70 eV) *m/e* (rel intensity) 256 (11), 255 (51), 254 (77), 253 (100), 252 (19), 219 (19), 218 (23), 217 (6), 216 (6), 190 (6), 165 (4), 164 (4), 163 (4), 162 (8), 128 (13), 127 (21), 126 (17), 115 (11), 114 (11), 110 (4), 109.5 (31), 109 (21), 108.5 (6.4), 101 (13), 100 (8), 99 (8), 96 (6), 95.5 (8), 95 (6), 91 (6), 90 (25), 89 (6), 88 (6), 77 (38), 76 (11), 75 (21), 74 (13), 66 (17), 65 (11), 64 (25), 63 (13), 57 (6), 55 (6), 52 (15), 51 (64), 50 (25), 44 (25), 43 (11), 44 (8), 40 (29), 39 (43), 38 (8), 37 (4), 36 (4).

The second compound to elute was 4-chloro-3-hydroxyquinoline: mp 205–207° (benzene) [lit.[20] mp 206–207°]; ir (KBr) 3150–2500 (br) (bonded OH), 1350, 1230 (OH deformation, C-O stretching), 1150, 835, and 755 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 181 (35), 179 (100), 152 (1.3), 150 (3.4), 143 (8), 115 (53).

Finally 4-chloroquinoline 1-oxide (0.04 g, 1%) eluted. Yields of all the above compounds were not determined accurately; however, with the exception of 4-chloro-3-quinolyl benzoate, all products were obtained in less than 10% yield. The total yield of 4-chloro-3-quinolyl benzoate was approximately 10%.

Reaction of 2,6-Dimethylpyridine 1-Oxide with *N*-Phenylbenzimidoyl Chloride. Preparative Run. A solution of 2,6-dimethylpyridine 1-oxide (2.70 g, 2.20 × 10^{-2} mol) in 1,2-dichloroethane (30 ml) was added to a solution of freshly distilled *N*-phenylbenzimidoyl chloride (4.2557 g, 1.98 × 10^{-2} mol) in 1,2-dichloroethane (20 ml) and the mixture heated under reflux for 24 hr. The mixture was cooled to room temperature, transferred to a 100-ml volumetric flask, and made up to volume with 1,2-dichloroethane. The products were isolated by preparative thin-layer chromatography on silica gel (25 g per 40 × 20 × 0.85 cm plate) using light petroleum–acetone (85:15 v/v) as eluent. Each plate was developed five times, then the products were extracted from the silica gel using acetone. Yields obtained from these preparative thin-layer separations were not calculated. Products are described in order, the fastest moving compound (highest R_f value) first, the slowest moving compound last.

The top band was found to be due to 3-chloro-2,6-dimethylpyridine: bp 174–176° [lit.[4] bp 175–176°]; nmr (CCl_4) δ 8.02 (AB quartet, 2 H, $J_{4,5}$ = 8 Hz, H-4,5), 2.46 (s, 3 H, 2-CH_3), 2.36 (s, 3 H, 6-CH_3); identical with an authentic sample.

The second band was due to 2-chloromethyl-6-methylpyridine: bp 90° (30 mm) [lit.[5] bp 81° (12 mm)]; nmr (CCl_4) δ 7.45 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ = 7.8 Hz, H-4), 7.15 (d, 1 H, $J_{3,4}$ = 7.8 Hz, H-3), 6.92 (d, 1 H, $J_{4,5}$ = 7.8 Hz, H-5), 4.51 (s, 2 H, CH_2Cl), 2.43 (s, 3 H, CH_3); identical with an authentic sample.

The component contained in the third band was recrystallized from light petroleum–acetone to give ***O*-3-(2,6-dimethylpyridyl)-*N*-phenylbenzimidate:** mp 129–130°; ir (KBr) 1660 (C=N), 1230 cm^{-1} (C-O); nmr (acetone-d_6) δ 8.00–6.90 (m, 12 H), 2.55 (s, 3 H, CH_3), 2.50 (s, 3 H, CH_3), mass spectrum (70 eV) *m/e* (rel intensity) 302 (0.53), 182 (1), 181 (16), 180 (100), 152 (1), 105 (4), 78 (4), 77 (50), 76 (2), 57 (1), 53 (4), 52 (2), 51 (17), 50 (3), 43 (1), 42 (2), 41 (1), 39 (2).

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.47; H, 5.96. Found: C, 79.31; H, 5.91.

The fourth component was benzanilide.

The sixth component was found to be 2,6-dimethylpyridine 1-oxide.

Quantitative Analysis. A mixture of 2,6-dimethylpyridine 1-oxide (2.70 g, 2.20 × 10^{-2} mol) and *N*-phenylbenzimidoyl chloride (4.2557 g, 1.98 × 10^{-2} mol) in 1,2-dichloroethane (50 ml) was boiled under reflux for 24 hr. The mixture was cooled to room temperature, transferred to a 100-ml volumetric flask, and made up to volume with 1,2-dichloroethane. Exactly 5 ml of this solution was added to *n*-octadecane (0.0688 g, 2.71 × 10^{-4} mol), the mixture was washed with 10% potassium carbonate (2 × 5 ml), the aqueous

phase was extracted with 1,2-dichloroethane (5 ml), and the combined organic phases were dried ($CaCl_2$) and analyzed by gas chromatography. The product yields are given in the Discussion section.

3-(2,6-Dimethylpyridyl)-*N*-phenylbenzimidate. To a solution of sodium ethoxide (0.28 g, 0.0035 mol) in absolute ethanol (10 ml) were added in quick succession 2,6-dimethyl-3-hydroxypyridine (0.43 g, 0.0033 mol) in absolute ethanol (10 ml) and distilled *N*-phenylbenzimidoyl chloride (0.70 g, 0.0033 mol) in dry ether (5 ml). The mixture was allowed to stand for 3 hr at room temperature then filtered through Celite filter-aid. The solvent was evaporated to give a crystalline material. Recrystallization from light petroleum–acetone gave 3-(2,6-dimethylpyridyl)-*N*-phenylbenzimidate (0.75 g, 75%), identical with the compound obtained above.

Acknowledgments. This work was carried out with the financial support of a National Institutes of Health grant (GM 16626) for which we are grateful. We also wish to thank Reilly Tar & Chemical Corp. for the gift of pyridine derivatives.

Registry No.—**1**, 1613-37-2; **2**, 53112-31-5; **3**, 5468-85-9; **4**, 32888-92-9; **7**, 32888-93-0; **10**, 32953-48-3; **11**, 2405-06-3; **12**, 3099-29-4; **14**, 32888-94-1; **15**, 4637-59-6; **17**, 32888-95-2; *N*-phenylbenzimidoyl chloride, 4903-36-0; *N*-phenylbenzonitrilium hexachloroantimonate, 51293-24-4; *o*-nitro-*N*-benzylformanilide, 53112-32-6; 2-anilino-1-benzylbenzimidazole, 24068-33-5; 1-anilinoisoquinoline, 13797-20-1; 3-hydroxyquinoline, 580-18-7; 4-nitroquinoline 1-oxide, 56-57-5; 4-chloro-3-hydroxyquinoline, 32435-60-2.

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Pyridazino[1,2-*a*]pyridazine Chemistry. An Attempted Synthesis of 1,6-Diazacyclodecapentaene

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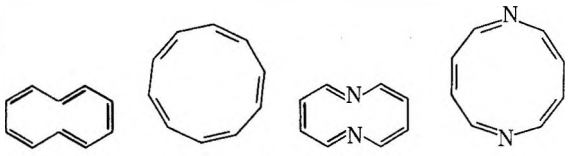
Some new derivatives of the pyridazino[1,2-*a*]pyridazine ring system have been prepared and their chemistry has been studied as possible synthetic precursors to 1,6-diazacyclodecapentaene.

Several years ago it was suggested[1] that the destabilizing effect[2a] of interior nonbonded hydrogen repulsion in *trans,trans*-cyclodecapentaene (**1a**) could be avoided in *trans,trans*-1,6-diazacyclodecapentaene (**2a**). It was felt



1a **1b** **2a** **2b**

3 **4**

that interaction between electron pairs on nitrogen in **2a** might not be serious and therefore the molecule might possibly exist in a nearly strain-free planar configuration. Furthermore, differences in bond angle requirements for the carbon–nitrogen bonds might be sufficient to enable the *all-cis*-1,6-diazacyclodecapentaene (**2b**) to exist as a stable planar species as opposed to the all carbon system **1b**.[2a,b]

The above considerations, as related to obtaining a monocyclic 10π-electron system exhibiting aromatic stability, indicated **2** to be an interesting synthetic objective.

Results and Discussion

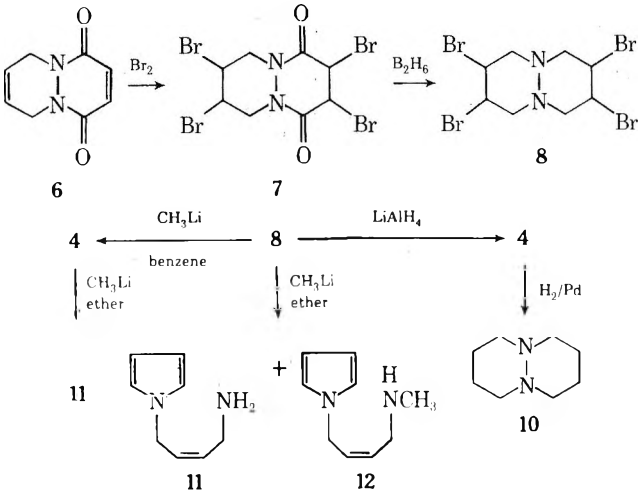
Consideration of various synthetic approaches to **2** suggested a "valence-bond"[3] route as an attractive possibility. Accordingly, the synthetic objective was reduced to one of devising a suitable method for the preparation of the unknown pyridazino[1,2-*a*]pyridazine (**3**).

Scrutiny of the literature reveals no known derivatives of ring system **3**; indeed, even saturated derivatives of **3** have been little studied.[4] A reasonable synthetic path appeared to be to prepare a partially saturated derivative of **3** (*e.g.*, **4**) and introduce the additional unsaturation *via* a halogenation–dehydrohalogenation sequence.

The readily available dihydropyridazino[1,2-*a*]pyridazinedione **6**[5] appeared an obvious precursor to **4** if reduction of the hydrazide function to the corresponding hydrazine could be carried out. In practice, this was accom-

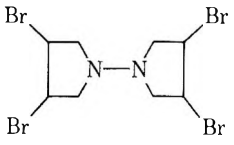
plished by first protecting the troublesome α,β-unsaturated system in **6** followed by reduction (Scheme I).

Scheme I



Treatment of **6** in chloroform with 2 equiv of bromine at room temperature led to the tetrabromo derivative **7** in high yield as evidenced by the elemental analysis, correct molecular weight by mass spectroscopy, and the nmr spectrum, which exhibited a sharp singlet at δ 5.05 assignable to the equivalent protons α to the hydrazide carbonyl groups.

Reduction of **7** with diborane in boiling tetrahydrofuran[6] gave **8** in 60% yield as a white crystalline solid, probably a mixture of bromo isomers. The formulation of **8** as the desired tetrabromoperhydropyridazino[1,2-*a*]pyridazine and not as the isomeric *N,N'*-bispyrrolidine ring system (*e.g.*, **9**)[7] followed from chemical degradation studies. Thus, pro-



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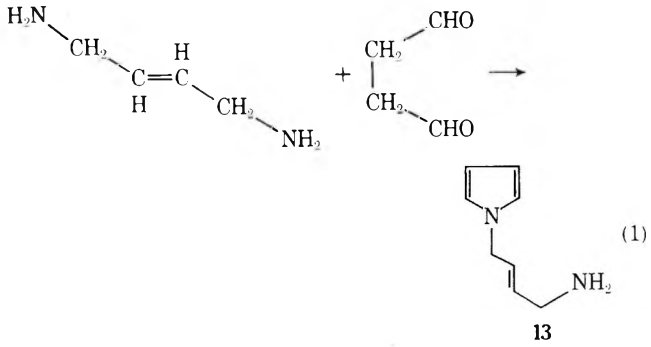
longed treatment of **8** with lithium aluminum hydride in boiling tetrahydrofuran gave a liquid product assigned structure **4** (see below).[8] Catalytic hydrogenation of this product at room temperature and atmospheric pressure gave perhydropyridazino[1,2-*a*]pyridazine (**10**) which had identical ir and nmr spectra and picrate melting point with those of an authentic sample.[9] In addition, the nmr spectrum of authentic[10] *N,N'*-bispyrrolidine was different from the spectrum of **10** obtained from **8** *via* **4**. These results established that no rearrangement[7] of the pyridazino[1,2-*a*]pyridazine ring system had taken place either during the bromination of **6** or the reduction of **7** to **8**.

The last step in the proposed synthetic sequence, the elimination of four molecules of hydrogen bromide from **8** in hopes of producing the desired **3**, unfortunately, proved completely frustrating. Treatment of **8** with a variety of bases in various solvents under nitrogen resulted in either no reaction (*e.g.*, boiling triethylamine, bis(1,8-dimethylamino)naphthalene in boiling tetrahydrofuran) or black, intractable tars (potassium *tert*-butoxide in tetrahydrofuran, sodium amide in liquid ammonia, sodium isopropoxide in tetrahydrofuran). Boiling a solution of **8** and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in tetrahydrofuran for several hours under nitrogen gave intractable dark mixtures, whereas limiting the reaction to shorter periods gave mixtures of partially brominated products. When these mixtures were treated again with DBU, dark products were obtained from which no identifiable materials could be isolated.

In contrast to the above results, treatment of a suspension of **8** in ether with ethereal methyllithium under nitrogen gave a rapid reaction. Work-up with water and separation of the mixture by vpc gave two products assigned structures **11** and **12** on the basis of the following lines of evidence. First, mass spectroscopy established a molecular formula of $C_8H_{12}N_2$ and $C_9H_{14}N_2$ for **11** and **12**, respectively. In addition, the cracking patterns of both compounds were very similar with fragments in **12** that suggested an $NHCH_3$ group.

Second, the nmr spectra of the two compounds were essentially identical except for the presence in **12** of a sharp three-proton singlet in the region expected for an $NHCH_3$ (δ 2.42). A characteristic AA'XX' pattern in both compounds suggested an N-substituted pyrrole derivative, whereas absorptions attributable to two different allylic methylene groups and two vinyl protons were clearly recognizable in kind and number (see Experimental Section).

Finally, synthesis of a model compound[11] was carried out, eq 1. Addition of an aqueous solution of succindial-



(1)

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dehyde to *trans*-2-butene-1,4-diamine[11,12] gave **13** in low yield. Spectral data clearly established the similarity between **11** and **13**. For example, the nmr spectrum of **13** was very similar to that of **11** with only small differences (see Experimental Section) in chemical shift and coupling constants of the vinyl and allylic methylene protons, attributable to different stereochemistry about the double bond.[14] The above observations establish a cis stereochemistry about the double bond in **11** and **12**.

That **12** arises as a secondary product from **11** (or precursor to **11**) during the reaction was established from consideration of the intermediate in the rearrangement (see below) and the fact that varying reaction conditions dramatically affected the ratio of **11** and **12** in the product mixture. For example, when the reaction between **8** and methyllithium was carried out at room temperature with a stream of nitrogen passing through the solution, much less **12** than **11** was produced. On the other hand, running the reaction in a closed system led to a marked increase in the yield of **12** relative to **11**. These results point to the formation of **12** *via* methylation of a nitrogen anion of **11** (or precursor to **11**) by methyl bromide produced from initial metal–halogen exchange between **8** and methyllithium in the early stages of the reaction.

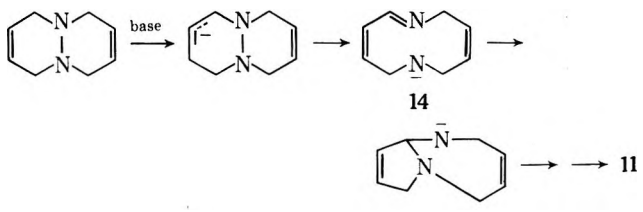
When a benzene suspension of **8** was treated with ethereal methyllithium, a single new product was obtained which proved identical with the product previously obtained from $LiAlH_4$ reduction of **8**, *i.e.*, **4**. The structure of **4** followed from the previous hydrogenation results giving the known perhydropyridazino[1,2-*a*]pyridazine and the fact that the nmr spectrum of **4** showed only a broadened singlet (δ 5.55) assignable to the vinyl hydrogen and a broad multiplet (δ 3.6–2.8) for the remaining allylic hydro-

gens. This nmr spectrum is consistent only with the symmetrical disposition of double bonds indicated in **4**.

That **4** is an intermediate in the formation of **11** (and ultimately **12**) was established by the fact that pyrrole **11** was readily produced when an ether solution of **4** was treated with methyllithium. Furthermore, when the reaction between **8** and methyllithium in ether was interrupted after short reaction time, nmr and vpc analysis definitely established the presence of **4** in the reaction mixture.

While there exists no direct experimental evidence regarding the mechanism of the rearrangement of diene **4** to pyrrole **11**, a possibility is outlined in Scheme II.

Scheme II



It is interesting to compare the proposed cyclization of anion **14** to the cyclization step in the generally accepted mechanism of the classical Fischer indole synthesis;[15] the overall driving force for both rearrangements, of course, is related to the formation of pyrrole rings.

Experimental Section[16]

2,3,7,8-Tetrabromoperhydropyridazino[1,2-*a*]pyridazine-1,4-dione (7). To a solution of 10.7 g (0.065 mol) of 6,9-dihydropyridazino[1,2-*a*]pyridazine-1,4-dione (**6**)[5] in 200 ml of chloroform cooled in a water bath was added dropwise a solution of 20.8 g (0.13 mol) of bromine in 50 ml of chloroform. The resulting mixture was stirred at room temperature for 2 days. After this time the yellow solution was filtered from a small amount of insoluble solid and the solvent was removed under reduced pressure leaving 30.7 g (98%) of yellow solid, mp 164–166°. Recrystallization of a small portion from a minimum volume of chloroform gave an analytical sample: mp 181–183° dec; ir (KBr) 5.97 μ (C=O); mass spectrum *m/e* 480 (M^+), 401 (M − Br).

Anal. Calcd for $C_8H_8Br_4N_2O_2$: C, 19.9; H, 1.67; N, 5.77; Br, 66.1. Found: C, 19.6; H, 2.0; N, 5.7; Br, 66.0.

2,3,7,8-Tetrabromoperhydropyridazino[1,2-*a*]pyridazine (8). To a slurry of 10.0 g (0.021 mol) of **7** in 50 ml of tetrahydrofuran was added 55 ml (0.055 mol) of commercially available 1 *M* borane in tetrahydrofuran. The mixture was stirred and refluxed under nitrogen for 30 min and cooled, and 10 ml of 6 *N* hydrochloric acid was carefully added. The acidic reaction mixture was then refluxed for 4 min and then concentrated to about one-quarter volume under reduced pressure. The white solid was collected, washed well with a large volume of water, and dried. A white product was obtained: 5.8 g (60%); mp 198–199° dec. An analytical sample was prepared by recrystallization from tetrahydrofuran: mp 210–211° dec; mass spectrum *m/e* 452 (M^+), 373 (M − Br).

Anal. Calcd for $C_8H_{12}Br_4N_2$: C, 21.1; H, 2.65; N, 6.14; Br, 70.1. Found: C, 20.9; H, 2.8; N, 5.9; Br, 69.8.

Reaction of 8 in Benzene With Methyllithium. To 300 ml of benzene under nitrogen was added 44 ml (0.088 mol) of 2 *M* methyllithium in ether. To this stirred mixture was added all at once 9.12 g (0.02 mol) of **8**. The reaction mixture was stirred at room temperature for 2 hr under nitrogen, after which 40 ml of water was added. The clear benzene layer was separated, dried over anhydrous calcium sulfate, and concentrated by distillation through a 6-in. Vigreux column. The residue was distilled under reduced pressure giving 1.1 g (41%) of **4** as a colorless liquid: bp 72–75° (4 Torr); nmr (CCl_4) δ 5.55 (br s, 4 H), 3.6–2.8 (br m, 8 H); mass spectrum *m/e* 136 (M^+). A yellow monopicrate was prepared in the usual manner, mp 138–139° (from methanol).

Anal. Calcd for $C_{14}H_{15}N_5O_7$: C, 46.0; H, 4.14; N, 19.2. Found: C, 46.1; H, 4.2; N, 19.2.

Reaction of 8 with Lithium Aluminum Hydride in Tetrahydrofuran. To a slurry of 2.0 g of $LiAlH_4$ in 200 ml of tetrahydrofuran was added all at once 2.28 g (0.005 mol) of **8**. The mixture was heated at reflux for 72 hr and cooled, and 1 ml of water was carefully added followed by 1 ml of 15% aqueous sodium hydroxide solution and then 2 ml of water. The precipitate was removed by filtration and the clear tetrahydrofuran filtrate was dried over anhydrous calcium sulfate. The solvent was removed by distillation leaving a colorless liquid residue. Nmr analysis showed only absorptions attributable to **4** (in addition to butanol). A small sample of the material was treated with ethanolic picric acid giving a yellow picrate, mp 136–138°, with ir spectrum identical with that of the picrate of **4** prepared above. A sample of **4** in ether was hydrogenated at room temperature and atmospheric pressure over 10% palladium on carbon. Concentration of the filtered ether solution gave a colorless liquid with ir and nmr spectra identical with those of an authentic sample[9] of perhydropyridazino[1,2-*a*]pyridazine, picrate mp 152–153° (lit.[9] mp 155°).

Reaction of 8 in Ether with Methyllithium. A slurry of 4.56 g (0.01 mol) of **8** in 15 ml of dry ether was cooled in an ice bath under nitrogen. To this stirred slurry was added dropwise 30 ml (0.06 mol) of 2 *M* methyllithium in ether. The solid material slowly dissolved. The reaction mixture was stirred an additional hour after all the solid had dissolved and then water was carefully added. The ether layer was separated, dried over anhydrous calcium sulfate, and concentrated to an oil. The crude product was separated into two major components by preparative vpc (5 ft × 0.25 in. 15% SE-30 on Anakrom ABS) at 130°. The first component (**11**) was collected as a colorless liquid: nmr ($CDCl_3$, 90 MHz) δ 6.64 (t, 2 H), 6.15 (t, 2 H), 5.67 (m, 2 H), 4.53 (d, 2 H), 3.40 (d, 2 H), 1.24 (s, 2 H (exchangeable)); mass spectrum *m/e* calcd for $C_8H_{12}N_2$, 136.1000; found, 136.1013. The second component (**12**) also was a colorless liquid: nmr ($CDCl_3$, 90 MHz) δ 6.64 (t, 2 H), 6.15 (t, 2 H), 5.71 (m, 2 H), 4.55 (d, 2 H), 3.31 (d, 2 H), 2.42 (s, 3 H), 1.40 (s, 1 H (exchangeable)); mass spectrum *m/e* calcd for $C_9H_{14}N_2$, 150.1157; found, 150.1169.

Reaction of *trans*-2-Butene-1,4-diamine with Succindialdehyde. Preparation of 13. An aqueous solution containing 0.0025 mol of succindialdehyde[17] was added dropwise to a solution of 0.215 g (0.0025 mol) of *trans*-2-butene-1,4-diamine[13] in 10 ml of water at room temperature. The mixture was stirred for 30 min and then filtered from a solid which had formed. The filtrate was extracted with ether. The combined dried ether extracts were concentrated to an oil, 0.049 g, which was purified by preparative vpc (5 ft × 0.25 in. 15% SE-30 on Anakrom ABS) at 140° to give **13** as a colorless liquid: nmr ($CDCl_3$, 90 MHz) δ 6.64 (t, 2 H), 6.15 (t, 2 H), 5.73 (m, 2 H), 4.46 (m, 2 H), 3.31 (m, 2 H), 1.21 (br s, 2 H (exchangeable)); mass spectrum *m/e* calcd for $C_8H_{12}N_2$, 136.1000; found, 136.0986.

Acknowledgment. The author wishes to thank Mr. D. P. Maier and Dr. T. H. Regan of these laboratories for assistance in obtaining and interpreting mass spectral and nmr data, respectively.

Registry No.—**4**, 38704-81-3; **4** monopicrate, 53166-04-4; **6**, 3661-09-4; **7**, 53166-05-5; **8**, 53166-06-6; **11**, 53166-07-7; **12**, 53166-08-8; **13**, 53166-09-9; *trans*-2-butene-1,4-diamine, 40930-37-8; succindialdehyde, 638-37-9; methyllithium, 917-54-4; lithium aluminum hydride, 16853-85-3.

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A Novel Synthesis of 8-Aza Steroids[1]

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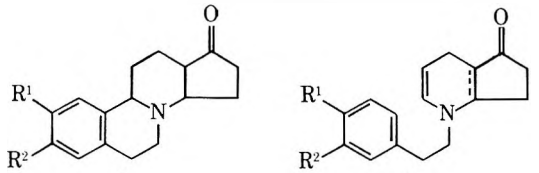
A general synthesis of A-aromatic 18-nor-8-aza steroids have been demonstrated from the enamine of a β-arylethylamine and 1,3-cyclopentandione. The C-ring atoms were introduced by reaction of the enamine with β-propiolactone. Cyclization to form the B ring occurred with redox dispropionation to give an 8-aza steroid with the C-ring aromatic (**7**) and the C ring in the tetrahydro state (**9**). Reductions of **7** and **9** were investigated to form the trans-anti-cis isomer of 2,3-dimethoxy-18-nor-8-azaesterone (**13**). The reaction of **9** with electrophiles occurred at oxygen.

The potential of heterocyclic analogs of the cyclopentanophenanthrenes to function as steroidal antagonists or antimetabolites has prompted an interest in the synthesis of many nitrogen heterocycles as aza or diaza steroids.[2-6] Except for the preparation of 8-aza steroids by Brown and coworkers,[5a] the syntheses usually involve the formation of the 8–14 and/or 12–13 bond(s) in an intermediate having preformed A, B, and D rings. In order to provide for the possibility of introducing 11 and 12 substituents in an 8-aza steroid nucleus, a study was made of synthetic approaches to 8-aza steroids (**1**) *via* formation of the 9–10 bond with an intermediate having preformed A, C, and D rings (**2**).

A logical intermediate for forming the 9–10 bond of an 8-aza steroid, based on the enamine nature of dihydro-[7] and tetrahydropyridines,[8] is the reduced form of 1-(2-arylethyl)-5-pyrindanone salt (**3a**). The 5-pyrindanone (**3b**) was prepared by oxidation of pyrindan (**4**)[9] by buffered po-



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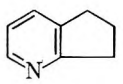

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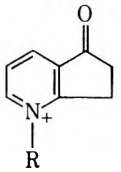
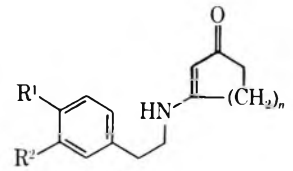


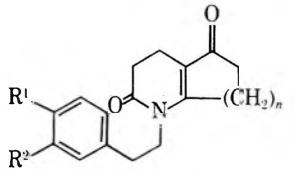
3a. R = $ArCH_2CH_2$
b. R = H

tassium permanganate.[10] This 5-pyrindanone,[11a] unlike the isomeric 7-pyrindanone, prepared from 7-pyrindanol,[11b] showed no evidence of existing as the enolic tautomer. Quaternary salt formation proved to be difficult, because the electron attraction of the 3-carbonyl and steric interference of the α-methylene had the effect of reducing the nucleophilicity of the heterocyclic nitrogen. The competing reaction, dehydrohalogenation of the arylethyl halide, was a serious side reaction. As a result this approach was abandoned.

The synthesis of a similar intermediate which could be used to prepare 11- and/or 12-substituted 8-aza steroids was investigated using a modification of the route of Brown and coworkers[5a] and Nagata and Castle and coworkers.[2] The reaction of methoxylated β-arylethylamines with 1,3-cyclohexadione and 1,3-cyclopentadione gave quantitative yields of enamino ketones (**5**). The vinylogous amide of the



5a, $R^1 = R^2 = CH_3O$; $n = 1$
b. R^1 = H; $R^2 = CH_3O$; $n = 1$
c. $R^1 = R^2 = CH_3O$; $n = 2$



6a, $R^1 = R^2 = CH_3O$; $n = 1$
b. R^1 = H; $R^2 = CH_3O$; $n = 1$
c. $R^1 = R^2 = CH_3O$; $n = 2$

enamine system of **5** decreases the nucleophilicity of the enamine, and similar systems undergo alkylation largely on oxygen.[12] Thus the choice of the 3-carbon molecule with which to form the C ring was complicated, for the cyclization must occur with formation of a functional group capable of undergoing 9–10 bond formation to form the B ring.

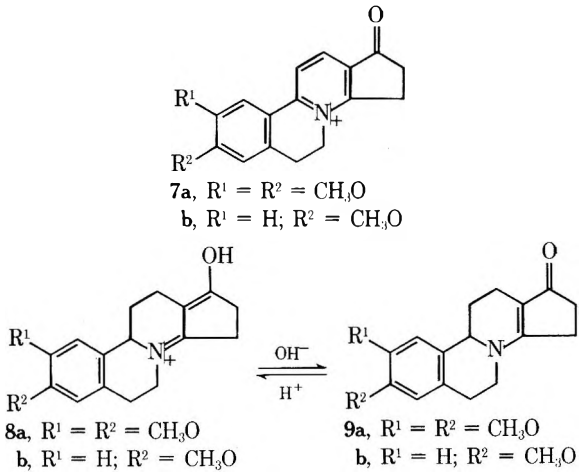
The logical reagent to accomplish this result would be a derivative of acrylic acid in view of the success of this route in the synthesis of lycopodium alkaloids.[13] Acrylonitrile or ethyl acrylate gave no reaction with **5c**. This is surprising in view of the successful reaction of acrylonitrile with comparable systems.[5a] The use of the more reactive acrolein or acrolein dimethyl acetal also failed to undergo reaction. Dimethyl acetylenedicarboxylate gave a reaction with **5c**; however, the product contained more than one of the acetylenic moieties. As might have been predicted from the work of Meyers and coworkers,[3,5] the reaction of **5c** with β-chloropropionic acid did not occur.

The reaction of a limited number of enamines with β-propiolactone was reported to give the substituted propioamide.[14] This suggested that the alkylation of **5c** would

occur with subsequent cyclization to form the desired intermediate **6c**. Reaction did not occur at the reflux temperature of benzene or toluene; however, with chlorobenzene as solvent **5c** gave a moderate yield of **6c**. The isolation of the product was improved by using xylene as solvent. Comparable results were obtained from the reaction of **5a** and **5b** with β-propiolactone, giving good yields of **6a** and **6b**. The dihydropyridone structures for **6a–c** were conclusively evident from the spectral data.

The cyclodehydration reaction of **6a–c** to form the bisnor-8-aza steroids appeared to be analogous to the cyclization used by Meltzer and coworkers to form aza steroids.[5a] However, the reaction of **6a** with polyphosphoric acid gave a high yield of product which was shown by proton magnetic spectrum to be a mixture of two aza steroids. Separation of the two products by precipitation of the perchlorate from acetonitrile–ethanol gave, as the more insoluble material, the A,C-bisaromatic-8-aza steroid (**7a**). The aromatic nature of the heterocyclic ring was clear from the presence of an AB quartet at 9.0-ppm downfield from TMS in the pmr spectrum, and the orientation of the cyclization to give the 2,3-dimethoxy rather than the 3,4-dimethoxy-8-aza steroid was indicated by the sharp singlets for the protons attached to the oxygenated aromatic ring. The formation of this pyridinium derivative required that dehydrogenation as well as cyclodehydration had occurred. This suggested that the second product should be in the oxidation state of a tetrahydropyridine. Evaporation of the solvent from the isolation of **7a** gave an oil which was crystallized. This soluble salt was shown to have the structure **8a** by spectral analysis. Treatment of the salt with base gave the enamino ketone **9a**, which was protonated on oxygen by perchloric acid to give **8a**, identical with the original material.

Protonation of enamino ketones on treatment with acid has been reported with a number of aza steroids.[15–18] The properties reported for these compounds compare well with those observed for **8a** and **8b**.

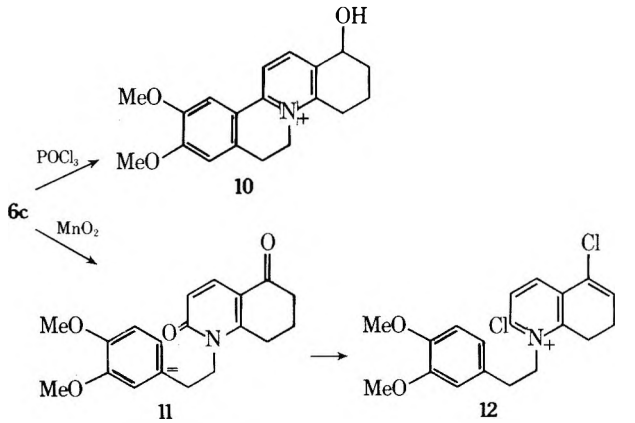


The relative yields of the two cyclization products **7a** and **8a** did not vary with the reaction time for the ratio of 1 to 1 was observed at 80% completion, complete reaction, and two times the reaction time for complete reaction. This suggests that two molecules of an intermediate cyclization product, probably a dihydropyridine, undergo disproportionation to form **7a** and **8a** and argues against the possibility that **7a** or **8a** could be the intermediate in the formation of the other. These results are similar to those described in the synthesis of partially reduced lepidine by cyclization.[19] No evidence for a dihydrointermediate could be obtained for the cyclization.

The reaction of **6b** with polyphosphoric acid also gave two products (**7b** and **8b**) in a ratio of 1 to 1 resulting from disproportionation of the intermediate. The position of cyclization was para to the methoxy group to give 8-aza steroids, **7b** and **8b**, with a 3-methoxy substituent as was shown by the nmr spectra of the aromatic protons of **7b** and **8b**.

The decomposition of the intermediate dihydropyridine, formed by the cyclodehydration of **6c** with phosphorus oxychloride, apparently took a different course. A single product was detected and had the properties of a quaternary salt. The spectral data of the product were consistent with structure **10** in which the carbonyl group was reduced as the dihydropyridine underwent oxidation.

In an effort to avoid the complications of the oxidation–reduction reaction, the dihydropyridone of **6c** was oxidized to the pyridone **11** which was then subjected to cyclodehydration conditions. The oxidation of **6c** was caused most conveniently by activated manganese dioxide. No reaction of **11** was observed with phosphorus oxychloride in a solvent; however, using the reagent itself as solvent gave a dichloro derivative, **12**. Cyclodehydration of **11** by other re-

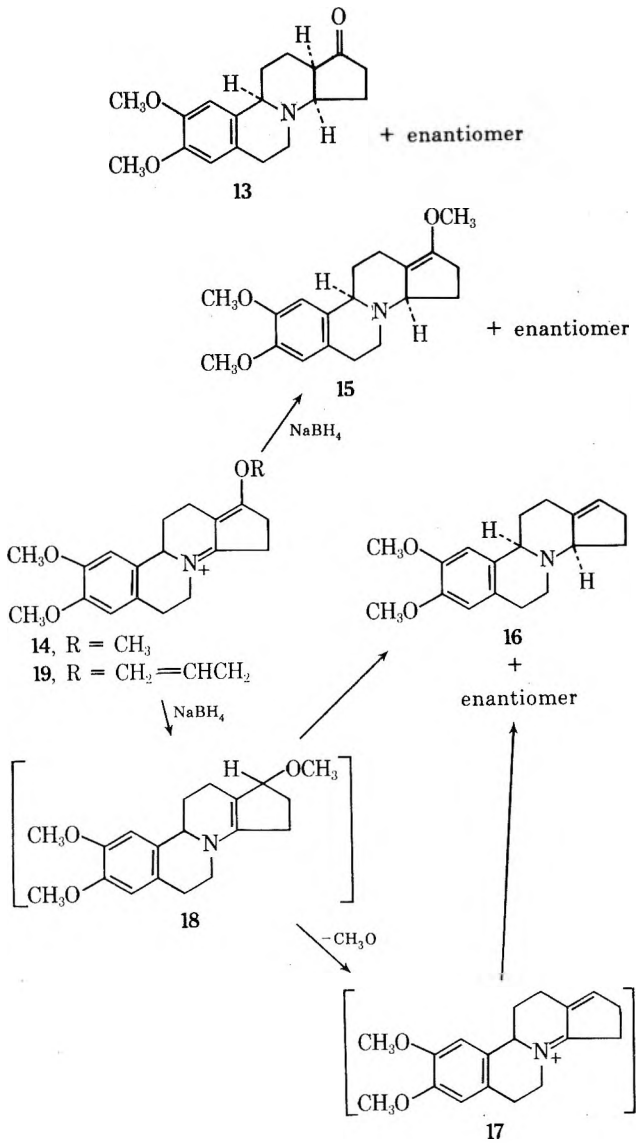


agents or cyclodehydrohalogenation of **12** failed and the synthesis of D-homo-8-aza steroids by this route was not investigated further.

The reactions of the A,C-bisaromatic-8-aza steroids **7a** and **7b** and the tetrahydro derivatives **8a** and **8b** were studied as a means for preparing other 8-aza steroid derivatives. The pyridinium ring C of **7a** or **7b** should provide a reactive site for reduction by hydrogenation[20] or complex metal hydrides[21] or addition of cyanide.[22] The catalytic hydrogenations gave no reaction and sodium borohydride reduction of **7a** gave a small yield of **8a**. Addition of cyanide appeared to give formation of a dimer related to viologen.[23]

The reduction of the salt **8a** with hydrogen over catalysts or by complex metal hydrides gave only **9a** on work-up. The reduction of **9** with lithium aluminum hydride did give saturation of the 13–14 double bond, for the infrared spectrum of the product **13** gave the carbonyl stretching vibration at 1740 cm^{-1} indicating the absence of conjugation. The appearance of Bohlmann bands at 2810 and 2890 cm^{-1} in the infrared spectrum[24] and the comparison of the pmr spectrum with related aza steroids[25] allowed the assignment of the trans-anti-cis stereochemistry to the product, 2,3-dimethoxy-1,3,5(10)-triene-8-azagonan-17-one (**13**).[26]

The alkylation of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) was investigated as a means for preparing other 8-aza steroids. The enamino ketone system of **9a** has three possible sites for reaction with electrophiles; however, in view of the exclusive reaction with protons at oxygen, alkylation of **9a** should also occur at oxygen to give **14**. The cisoid enamino ketones have been reported to give reaction at either carbon or oxygen depending on the solvent.[12] The reaction of **9a** with methyl iodide gave a high



yield of the *O*-methyl salt, **14**. The spectral properties of **14** were quite similar to those of the proton salt **8a** and supported the structural assignment of **14**.

The immonium bond of **14** would be expected to undergo reduction to give **15**, the enol ether of **13**. Treatment of **14** with hydrogen over palladium gave no reaction; however, reaction of **14** with sodium borohydride gave two products, **15** and **16**. The spectral data of **15** showed that it was the enol ether of **13**. The strong Bohlmann bands observed in the infrared spectrum of **15** provided evidence for the trans-anti stereochemistry for the **9**, **13**, and **14** positions.

The nmr spectrum of **16** provided the best clue of the structure of this unexpected product. Only two *O*-methyl signals were observed and a signal characteristic of a vinyl proton was evident. These results in conjunction with the other spectral data suggested that **16** was formed by reduction of the immonium bond and reductive cleavage of the 17-methoxyl goup. The loss of the methoxyl group may occur by an elimination reaction to form **17** or reductive cleavage of the allylic methoxyl group of **18** may give **16** directly.

The alkylation of **13** with allyl halides or tosylate proved to be more difficult than methylation; however, heating **13** with neat allyl bromide under reflux gave the O-alkylated product in moderate yield. No C-alkylated product was detected. Attempts to cause a Claisen-type rearrangement of the vinyl allyl ether[27] by heating **19** gave only the dealkylated product **13**.

Experimental Section

Melting points were determined using a Thomas-Hoover Capillary Melting Point apparatus or a Mel-Temp Apparatus and were not corrected for thermometer stem exposure. Elemental analyses were determined using an F and M Model 185 C, H, and N analyzer. Infrared spectra were determined using Perkin-Elmer Model 137 or 337 spectrometers with samples prepared as mulls or KBr pellets. The ultraviolet absorption spectra were measured on a Cary 15 spectrometer in the solvent indicated, and the nuclear magnetic resonance spectra were determined using a JEOL Model MH-100 spectrometer.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-3-aminocyclopent-2-en-1-one (5a). To a one-neck, 500-ml, round-bottom flask, equipped with a Dean-Stark trap and a condenser, were added 10.0 g (55.3 mmol) of β-3,4-dimethoxyphenethylamine, 5.0 g (51.0 mmol) of 1,3-cyclopentanedione, and 250 ml of dry benzene. The suspension was stirred magnetically and heated under reflux until the theoretical amount of water was collected (*ca.* 2–3 hr). At this time the reaction was homogeneous. The solvent was removed under reduced pressure and the resulting solid was triturated with anhydrous ether to give, on filtration, 13.1 g (98.3%) of *N*-(β-3,4-dimethoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5a**) as an off-white solid: mp 125–128°; pmr ($CDCl_3$) δ 6.61 (broad, 1 H), 6.58 (s, 3 H), 4.87 (s, 1 H), 3.73 (s, 6 H); ir (KBr) 1560 (C=O), 3180 (NH) cm^{-1}; uv (95%, C_2H_5OH) 229 (log ε 3.96), 271 nm (log ε 4.56).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.82; H, 7.20; N, 5.19.

Preparation of *N*-(β-3-Methoxyphenethyl)-3-aminocyclopent-2-en-1-one (5b). Following the procedure for the preparation of **5a**, 3.0 g (19.8 mmol) of β-3-methoxyphenethylamine, 1.94 g (19.8 mmol) of 1,3-cyclopentanedione, and 50 ml of dry benzene were converted to 4.5 g (98.5%) of *N*-(β-3-methoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5b**): mp 104–106°; pmr ($CDCl_3$) δ 7.27 (m, 1 H), 7.13 (m, 1 H), 6.9–6.65 (m, 3 H), 4.98 (s, 1 H), 3.75 (s, 3 H), 3.65–3.2 (m, 2 H), 2.87 (t, 3 H, *J* = 6.5 Hz), 2.7–2.1 (m, 4 H); ir (KBr) 1570 (C=O), 3190 (NH) cm^{-1}; uv max (95% C_2H_5OH) 271 nm (log ε 4.498).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.91; H, 7.42; N, 5.98.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-3-aminocyclohex-2-en-1-one (5c). Using the procedure for the preparation of **5a**, 36.2 g (0.20 mol) of 3,4-dimethoxyphenethylamine, 22.4 g (0.20 mol) of 1,3-cyclohexanedione, and 500 ml of dry benzene gave 55.0 g (100%) of *N*-(β-3,4-dimethoxyphenethyl)-3-aminocyclohex-2-en-1-one (**5c**) which on recrystallization from xylene melted at 116 to 119°: pmr ($CDCl_3$) δ 6.75 (m, 3 H), 5.80 (broad, N-**H**), 5.14 (s, 1 H, vinyl), 3.88 (s, 6 H, OCH_3); ir (KBr) 1575 (C=O) and 3180 (NH) cm^{-1}; uv max (95% C_2H_5OH) 229 (log ε 3.914), 288 nm (log ε 4.538).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.74; H, 7.58; N, 4.86.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (6a). A solution of 100.0 g (0.38 mol) of *N*-(β-3,4-dimethoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5a**), 150 g (2.08 mol) of β-propiolactone, and 3 l. of chlorobenzene was heated under reflux for 7 days. Every 24 hr 200 ml of chlorobenzene was distilled off to remove any water formed from the reaction and was replaced by an equal amount of dry chlorobenzene. The solvent was removed under reduced pressure and the resulting red oil was chromatographed on neutral alumina and eluted with ethyl acetate. Evaporation of the ethyl acetate under reduced pressure gave a solid which was recrystallized from 2-propanol to give 81.5 g (67.5%) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (**6a**): mp 156–158°; pmr ($CDCl_3$) δ 6.74 (m, 3 H), 3.88 (m, 8 H); ir (KBr) 1640 (C=O pyridone), 1680 (C=O, conjugated) cm^{-1}; uv max (95% C_2H_5OH) 228 (log ε 4.1), 286.5 nm (log ε 4.2).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.64; H, 6.78; N, 4.43.

Alternatively the reaction could be run using a mixture of xylenes as the solvent. In this case the water was removed with a Dean-Stark trap, the reaction time was decreased to 20 hr, and a slightly larger excess of β-propiolactone was used (approximately 15%). Under these conditions the yields of **6a** varied from 41 to 50%.

Preparation of *N*-(β-3-Methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (6b). Following the procedure for the synthesis of **6a**, except for decreasing the frequency of removing the chlorobenzene–water azeotrope to every 3 days, 4.0 g (17.35

mmol) of *N*-(β-3-methoxyphenethyl)-3-aminocyclopent-2-en-1-one (**5b**), 4.0 g (55.5 mmol) of β-propiolactone, and 125 ml of chlorobenzene were converted to 3.4 g (68.8%) of *N*-(β-3-methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (**6b**): mp 119–120°; pmr ($CDCl_3$) δ 3.82 (t, 2 H, J = 7.0 Hz), 3.74 (s, 3 H), 2.87 (t, 2 H, J = 7.0 Hz), 2.33 (s, 4 H); ir (KBr) 1620 (C=O, pyridone), 1670 (C=O, conjugated) cm^{-1}; uv max (95%, C_2H_5OH) 291 (log ε 4.23), 282 (log ε 4.21), 218 nm (log ε 4.09).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.67; H, 6.66; N, 4.82.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,3,4,5,-6,7,8-octahydroquinoline-2,5-dione (6c). Using the method described for the preparation of **6a**, 18.0 g (0.065 mol) of *N*-(β-3,4-dimethoxyphenethyl)-1-aminocyclohexen-3-one, 10.0 g (0.139 mol) of β-propiolactone, and 400 ml of xylene gave 13.9 g (65%) of **6c**: mp 82.5–83.5° (recrystallized from ether); nmr ($CDCl_3$) δ 6.74 (s, 3 H), 3.82 (m, 8 H, OCH_3N–CH_2), 2.47 (s, 4 H); ir (KBr) 1510, 1605, 1640 (C=O, pyridone), and 1685 (C=O, keto) cm^{-1}; uv max (95% C_2H_5OH) 230 (log ε 4.071), 299 nm (log ε 4.182).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.46; H, 7.16; N, 4.22.

Cyclization of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (6a). To 30 g of polyphosphoric acid at 90° in a 125-ml beaker was added 3.8 g (12.05 mmol) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione(**6a**). The solution was heated 6 hr with occasional stirring and was quenched with 90 g of crushed ice. Aqueous perchloric acid (10%) was added dropwise with stirring until precipitation ceased, and the beaker was covered and cooled overnight at approximately 5°. The precipitate was removed by filtration, washed with cold water, and dried to a constant weight to yield 4.42 g (92.5%) of the crude mixture of cyclization products **7a** and **8a**. In several reactions the yields ranged between 92 and 100%. The solid was dissolved in 150 ml of boiling acetonitrile. To this was added 300 ml of absolute ethanol. The mixture was concentrated to 175 ml by evaporation and was allowed to cool. After standing overnight at room temperature, the solution deposited crystals which were collected by filtration and dried to give 2.0 g (42.2%) of **2,3-dimethoxy-1,3,5(10),8,11,13-hexaene-8-azagonan-17-one perchlorate (7a)**: mp 294–295° dec; pmr (DMSO-d_6). δ 8.95, 8.86, 8.84, 8.76 (q, 2 H), 7.95 (s, 1 H), 7.42 (s, 1 H), 4.86 (t, 2 H, J = 7.0 Hz), 3.74 (m, 2 H), 3.43 (t, 2 H, J = 7.0 Hz), 3.10 (m, 2 H); ir (KBr) 1720 (C=O), 1605 (s, Ar, C=C); uv max (95% C_2H_5OH) 337 (log ε 3.85), 299 (log ε 3.99), 281 (log ε 3.94), 236 nm (log ε 3.90).

Anal. Calcd for $C_{18}H_{18}ClNO_7$: C, 54.62; H, 4.58; N, 3.54. Found: C, 54.52; H, 4.63; N, 3.56.

Evaporation of the filtrate gave 1.9 g (39.9%) of **2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (8a)**: mp 208–209° dec; pmr (DMSO-d_6) δ 8.44 (s, 2 H), 6.96 (s, 1 H), 6.82 (s, 1 H), 4.76 (d, 1 H, J = 9.0 Hz), 3.74 (s, 6 H); ir (KBr) 3300 (OH), 1610 (C=CC=N), 1500 cm^{-1}; uv max (95% C_2H_5OH) 293.5 nm (log ε 4.58).

Anal. Calcd for $C_{18}H_{22}ClNO_7$: C, 54.35; H, 5.07; N, 3.52. Found: C, 54.22; H, 5.39; N, 3.47.

Cyclization of *N*-(β-3-Methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-pyrindan-2,5-dione (6b). Using the procedure for the cyclization of **6a**, 10 g of polyphosphoric acid caused the conversion of 1.5 g of *N*-(β-3-methoxyphenethyl)-1,2,3,4-tetrahydropyrindan-2,5-dione (**6b**) to a 1.9-g (quantitative) yield of a mixture of **7b** and **8b**. The precipitate from ethanol–acetonitrile was 0.78 g (41%) of3-methoxy-1,3,5(10),8,11,13-hexaene-8-azagonan-17-one perchlorate (**7b**): mp 263–264° dec; pmr (DMSO-d_6) δ 8.60 (AB, 2 H), 8.32 (d, 1 H, J = 8.5 Hz), 4.27 (t, 2 H, J = 6.5 Hz), 3.91 (s, 3 H), 3.34 (t, 2 H, J = 6.5 Hz); ir (KBr) 1700 (C=O), 1596 (Ar, C=C) cm^{-1}; uv max (95% C_2H_5OH) 286 (log ε 3.78), 265 nm (log ε 3.83).

Anal. Calcd for $C_{17}H_{16}ClNO_6$: C, 55.82; H, 4.41; N, 3.83. Found: C, 55.65; H, 4.45; N, 4.10

Evaporation of the filtrate and recrystallization of the residue from acetone–petroleum ether gave 0.75 g (39%) of 3-methoxyl-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8b**) as a yellow solid: mp 220–222°; pmr (TFA) δ 7.12 (d, 1 H, J = 8.0 Hz), 4.70 (d, 1H, J = 11.0 Hz), 3.76 (s, 3 H); ir (KBr) 1650 (C=C-C=N) cm^{-1}; uv max (95% C_2H_5OH) 293 nm (log ε 4.52).

Anal. Calcd for $C_{17}H_{20}ClNO_6$: C, 55.22; H, 5.45; N, 3.79. Found: C, 55.37; H, 5.46; N, 3.71.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (11). A solution of 1 g (3.02 mmol) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione (**6c**) in 75 ml of methylene chloride was treated with 12 g of activated MnO_2. After stirring for 24 hr, the mixture was filtered, and the insoluble residue was washed well with methylene chloride. Evaporation of the solvent from the combined methylene chloride solutions gave an oil which crystallized from methanol to give 0.40 g (40%) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (**11**): mp 184–185.5°; nmr ($CDCl_3$), δ 7.73 (d, 1 H, J = 9.5 Hz), 6.6–6.4 (m, 3 H), 6.30 (d, 1 H, J = 9.5 Hz), 4.33 (t, 2 H, J = 6.5 Hz), 3.73 (s, 3 H), 3.67 (s, 3 H), 2.88 (t, 2 H, J = 6.5 Hz); ir (KBr) 1510, 1540, 1590 (C=O pyridone), 1665 (C=O, keto) cm^{-1}; uv max (95% C_2H_5OH) 227 (log ε 4.00), 283 nm (log ε 4.32).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.51; H, 6.51; N, 4.14.

Preparation of *N*-(β-3,4-Dimethoxyphenethyl)-2,5-dichloro-7,8-dihydroquinolinium Perchlorate (12). A solution of 1.0 g (3.06 mmol) of *N*-(β-3,4-dimethoxyphenethyl)-1,2,5,6,7,8-hexahydroquinoline-2,5-dione (**11**) in 20 ml of phosphorus oxychloride was heated under reflux for 0.5 hr. Excess phosphorus oxychloride was removed by evaporation under reduced pressure, and the red residue was dissolved in 20 ml of water, treated with charcoal, and filtered to give a yellow solution. Perchloric acid (10%, aqueous) was added dropwise until precipitation ceased, and the mixture was cooled overnight at 0–5° to complete precipitation. The solid was isolated by filtration and recrystallized twice from acetone to give 0.74 g (59%) of **12**: mp 206–207.5°; nmr (TFA) δ 8.25 (d, 1 H, J = 9.0 Hz), 7.67 (d, 1 H, J = 9.0 Hz), 6.56 (m, 3 H), 6.21 (t, 1 H, J = 4.5 Hz), 4.73 (t, 2 H, J = 6.5 Hz), 3.51 (s, 6 H); ir (KBr) 1455, 1505, 1575, and 1620 cm^{-1} (no C=O); uv max (95% C_2H_5OH) 231 (log ε 4.10), 252 (log ε 3.85), 281 (log ε 4.02), 327 nm (log ε 3.80).

Anal. Calcd for $C_{19}H_{20}Cl_3NO_6$: C, 49.11; H, 4.33; N, 3.01. Found: C, 49.21; H, 4.46: N, 3.03.

Preparation of 2,3-Dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (9a). A suspension of 0.50 g (1.52 mmol) of 2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8a**) in 25 ml of methylene chloride was treated with 10 ml of 5% aqueous sodium hydroxide. The reaction mixture was stirred under nitrogen for 15 min and the layers were separated. The aqueous phase was extracted twice with 10-ml portions of methylene chloride, and the combined organic layers were washed with two 20-ml portions of water and dried over magnesium sulfate under nitrogen. The drying agent was removed by filtration and the solvent was evaporated. The addition of ether to the residue gave a white solid which was recrystallized from ethyl acetate–hexane to give 0.24 g (64%) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**): mp 158–160°; pmr ($CDCl_3$) δ 6.80 (s, 1 H), 6.68 (s, 1 H), 4.52 (d, 1 H, J = 10.0 Hz); ir (KBr) 1640 (C=O), 1560, 1490 cm^{-1}; uv max (95% C_2H_5OH) 293 (log ε 4.63), 228 nm (log ε 4.00); mass spectrum M^+, 299.

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.04; H, 7.00; N, 4.61.

Preparation of 2,3-Dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol Perchlorate (8a) from 9a. To a solution of 0.10 g (0.33 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) in 5 ml of 95% ethanol was added 10 drops of 10% aqueous perchloric acid. The solution was cooled overnight, and the precipitate which formed was collected by filtration to give 0.10 g (75%) of2,3-dimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8a**) as the monohydrate, mp 120–122°.

Anal. Calcd for $C_{18}H_{24}ClNO_8$: C, 51.74; H, 5.79; N, 3.35. Found: C, 51.26; H, 5.80; N, 3.28.

The solid was dissolved in 20 ml of acetonitrile and 40 ml of absolute ethanol. The volume of the solution was reduced to 20 ml. Hexane was added and the solution was cooled. The resulting solid, mp 208–209°, was collected by filtration. This material was identical in all respects with the material from cyclization of **6a**.

Anal. Calcd for $C_{18}H_{22}ClNO_7$: C, 54.35; H, 5.07; N, 3.52. Found: C, 54.02; H, 5.70; N, 3.47.

Preparation of 3-Methoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (9b). A stirred suspension of 0.50 g (1.34 mmol) of 3-methoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonan-17-ol perchlorate (**8b**) in 30 ml of methylene chloride was treated with 10 ml of 5% aqueous sodium hydroxide as in the preparation of **9a** to give 0.30 g (82.4%) of 3-methoxyl-1,3,5(10),13-tetraene-8-azagonan-17-one (**9b**): mp 122–125°; pmr ($CDCl_4$) δ 4.67 (m, 1 H), 3.90 (s, 1 H); ir (neat) 1670 (C=O), 1600 (Ar, C=C) cm^{-1}; uv max (95% C_2H_5OH) 293 nm (log ε 4.5); mass spectrum M^+, 269.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 74.40; H, 7.19; N, 5.02.

Preparation of 2,3-Dimethoxy-1,3-5(10)-triene-9β,13β-8-azagonan-17-one (13). A solution of 1.0 g (3.3 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) dissolved in 80 ml of dry tetrahydrofuran was treated with 0.25 g of lithium aluminum hydride and was heated under reflux for 3 hr. Aqueous 10% sodium hydroxide was added to decompose the excess lithium aluminum hydride, and the resulting solid was removed by filtration. The solution was evaporated under reduced pressure and the residue was recrystallized from hexane to give 0.25 g (25%) of 2,3-dimethoxy-1,3,5(10)-triene-9β,13β,14β-8-azagonan-17-one (**13**): mp 150–152°; pmr ($CDCl_3$ δ 6.71 (s, 1 H), 6.58 (s, 1 H), 3.85 (s, 6 H); ir (KBr) 2900, 2800, 1740 (C=O), 1600, 1520 cm^{-1}; uv max (95% C_2H_5OH) 281 nm (log ε 3.84).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.64. Found: C, 71.65; H, 7.88; N, 4.44.

Preparation of 2,3,17-Trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane Iodide (14). A mixture of 103.6 mg (0.346 mmol) of 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) and 5 of methyl iodide was heated under reflux under a positive pressure of nitrogen for 17 hr. The solid which formed was collected by filtration and washed with dry ether. Recrystallization of the solid from methanol gave 136.6 mg (90%) of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane iodide (**14**): mp 166–167°; pmr (DMSO-d_6) δ 7.01 (s, 1 H), 6.86 (s, 1 H), 4.92 (d, 1 H, J = 10.5 Hz), 4.14 (s, 3 H), 3.74 (s, 6 H), 1.50 (m, 1 H); ir (KBr) 1580 (ROC=CC=N), 1500, 1455 cm^{-1}; uv max (95% C_2H_5OH) 290 nm (log ε 4.58).

Anal. Calcd for $C_{19}H_{24}INO_3$: C, 51.81; H, 5.49; N, 3.18. Found: C, 51.65; H, 5.43; N, 3.07.

Preparation of 2,3-Dimethoxy-17-allyloxy-1,3,5(10),8(14),-13(17)-pentaene-8-azagonane Bromide (19). A solution of 1.0 g (3.35 mmol) of2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**) in 25 ml of dry acetone was added 0.5 ml of allyl bromide. The solution was heated under reflux for 24 hr. Dry ether (25 ml) was added to cause the precipitation of all salts. The solid material was removed by filtration and recrystallized from methanol to give 0.35 g (25%) of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane bromide (**19**): mp 142–143°; pmr (DMSO-d_6) δ 7.04 (s, 1 H), 6.88 (s, 1 H), 6.02 (m, 1 H), 5.24–5.64)m, 2 H), 5.00 (m, 2 H), 3.72 (s, 6 H); ir (KBr) 1600, 1575 (C=CC=N), 1515 cm^{-1}; uv max (95% C_2H_5OH) 290 nm (log ε 4.54).

Anal. Calcd for $C_{21}H_{26}BrNO_3$: C, 58.83; H, 6.42; N, 3.43. Found: C, 58.56; H, 6.35; N, 3.73.

Attempted Rearrangement of 2,3-Dimethoxy-17-allyloxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane Bromide (19). A suspension of 25.6 mg (0.061 mmol) of 2,3-dimethoxy-17-allyloxy-1,3,5(10),8,(14),13(17)-pentaene-8-azagonane bromide (**19**) in 25 ml of dry toluene was heated under reflux for 19 hr. At that time all material had dissolved. The solvent was removed under reduced pressure to give an oily residue. An infrared spectrum (neat) of the oil was identical with that obtained for 2,3-dimethoxy-1,3,5(10),13-tetraene-8-azagonan-17-one (**9a**).

Reduction of 2,3,17-Trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane Iodide (14). A solution of 0.50 g (1.13 mmol) of 2,3,17-trimethoxy-1,3,5(10),8(14),13(17)-pentaene-8-azagonane iodide (**14**) in 50 ml of absolute ethanol was treated with 30 mg (0.79 mmol) of sodium borohydride in 10 ml of absolute ethanol. The resulting solution was stirred at room temperature for 0.5 hr, and the solvent was evaporated at reduced pressure. The residue was dissolved in 50 ml of methylene chloride and washed twice with 10-ml portions of 5% aqueous sodium bicarbonate and once with 10 ml of water and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was evaporated under reduced pressure. The resulting material was dissolved in a minimum amount of benzene and put on a column of neutral alumina (10 g). Elution of the column with 325 ml of benzene gave 0.10 g (31.1%) of 2,3-dimethoxy-1,3,5(10),13(17)-tetraene-9β,14β-8-azagonane (**16**): mp 135–137° after sublimation at 120° (0.2 mm); pmr ($CDCl_3$) δ 6.73 (s, 1 H), 6.68 (s, 1 H), 5.53 (m, 1 H), 3.91 (m, 7 H); ir (KBr) 2910, 2810, 2700, 1675, 1630, 1600, 1525, 767 cm^{-1}; uv max (95% C_2H_5OH) 282 (log ε 3.58), 286 nm (log ε 3.58).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.45; H, 8.13; N, 5.11.

Elution of the column with 30 ml of ethyl acetate gave 0.13 g (36.5%) of 2,3,17-trimethoxy-1,3,5(10),13(17)-tetraene-9β,14β-8-azagonane (**15**): mp 109–110° (recrystallized from petroleum ether); nmr ($CDCl_3$) δ 6.82 (s, 1 H), 6.68 (s, 1 H), 3.89 (m, 9 H), 3.67 (s, 3 H); ir (KBr) 2900, 2800, 2700 (CH), 1690 (C=O), 1600 1520, 770 cm^{-1}; uv max (95% C_2H_5OH) 282 (log ε 3.61), 286 nm (log ε 3.62).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.38; H, 7.89; N, 4.59.

Registry No.—**5a,** 53129-00-3; **5b,** 53129-01-4; **5c,** 27032-09-3; **6a,** 2349-42-0; **6b,** 2118-99-2; **6c,** 2349-40-8; **7a,** 53129-03-6; **7b,** 53129-05-8; **8a,** 53129-07-0; **8b,** 53129-09-2; **9a,** 53129-10-5; **9b,** 53129-11-6; **11,** 53129-12-7; **12,** 53129-14-9; **13,** 53129-15-0; **14,** 53129-16-1; **15,** 53129-17-2; **16,** 53129-18-3; **19,** 53129-19-4; β-3,4-dimethoxyphenethylamine, 120-20-7; 1,3-cyclopentanedione, 3859-41-4; β-3-methoxyphenethylamine, 2039-67-0; 1,3-cyclohexanedione, 504-02-9; β-propiolactone, 57-57-8; methyl iodide, 74-88-4.

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The Reduction of 2,2,2-Trichloroacetanilide by Vanadium(II)

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The reduction of 2,2,2-trichloroacetanilide by $VCl_2(py)_4$ yields only 2,2-dichloroacetanilide and V(III), in contrast to the reductions of aralkyl halides, RX, studied previously which selectively formed coupling products, R_2. In the presence of small concentrations of water, the reaction rate in THF is first order in oxidant and V(II) and is accelerated by electron-withdrawing substituents. However, the rate decreases with decreasing water concentration and the rate law becomes complex under anhydrous condions. The yield of 2,2-dichloroacetanilide is unaffected by the presence or absence of water, but it increases with oxidant concentration and is higher than predicted by the stoichiometry

$$PhNHCOCCl_3 + 2V(II) + H^+ \longrightarrow PhNHCOCHCl_2 + 2V(III) + Cl^-$$

indicating the occurrence of unknown secondary reactions.

The selective reductive coupling of aralkyl halides by vanadium(II), and in particular by the complex $VCl_2(py)_4$, was previously reported by one of us.[1] We have now extended this investigation to the reduction of 2,2,2-trichloroacetanilides and have discovered marked differences between the two series of reactions.

Experimental Section

Unless otherwise noted, experimental techniques, preparations, and purifications used were as described previously.[1,2]

Materials. 2,2,2-Trichloroacetanilide and its ring-substituted derivatives were prepared by reaction of trichloroacetyl chloride with the corresponding aniline.[3] 2,2-Dichloroacetanilide was prepared by the method of McVie.[4] All compounds were recrystallized and their purities checked by melting point and elemental analysis.

Results

Product Analysis. 2,2,2-Trichloroacetanilide oxidizes $VCl_2(py)_4$ to V(III) species only. This was demonstrated by polarographic measurements[1] over a wide range of conditions (Table I) and also by the colors of the final solutions which, as in the case of oxidation of $VCl_2(py)_4$ by aralkyl halides, were diagnostic: yellow in the presence of water and pink in its absence.[1] (In contrast, reactions which convert $VCl_2(py)_4$ to V(IV) species, *e.g.*, oxidation by air or nitrobenzene, yield apple green final solutions.) Gas chromatography,[1] mass spectroscopy, and thin layer chromatography (silica gel G, benzene eluent) indicated that the only organic reduction product is 2,2-dichloroacetanilide, whether reaction is carried out in benzene or THF solvent. Product yields measured by gas chromatography as described previously[1,2] are shown in Table I. The presence or absence of trace water had no effect on the nature or yield of the product. There is no appreciable further reduction of 2,2-dichloroacetanilide under these conditions.

Reaction Kinetics. Rates were measured by following the decrease in V(II) concentration at 480 nm as described previously.[1] In tetrahydrofuran (THF) solution containing a small quantity of water, the oxidation of $VCl_2(py)_4$ by 2,2,2-trichloroacetanilide followed eq 1 over at least three

$$-d[VCl_2(py)_4]/dt = k_2[VCl_2(py)_4][PhNHCOCCl_3] \quad (1)$$

half-lives (correlation coefficients >0.9993) (Table II). ΔH^* and ΔS^* were 16.4 kcal mol^{-1} and −2.7 eu, respectively (Table III). 2,2,2-Trichloroacetanilides substituted on the ring or the nitrogen atom also followed eq 1 over at least two half-lives, and electron-attracting substituents increased the reaction rate while electron-releasing substituents decreased it (Table IV), although this effect was relatively small. The range of substituents permissible was limited by their oxidation or complexing of the V(II).[1] Oxidation by *N*-methyl-2,2,2-trichloroacetanilide was less than a tenth as fast as that by 2,2,2-trichloroacetanilide although it followed the same rate law (Table IV).

In contrast to the oxidation of $VCl_2(py)_4$ by aralkyl halides, when the presence or absence of water had little effect,[1] the rate of oxidation of $VCl_2(py)_4$ by 2,2,2-trichloroacetanilides was increased somewhat by increasing water concentration (Table V) (although there is no effect on the products), and eq 1 holds only at appreciable water concentrations (above about 3×10^{-4} *M*; the kinetic results given above are for $[H_2O] = 5 \times 10^{-4}$ *M*). In anhydrous THF, the reaction is approximately first order in V(II) only at low oxidant concentrations; at higher oxidant concentrations it approaches toward second order in V(II). Nonlinear regression analysis[5] shows a good fit to expressions such as

Table I
Product Yields from Reduction of $PhNHCOCCl_3$ by $VCl_2(py_4)$[a]

10^3 initial $[VCl_2(py)_4]$, (*A*)	10^2 initial $[PhNHCOCCl_3]$, *M*	10^3 [PhNHCOCHCl$_2$] produced, *M* (*B*)	*B*/*A*	*K*[b]
		A. No Water		
7.6	0.84	3.9	0.51	0.003
7.9	1.01	4.3	0.54	0.03
7.9	1.68	5.3	0.67	0.18
7.6	2.52	4.2	0.55	0.02
7.9	3.36	5.2	0.65	0.07
7.6	5.0	5.1	0.67	0.06
7.9	6.7	6.0	0.76	0.10
7.6	8.4	6.5	0.85	0.19
7.6	12.6	6.7	0.87	0.15
		B. $[H_2O] = 0.010$ *M*		
7.6	0.84	4.4	0.58	0.10
7.6	2.52	5.3	0.69	0.13
7.6	5.0	5.8	0.75	0.13
7.6	8.4	6.4	0.84	0.17
7.6	12.6	6.6	0.86	0.14

[a] THF solution, 22°. V(III) was the only inorganic oxidation product over the concentration ranges studied. [b] From eq 13.

Table II
Oxidation of $VCl_2(py)_4$ by $PhNHCOCCl_3$[a]

10^2 [PhNHCOCCl$_3$], M	$10^2 k'$, sec^{-1} [b]	k_2, M^{-1} sec^{-1} [c]
3.36	3.11	0.93
1.68	1.69	1.01
0.60	0.61	1.02
0.46	0.48	1.05
0.228	0.220	0.96
0.114	0.117	1.03

[a] 20°, THF solvent containing 5.0×10^{-4} M H_2O; initial $[VCl_2(py)_4] = 3.5 \times 10^{-4}$ M. [b] $k' = -d \ln [VCl_2(py)_4]/dt$. [c] $k_2 = k'/[PhNHCOCCl_3]$. Regression line through the origin gives $k_2 = 0.945$ M^{-1} sec^{-1} (standard deviation 0.016, correlation coefficient 0.9993).

Table III
Activation Parameters for the Oxidation of $VCl_2(py)_4$ by $PhNHCOCCl_3$[a]

Temp, °C	k_2, M^{-1} sec^{-1} [b]	Temp, °C	k_2, M^{-1} sec^{-1} [b]
1.6	0.130	30.0	2.46
6.0	0.200	34.9	3.83
10.5	0.345	39.8	5.60
15.4	0.631	44.7	9.26
20.0	0.945	49.6	12.7
25.0	1.54		

[a] Initial $[VCl_2(py)_4] = 3.3 \times 10^{-4}$ M. THF solvent containing 5.0×10^{-4} M H_2O. [b] Activation parameters calculated from regression of ln k_2 upon 10^3 T_{abs} °K^{-1} are $\Delta H^* = 16.4$ kcal mol^{-1} ($S_{\Delta H}^* = 0.12$); $\Delta S^* = -2.7$ eu at 25.6° ($S_{\Delta S}^* = 0.41$); $\Delta G^* = 17.2$ kcal mol^{-1} at 25.6°, ($S_{\Delta G}^* = 0.17$); correlation coefficient = 0.9998. (Compare for the reduction of $PhCCl_3$: $\Delta H^* = 17.3$ kcal mol^{-1}. ($S_{\Delta H}^* = 0.38$); $\Delta S^* = -3.5$ eu ($S_{\Delta S}^* = 1.21$.)

$$-d[VCl_2(py)_4]/dt = k[VCl_2(py)_4]^{1.8}[PhNHCOCCl_3]^{1.5} \quad (2)$$

but such equations are difficult to interpret mechanistically. Similar substituent effects are also observed in anhydrous solution as in anhydrous sclutions.

Discussion

The oxidation of $VCl_2(py)_4$ with 2,2,2-trichloroacetanilides differs strikingly from the oxidation with aralkyl halides reported previously.[1] The reaction with aralkyl halides gives high yields of coupling products even in the presence of proton or hydrogen atom sources.

$$2RHal + 2V(II) \longrightarrow R_2 + 2V(III) + 2Hal^- \quad (3)$$

In contrast, reduction of 2,2,2-trichloroacetanilides gives only the 2,2-dichloroacetanilide even in dry solutions.

$$PhNHCOCCl_3 + 2V(II) + H^+ \longrightarrow PhNHCOCHCl_2 + 2V(III) + Cl^- \quad (4)$$

Reaction paths such as (4) are followed in many reductions of organic halo compounds by transition metal compounds,[1] often concurrently with the formation of coupling products. There appear to have been no studies on the reduction of 2,2,2-trichloroacetanilides by other low-valent transition-metal compounds, although with regard to halogen α to a carbonyl group, Cr(II) reduces trichloroacetaldehyde and trichloroacetic acid to acetaldehyde and acetic acid respectively in aqueous methanol[6] and p-bromophenyl dibromomethyl ketone to a mixture of p-bromoacetophenone and 1,2-bis(p-bromobenzoyl)ethane in aqueous dimethylformamide.[7]

Table IV
Rates of Oxidation of $VCl_2(py)_4$ by Substituted 2,2,2-Trichloroacetanilides[a]

Substituent		k_2, M^{-1} sec^{-1}	Standard error of k_2	σ-value[c,d]
4-CN	53165-95-0	2.17	0.042	1.00
4-CF_3	2107-36-0	1.81	0.012	0.74
4-EtOOC	53165-96-1	1.41	0.029	0.68
3-CF_3	1939-29-3	1.37	0.047	0.41
3-Cl	3004-73-7	1.21	0.006	0.37
4-Cl	2877-13-6	1.20	0.031	0.23
3-CH_3O	4257-82-3	0.97	0.023	0.11
H	2563-97-5	0.95	0.016	0.00
3-CH_3	2563-96-4	0.97	0.013	−0.07
4-CH_3	2564-09-2	0.81	0.016	−0.17
4-CH_3O	4257-81-2	0.80	0.006	−0.27
4-$NHCOCCl_3$	4257-74-3	1.58[b]	0.050[b]	
(N-CH_3)		(0.081)	(0.0026)	

[a] 20.0°; THF solvent containing 5.0×10^{-4} M water; initial $[VCl_2(py)_4]$ *ca.* 3.4×10^{-4} M. [b] Per -$NHCOCCl_3$ group. [c] H. H. Jaffé, *Chem. Rev.*, 53, 191 (1953); P. R. Wells, "Linear Free Energy Relationships," Academic Press, London, 1968, Chapter 2. [d] ρ derived by unweighted linear least squares (correlation coefficient 0.978) is 0.34 (standard error 0.024). There is only poor correlation between log k_2 and Hammett σ values.

Table V
Effect of Water on Rate of Oxidation of $VCl_2(py)_4$ by 2,2,2-Trichloroacetanilides[a]

	k_2, M^{-1} sec^{-1} [b]		
10^4[H_2O], M	$PhNHCOCCl_3$	p-$ClC_6H_4NHCOCCl_3$	p-$MeC_6H_4NHCOCCl_3$
0.00	0.57	0.83	0.55
0.16	0.62		
0.63	0.74	0.99	0.64
1.59	0.70	1.10	0.66
3.18	0.96		0.72
6.35	0.97	1.36	0.81
15.9	1.19	1.55	0.88

[a] 20°; THF solvent; initial $[VCl_2(py)_4]$ *ca.* 3.5×10^{-4} M. [b] At low [H_2O], this is calculated assuming eq 1 from reactions performed at low [oxidant], when the rate is approximately first order in [V(II)].

The product yields (Table I) show that the reaction stoichiometry is not constant. The ratio ([$PhNHCOCHCl_2$] produced/[$VCl_2(py)_4$] consumed) decreases at lower $PhNHCOCCl_3$ concentrations and extrapolates to 0.5 (the value corresponding to eq 4) only at zero oxidant concentration. Despite this apparent change in stoichiometry, only V(III) was obtained in the oxidation products in all concentration ranges studied. This suggests that there are secondary reactions involving $PnNHCOCCl_3$ (see below).

The reduction of 2,2,2-trichloroacetanilides by $VCl_2(py)_4$ follows the same rate law as the reduction of aralkyl halides despite the difference in reaction path. However, the present reactions are much faster, owing to a lower ΔH^* (Table III; the ΔH^* values for $PhCCl_3$ and $PhNHCOCCl_3$ are significantly different at the 2% level, while the ΔS^* values are statistically indistinguishable). This indicates that the electronic effect of the adjacent carbonyl group is important. Similar rate enhancement by carbonyl groups is observed in reductions of halo compounds by Cr(II)[7] and cobaloximes[8] and in the faster reduction of NH_2COCH_2Hal than of CH_3Hal by pentacyanocobalt(II).[9]

Consistent with this, electron-withdrawing substituents increase the rate of reduction of 2,2,2-trichloroacetanilides while electron-donating substituents decrease it, similar to the case of the aralkyl halides,[1] although the effect is much smaller in the present case. The much larger effect observed when a methyl group is substituted on the side chain nitrogen atom rather than on the ring (Table IV) may also reflect a greater increase in electron density at the reaction center, although steric effects could be important.

Two distinct types of mechanism are possible for the reactions in hydrous solution, analogous to those proposed previously for aralkyl halides.[1] A one-electron transfer

$$PhNHCOCCl_3 + V(II) \xrightarrow{k_5} PhNHCOCCl_2\cdot + V(III) + Cl^- \quad (5)$$

could be followed immediately by

$$PhNHCOCCl_2\cdot + V(II) \xrightarrow{k_6} [PhNHCOCCl_2\text{–}V(III)] \quad (6)$$

and then

$$[PhNHCOCCl_2\text{–}V(III)] + H^\cdot \longrightarrow PhNHCOCHCl_2 + V(III) \quad (7)$$

The electron transfer (eq 5) could be either inner or outer sphere, consistent with the small negative ΔS^*, but in contrast to the case of the aralkyl halides it could be assisted by complexing of vanadium with the nitrogen or carbonyl group forming a halogen-bridged five-membered cyclic transition state. However, there is no evidence for such complex formation.

Alternatively, an organovanadium(IV) intermediate might result from an inner-sphere redox step

$$PhNHCOCCl_3 + V(II) \xrightarrow{k_8} [PhNHCOCCl_2\text{–}V(IV)] + Cl^- \quad (8)$$

followed by

$$[PhNHCOCCl_2\text{–}V(IV)] + V(II) \xrightarrow{k_9} [PhNHCOCCl_2\text{–}V(III)] + V(III) \quad (9)$$

Direct insertion of the metal into the C–Cl bond *via* attack at the carbon center is unlikely, as discussed previously.[1]

The positive ρ^- shows that the organic moiety gains some anionic character on attainment of the transition state, as might be expected for both paths in (5) and (8). The measured value of ρ^- (0.34) is much lower than that for reactions such as $ArNHCOMe + MeO^- \rightarrow ArNH_2$ (2.15)[10] or than the ρ value for reduction of benzotrichloride by $VCl_2(py)_4$ (1.2).[1] This may be due to less development of negative character at the reaction center in the transition state, or to the longer distance through which the effect must be transmitted.

The reason for the difference in products between these reactions and the reduction of aralkyl halides is uncertain, but one possibility is that the organic moiety in the $PhNHCOCCl_2$–V(III) species has much more anionic character than in the $PhCCl_2$–V(III) species because of the electronegativity of the C=O group, and hence is more easily cleaved by protons. Alternatively, attack of a further molecule of $PhNHCOCCl_3$ on the $[PhNHCOCCl_2\text{–}V(III)]$ intermediate might be too slow to allow the formation of coupled products.

The reason for the increase in the ratio ([PhNHCOCHCl$_2$] produced/([$VCl_2(py)_4$] consumed) above the value of 0.5 (corresponding to eq 4) with increasing $PhNHCOCCl_3$ concentration is not known. The vanadium oxidation product formed is V(III) over all the concentration ranges studied, and the change in stoichiometry is not due to generation of V(IV) or V(V). A possibility is that reaction with the substrate by radicals liberated in step 5

$$PhNHCOCCl_2\cdot + PhNHCOCCl_3 \xrightarrow{k_{10}} PhNHCOCHCl_2 + PhN\dot{C}OCCl_3 \quad (10)$$

competes with reaction 6 in their subsequent removal. However, this step would caise the observed variation in stoichiometry only if it be assumed that the pathway for removal of $PhN\dot{C}OCCl_3$ does not involve oxidation of another V(II). While this route appears unlikely, it may be more feasible than the alternative of reaction 8 followed by

$$[PhNHCOCCl_2\text{–}V(IV)] + PhNHCOCCl_3 \longrightarrow PhNHCOCHCl_2 + [PhN(COCCl_3)\text{–}V(IV)] \quad (11)$$

when it must be assumed that the resultant V(IV) complex is resistant to reduction. A scheme involving only eq 5, 6, 7, and 10 and assuming stationary state conditions for $[PhNHCOCCl_2\cdot]$ and $[PhNHCOCCl_2\text{–}V(III)]$ would lead to

$$-dV/dt = k_5VA[1 + k_6V/(k_6V + k_{10}A)] \quad (12)$$

and

$$[PhNHCOCHCl_2] = V_0/2 + (kA/4)\ln[(2V_0/kA) + 1] \quad (13)$$

where $V = [VCl_2(py)_4]$, V_0 = initial $[VCl_2(py)_4]$, $A = [PhNHCOCCl_3]$, and $k = k_{10}/k_6$. Equation 13 is solved for k for each reaction in Table I, but the values found are larger than would be expected (considering that k_6 is likely to be about $10^8\ M^{-1}\ sec^{-1}$ [11] and k_{10} would be many orders of magnitude less[11]) and are not constant except for the runs performed in the presence of water, showing that this simple scheme is inadequate.

The effect of water on the reaction kinetics has likewise not been explained. Water is likely to preferentially solvate the $VCl_2(py)_4$, but this may have little effect on the electron transfer step since the oxidation of $VCl_2(py)_4$ by aralkyl halides is unaffected by water.[1] No reaction scheme has been found which will reconcile the rate and product yield data and explain the effect of water and the differences between the oxidations of $VCl_2(py)_4$ by 2,2,2-trichloroacetanilides and aralkyl halides.

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Registry No.—$VCl_2(py)_4$, 50436-99-2.

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Oxidation of α-Lipoic Acid

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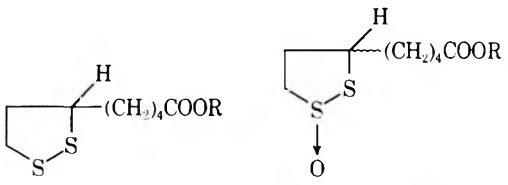
α-Lipoic acid has been oxidized (as its methyl ester, **3**) by a variety of oxidants, including singlet oxygen. An nmr chemical shift reagent, $Eu(fod)_3$-d_{27}, has been used to show that the products include four thiolsulfinates in all cases, and, in the case of singlet oxygen oxidation, two thiolsulfonates. The singlet oxygen oxidations are interpreted in terms of a mechanism involving initial formation of zwitterions by reaction of singlet oxygen at each of the two sulfur atoms in **3** followed by intramolecular or intermolecular reaction to give thiolsulfonate or thiolsulfinate, respectively.

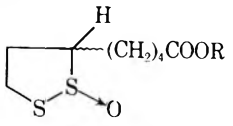
α-Lipoic acid (1,2-dithiolane-3-valeric acid, thioctic acid, protogen-A),[1] **1**, has been of interest to biological chemists for some time but particularly since its isolation[2] and identification.[3] It has been identified as a growth factor for many bacteria and protozoa.[4-12] α-Lipoic acid is also known to be a coenzyme in oxidative decarboxylation reactions. Calvin and coworkers have suggested that **1** is involved in the primary quantum conversion act of photosynthesis.[1b,13]

Interest in the oxidation products of α-lipoic acid began with the isolation from beef liver of a monooxidation product along with the parent compound.[14,15] This product was called β-lipoic acid (protogen-B) (**2a** or **2b**) and it was not



1. R = H
3. R = CH_3

2a, R = H
4a, R = CH_3



2b, R = H
4b, R = CH_3

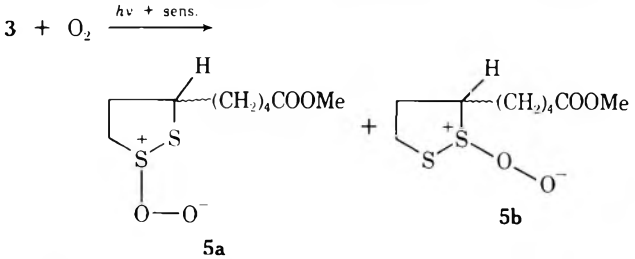
known whether it was a naturally occurring substance or whether it was produced by oxidation of α-lipoic acid during the work-up. Likewise it was not possible to determine which sulfur atom had been oxidized. Structure **2a** has generally been favored for β-lipoic acid since the specific rotation of the thiosulfinate prepared from (+)-α-lipoic acid is almost identical with that of the parent compound.[1e] Saito and Fukui[16] have oxidized *dl*-α-lipoic acid with hydrogen peroxide and isolated two monosulfoxides. They suggested that one of these is β-lipoic acid (assigned structure **2a**) and that the other is either a compound in which the other sulfur atom has been oxidized, **2b**, or a "conformational isomer" of β-lipoic acid by which they presumably meant the cis or trans isomer of **2a**.

The acid has also been oxidized to β-lipoic acid by *tert*-butyl hydroperoxide[17] and by hydrogen peroxide and potassium permanganate.[18] In most cases identification of the product was made by comparison of the infrared spectrum with that of protogen-B (β-lipoic acid) isolated from natural sources. In no case was it possible to distinguish between structure types **2a** and **2b** although Reed, *et al.*,[18] recognized that both possibilities existed.

We have been interested in the possible role of singlet oxygen in the photodynamic effect.[19,20] In particular, we have been studying the reactions of singlet oxygen with disulfides as models for biological substrates containing the cysteine residue or other disulfide linkage.[21-25] As part of this study we have oxidized *dl*-α-lipoic acid under singlet oxygen conditions as well as with other oxidants.

Results and Discussion

Preliminary results from the photosensitized oxidation of **1** indicated that work-up of the reaction mixture was made difficult by the presence of the polar acid group. Consequently, all further oxidation studies used the methyl ester, **3**. Photosensitized oxidation of **3** in chloroform, followed by preparative tlc work-up, led to the isolation of four tlc bands with R_f values of 0.27, 0.39, 0.68, and 0.77. On the basis of infrared and mass spectral analyses the bands with R_f values of 0.27 and 0.39 were determined to be thiolsulfinates, and the band with R_f of 0.68 was determined to be thiolsulfonate. The fourth band which is present only in trace amount was not identified. Total yield of thiolsulfinates was 64% and total yield of thiolsulfonates was 25.7%. A photosensitized oxidation of **3** in methanol solvent gave similar tlc results. However, in this case total yield of thiolsulfinates was 75.4% and total yield of thiolsulfonates was 15.4%. The photosensitized oxidation is almost completely quenched in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco), a known[24] singlet oxygen quencher. Likewise, the reaction does not proceed in the absence of photosensitizer. Also pertinent to these results is the recent observation by Stevens and coworkers[25] that **1** can act as an inhibitor of rubrene autoperoxidation. The photosensitized oxidation thus is presumably a singlet oxygen oxidation and probably involves a zwitterionic intermediate (**5a** and **5b**) similar to that invoked in the singlet oxygen oxidation of dialkyl disulfides[22,23] and dialkyl sulfides.[26,27] These zwitterionic intermediates then can react further with **3** to give thiolsulfinates **4a**, **4a'**, **4b**, and **4b'** or react intramolecularly to give thiolsulfonates **6a** and **6b**.



5a **5b**

Operation of this mechanism requires 0.5 mol of O_2/mol of **3** which compares reasonably favorably with the observed values of 0.477 and 0.622 in chloroform and methanol, respectively. Additional support for the mechanism is available from a consideration of the thiolsulfinate–thiolsulfonate distribution as a function of solvent. In a very elegant and convincing study[27] of the effect of solvent, temperature, and concentration on product distribution in the

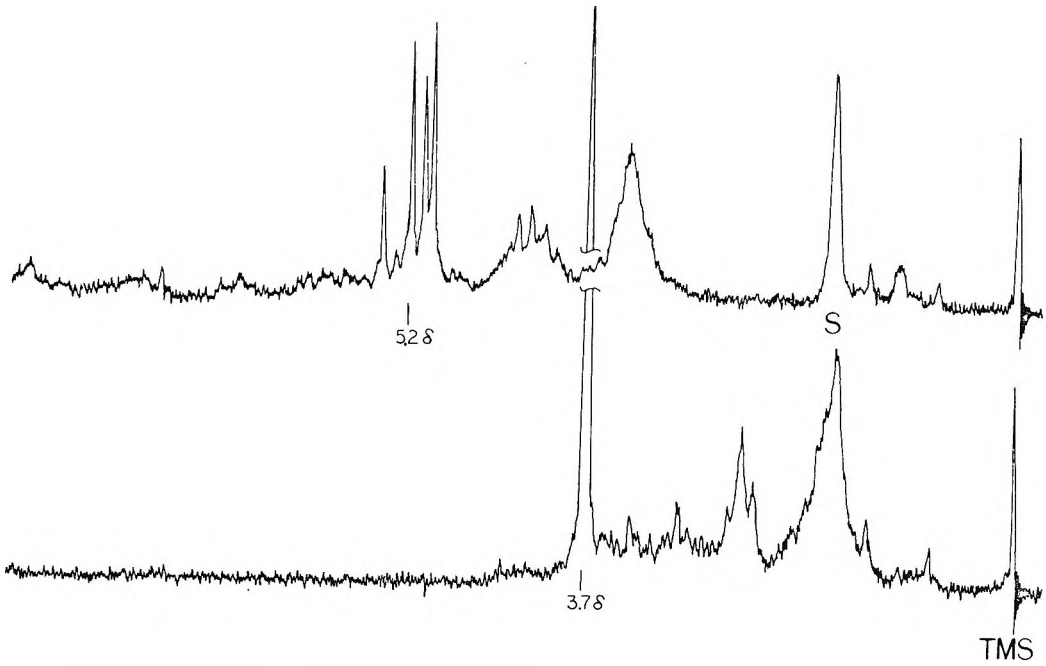
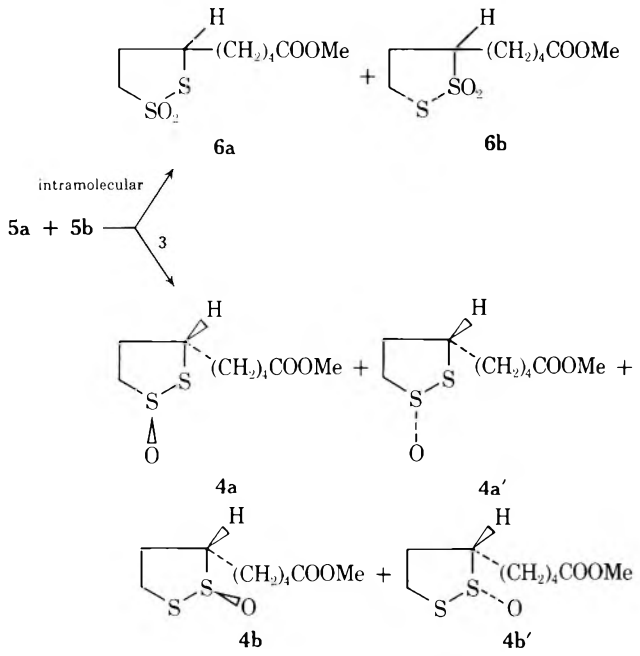


Figure 1. Effect of Eu(fod)$_3$-d_{27} on the nmr spectrum of the thiolsulfinate oxidation products of methyl α-lipoate. The bottom spectrum is the unshifted spectrum. The top spectrum was obtained with a ratio of shift reagent to substrate of 0.61. The peak marked S is due to the shift reagent.



singlet oxygen oxidation of sulfides, Foote and Peters have concluded that the sulfide-derived zwitterionic intermediate comparable to **5a** and **5b** is more likely to undergo the bimolecular reaction to give sulfoxide in protic solvents and high temperatures. On the other hand, the intramolecular reaction to give sulfone would be favored by aprotic solvent and low temperatures. These correlations were observed in the Foote and Peters work[27] and these workers have suggested that protic solvents favor intermolecular reaction by decreasing the negative charge density on the oxygen of the zwitterion by hydrogen bonding thus favoring nucleophilic attack by another molecule of sulfide. In aprotic solvents such stabilization is not present and the intramolecular reaction to sulfone (or decomposition to sulfide and ground state oxygen) is favored. Application of similar reasoning to the cases of **5a** and **5b** suggests that more thiolsulfonate should be formed in chloroform solvent than in methanol. The product distribution observed was 71.3% thiolsulfinate and 28.7% thiolsulfonate in chloroform solvent as compared to 83% thiolsulfinate and 17% thiolsulfonate in methanol. The product distribution results are thus consistent with a prediction based on the intermediacy of a zwitterionic species. It should be pointed out that our photosensitized oxidations were carried out at *ca.* 3–5° in both solvents. Presumably if a much lower temperature had been used for the chloroform case a higher percentage of thiolsulfinate would have been observed as predicted by the Foote and Peters scheme.

The singlet oxygen mechanism proposed for the oxidation of **3** suggests that four thiolsulfinate and two thiolsulfonate products are possible. During a major part of this investigation the available experimental results were very difficult to reconcile with this prediction. As indicated above, tlc analysis of the products in both reactions gave only two bands assignable to thiolsulfinate on the basis of ir and mass spectral analysis and only one band assignable to thiolsulfonate on the same grounds. Repeated analyses under a variety of tlc conditions did not change these results. Column and dry column chromatography did not disclose any evidence for the presence of additional products. Attempts to analyze the thiolsulfinate mixture by glpc led to disproportionation. This experience coupled with the approach we used to finally disclose the full range of products suggests that previous workers in this area may have treated difficultly separable mixtures as homogeneous substances.

We previously reported[28] the use of the nmr chemical shift reagent, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-4,6-octanedione-d_3)europium(III), Eu(fod)$_3$-d_{27}, in studying heterosteric groups in acyclic thiolsulfinates. Use of the same reagent in the present study proved to be very rewarding. By obtaining the Eu(fod)$_3$-d_{27} shifted nmr spectra of the combined thiolsulfinate fractions we were able to conclude that all four thiolsulfinates, **4a, 4a′, 4b,** and **4b′,** were included in the products. Separate spectra run on the tlc band with R_f 0.27 indicated that it contained three thiolsulfinates while the band at R_f 0.39 contained a single thiolsulfinate. An example of the results obtained on the combined fractions is shown in Figure 1. The unshifted spectrum is complex with the sharp methyl singlet as a

Table I
Summary of Results of Oxidation of Methyl α-Lipoate

Oxidant	Solvent	Percentage Distribution of Thiolsulfinates A	B	C	D	% Total Yield of Thiolsulfinates	Percentage Distribution of Thiolsulfonates[a] E	F	% Total Yield Thiolsulfonates
O_2, $h\nu$, S	$CHCl_3$	9	48	28	16	64	59	41	25.7
O_2, $h\nu$, S	MeOH	14	29	25	32	75.4	14	86	15.4
$(NH_4)_2S_2O_8$	90% EtOH	15	30	25	30	21			Trace
t-BuOOH	MeOH	10	35	20	34	69			Trace
$CH_3C(O)OOH$	Et_2O	4	37	26	33	42	10	90	Not determined
$CH_3C(O)OOH$	MeOH	11	29	26	34	52			Trace
$(PhO)_3PO_3$[b]	CH_2Cl_2	12	33	23	32	26			Trace
$(PhO)_3PO_3$[c]	CH_2Cl_2	8	33	24	35	21			Trace
$CH_3C(O)OOH$[d]	MeOH	10	28	27	35	~26			Trace

[a] Where no data are given there was insufficient material for an accurate analysis. [b] "Fast" warm up as described in text. [c] "Slow" warm up as described in text. [d] With deliberate light exposure (about 50% loss of products).

prominent feature at δ 3.7. In the shifted spectrum this sharp singlet becomes four sharp singlets at 4.98, 5.07, 5.17, and 5.42, corresponding to the four thiolsulfinates. Various ratios of shift reagent to substrate were used in order to obtain these near-optimum results for the methyl region. By near optimum we refer to conditions which clearly show the four methyl absorptions while at the same time moving underlying absorptions from this region as much as possible. This is important since the distribution of the thiolsulfinates given in Table I was determined from the methyl absorption peak heights in the shifted spectrum. The thiolsulfinates are arbitrarily assigned the designations A–D with A having the furthest downfield methyl absorption and D having the furthest upfield absorption in the shifted spectrum. By examining various cuts of the tlc band at R_f 0.27 it was possible to show a nonhomogeneous distribution of the three thiolsulfinates within this band. It was never possible, however, to further resolve this band into separate bands. Examination of the thiolsulfonate tlc band at R_f 0.68 in a similar fashion indicated that the single methyl absorption in the unshifted spectrum at δ 3.7 is split into two sharp singlets at δ 7.37 and 7.66 in the shifted spectrum corresponding to the presence of the two expected thiolsulfonates, **6a** and **6b**. Again the thiolsulfonates are given the arbitrary designations of E and F with E being the compound with the methyl group furthest downfield in the shifted spectrum. After obtaining these results attempts were made to examine the thiolsulfonate mixture with glpc. In this case disproportionation is not a problem and glpc evidence for the presence of two thiolsulfonates can be obtained.

The thiolsulfinate and thiolsulfonate products all have two possible sites for coordination with the shift reagent. Some information on the major site of coordination in all cases was obtained by examining the shifted spectrum of unoxidized **3**. In this case, the shifted spectrum was obtained with a ratio of shift reagent to substrate of 0.279 and the methyl absorption was observed to move downfield from δ 3.7 to 7.0 in the shifted spectrum. When the thiolsulfonate mixture was examined at the same ratio of shift reagent it was observed that the methyl groups are shifted to approximately the same extent as in the unoxidized ester, **3**. For the shift reagent, tris(dipivalomethanoto)-europium(III), $Eu(dpm)_3$, it is known[29] that the coordination at an ester group leads to a greater shift than coordination at the less basic sulfonyl group. Thus for the thiolsulfonates we are observing shifts which are almost identical with those observed for the ester **3**, presumably because coordination is occurring primarily at the ester group. This conclusion is further strengthened by an examination of the shifts in the thiolsulfinates (Figure 1). In this case a larger ratio of shift reagent to substrate (0.61) leads to a smaller shift than for either the unoxidized ester or the thiolsulfonates. In this case the more basic sulfinyl group is presumably coordinating to a much larger extent with the shift reagent. In all cases, coordination to the ester group must be making the greatest contribution to the observed shift because of its greater proximity to the methyl group.

Use of the nmr shift reagent has been successful in permitting us to show the presence of expected products which could not be revealed in the thiolsulfinate case by any other analytical technique used. It is possible that application of the same technique would be fruitful in similar cases such as in the oxidation of *cis*- and *trans*-3,6-dimethyl-*o*-dithiane[30] where products cannot be easily separated and where complex nmr spectra are obtained.

Chemical Oxidation Studies

We next turned our attention to a number of chemical oxidations of **3** using some reagents which had been used previously for the oxidation of **1** and where, theoretically at least, the range of products also include **4a**, **4a'**, **4b**, **4b'**, **6a**, and **6b** or their acid analogs. In all cases we used the nmr shift reagent technique to examine thiolsulfinate fractions obtained by tlc. In most cases these oxidations did not give enough thiolsulfonate product under the reaction conditions to permit application of the shift reagent technique. The results of this study as well as the data from the photosensitized oxidations are given in Table I. In all cases the oxidations gave all four predicted thiolsulfinates. The distribution of the thiolsulfinate products is somewhat, but not markedly, different. A determination of the further significance if any, of this distribution and distribution variation, awaits detailed structural assignments in the products.

Saito and Fukui[16] oxidized α-lipoic acid with excess *tert*-butyl hydroperoxide and reported obtaining a single thiolsulfinate. Although their product was homogeneous to paper chromatography, the results obtained here suggest that it may have been a mixture of the two possible thiolsulfinates. Likewise the oxidation of α-lipoic acid by hydrogen peroxide which was reported by these same workers[16] to give only two thiolsulfinates based on paper chromatography analysis may actually have given all four possible thiolsulfinates. Similar comments may apply to other reported oxidations using *tert*-butyl hydroperoxide[17] and potassium permanganate.[18]

Attempted Structure Assignments

Assignment of the structures **4a, 4a', 4b, 4b', 6a,** and **6b** to the products A–F has proven to be an extremely difficult problem. Kato and Numata[31] have been quite successful in making structural assignments in the isomeric 4-hydroxy-1,2-dithiolane 1-oxides based on an analysis of the $Eu(dpm)_3$, shifted nmr spectra. In our case the presence of four isomers has made a similar approach using our $Eu(fod)_3$-d_{27} shifted spectra a more difficult and to-date insolvable problem. Unlike Kato and Numata we do not have available an analytical technique which permits isolation of all of the individual thiolsulfinates. The use of deuterium exchange followed by nmr analysis has also proven unsuccessful. In the case of the thiolsulfonates some exchange occurred, but since we were always dealing with a mixture of the two possible products analysis of the resulting nmr spectrum does not provide conclusive results. In the case of the thiolsulfinates attempted exchange led only to complete or near-complete decomposition. We are now attempting to make individual assignments of the structures **4a, 4a', 4b, 4b', 6a,** and **6b** to compounds A–F through the use of ^{13}C nmr spectroscopy. When such assignments are available it may be possible to further interpret the data in Table I. The significance of the results reported here is that each of the oxidants used gives a full range of the possible thiolsulfinate products as well as some thiolsulfonate product which results suggest that some previously reported oxidation studies of α-lipoic acid may have to be reevaluated.

Experimental Section

The nmr spectra were measured on a Varian T-60 high-resolution nmr spectrometer. Chemical shift values are δ values relative to internal TMS. The spectra were measured in $CDCl_3$ solution unless otherwise noted. Infrared spectra were measured on a Perkin-Elmer 137 infrared spectrophotometer. The photolysis apparatus was similar to one described in the literature[32] and used a General Electric DWY 650-W lamp without filter. The mass spectral analyses were carried out on a AEI MS-12 mass spectrometer and were run at 70 eV. The glpc analyses were performed on a Varian-Aerograph Model 705 gas chromatograph, using a 0.25 in. × 6 ft column of 10% Carbowax on 60–80 mesh Chromosorb, operated at 140° with a He flow rate of 40 ml/min.

Materials. Reagent grade benzene (Fisher), chloroform (Mallinckrodt), diethyl ether (Fisher), ethanol (U. S. Industrial Chemicals Co.), ethyl acetate (Fisher), methanol (Fisher), and Methylene Blue (Fisher) were used without further purification. Methylene chloride was stirred with concentrated sulfuric acid, washed successively with H_2O, 5–10% $NaHCO_3$, and H_2O, and dried twice with $CaCl_2$. It was then distilled from CaH_2 after refluxing for *ca.* 30 min.

Other materials used were $Eu(fod)_3$-d_{27} (Merck), *dl*-α-lipoic acid (Fluka AG, Germany, mp 60–61°), methanol-d_4 (Bio-Rad, 99.5 atom % D), and chloroform-*d* (Merck, 99.8 atom % D). Diazomethane was prepared from a Diazald kit (Aldrich). Tlc analyses were carried out on Merck precoated silica gel, F-254, 5 × 10 cm plates with 0.25-mm thickness. Preparative tlc plates were made from Merck silica gel, PF-254, on 20 × 20 cm glass plates with a thickness of *ca.* 1 mm. All plates were activated by heating in an oven at 125° for a minimum of 3 hr. Products were visualized by ultraviolet radiation.

Preparation of Methyl α-Lipoate. To a solution of 3.32 g (16.1 mmol) of α-lipoic acid in 50 ml of $CHCl_3$ was added a solution of 0.676 g (16.1 mmol) of diazomethane in 40 ml of diethyl ether.[33] The addition generated some heat and gas (N_2) evolution. The resulting solution was then stored for 24 hr with light excluded and then used as a stock solution of the ester. Aliquot analysis indicated that the reaction had proceeded in an essentially quantitative fashion. The pure ester is a pale yellow oil. It has nmr absorptions at 3.65 (s, 3 H, CH_3) superimposed on triplet at 3.6 (t, 1 H), 3.2 (rough t, 2 H), 2.3 (m, 4 H), and 1.6 (broad s, 6 H). The mass spectrum of α-lipoic acid has a peak at *m/e* 206 (M^+) and the ester has a peak at *m/e* 220 (M^+). The infrared spectrum of the neat ester has a strong doublet at 1715 cm^{-1}.

Photosensitized Oxidation of Methyl α-Lipoate in Chloroform. A solution of 1.01 g (4.59 mmol) of methyl α-lipoate and 0.0522 g of Methylene Blue in 200 ml of $CHCl_3$ was photooxidized for *ca.* 10 min at which time oxygen absorption had essentially ceased. A total of 49 ml (2.19 mmol) of O_2 had been absorbed. The temperature of the reaction solution was maintained at 3–5°. Solvent was removed *in vacuo* to give 1.17 g of residue. A portion (40.2 mg) of this residue was analyzed by preparative tlc using ethyl acetate–benzene (1:1) for development. Four bands were obtained with weights, R_f, and spectral data as follows:

Band No.	R_f	Wt (mg)	% of Total	*m/e*	ir
1	0.27	13.4	36	236	1070 cm^{-1} (thiolsulfinate)
2	0.39	10.4	28	236	1080 cm^{-1} (thiolsulfinate)
3	0.68	10.2	26	252	1310 cm^{-1} 1130 cm^{-1} (thiolsulfonate)
4	0.77	2.8	6	279	Unidentified

The nmr spectrum of band 1 had absorptions at 3.65 (s, 3 H, CH_3), 3.2 (t), 2.4 (m), 1.6 (broad s), 1.3 (s), and 0.9 (m). The nmr spectrum of band 2 had absorptions at 3.65 (s, 3 H, CH_3), 3.6–2.6 (m), 2.4 (t) and 1.6 (broad s). The nmr spectrum of band 3 had absorptions at 4.3 (broad m), 3.65 (s, 3 H, CH_3), 3.6–3.1 (m), 2.9 (d), 2.8 (d), 2.4 (t), and 1.6 (broad s). These materials were analyzed further with the aid of an nmr shift reagent as described below. Total yield of thiolsulfinates was 64% and of thiolsulfonates was 25.7%. Analysis of the thiolsulfonate band by glpc showed the presence of two peaks.

Photosensitized Oxidation of Methyl α-Lipoate in Methanol. A solution of 0.52 g (2.36 mmol) of methyl α-lipoate and 0.0567 g of Methylene Blue in 300 ml of methanol was photooxidized for *ca.* 5 min at which time oxygen absorption had essentially ceased. A total of 33 ml (1.47 mmol) of O_2 had been absorbed. Removal of solvent gave 0.62 g of residue. A portion (91.5 mg) of this material was analyzed by preparative tlc as previously described. Four bands were obtained with weights, R_f, and spectral data as follows:

Band No.	R_f	Wt (mg)	% of Total	*m/e*	ir
1	0.27	53.6	60	236	1070 cm^{-1} (thiolsulfinate)
2	0.39	8.5	9.5	236	1080 cm^{-1} (thiolsulfinate)
3	0.68	13.5	14	252	1310 cm^{-1} 1130 cm^{-1} (thiolsulfonate)
4	0.77	4.0	4	279	Unidentified

Total yield of thiolsulfinates was 75.4% and of thiolsulfonates was 15.4%.

Use of an Nmr Chemical Shift Reagent. The thiolsulfinates obtained by photosensitized oxidation of methyl α-lipoate in methanol were examined further using the chemical shift reagent, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-4,6-octanedione-d_3)europium(III), $Eu(fod)_3$-d_{27}. When the material with R_f of 0.39 was treated with $Eu(fod)$-d_{27} all of the nmr absorptions were shifted to lower field. At ratios of shift reagent to substrate up to *ca.* 1.0 the methyl absorption remained a single sharp singlet. However, when the material with R_f of 0.27 was similarly treated the methyl absorption was shifted downfield and split into three sharp singlets at a ratio of shift reagent to substrate of 0.67. These observations are taken to indicate that these two tlc bands correspond to 1 and 3 thiolsulfinates, respectively. These thiolsulfinates are the cis and trans isomers arising from oxidation of each of the sulfur atoms of methyl α-lipoate and are designated thiolsulfinates A, B, C, and D with A being at lowest and D at highest field in the shifted spectrum. While it was never possible to completely separate by tlc the three thiolsulfinates found in the band with an R_f of 0.27, it was possible, by taking separate cuts of this broad band and using the nmr shift reagent, to show that the three thiolsulfinates are not distributed homogeneously in this band.

The thiolsulfonate tlc band (R_f 0.68) obtained from the photosensitized oxidation of methyl α-lipoate in chloroform was similarly treated with Eu(fod)$_3$-d_{27}. The nmr spectrum of the resulting solution now contains two sharp singlets for the methyl absorption thus indicating the presence of two thiolsulfonates. These are the thiolsulfonates corresponding to oxidation at each of the two sulfur atoms and are designated thiolsulfonates E and F with E being at lowest field in the shifted spectrum. The ratio of shift reagent to substrate at which the splitting of the methyl group was clearly visible was *ca.* 0.27.

By using methyl absorptions peak heights in the shifted spectra it was possible to determine the distribution of thiolsulfinates A–D, and thiolsulfonates E and F in the products of the photosensitized oxidations in the two solvents, methanol and chloroform. The results of this analysis are given in Table I.

Oxidation of Methyl α-Lipoate with Ammonium Persulfate. To a solution of 0.102 g (0.463 mmol) of methyl α-lipoate in 2.5 ml of diethyl ether and 5 ml of 90% ethanol was added 470 μl (0.47 mmol) of 1 *M* aqueous ammonium persulfate. The reaction solution was allowed to stand at room temperature for 16 hr and then analyzed by preparative tlc using ethyl acetate–benzene (1:1) for development as before. Bands corresponding to thiolsulfinate were removed and weighed (22.6 mg, 21%). A small band corresponding to thiolsulfonate was also present. The distribution of thiolsulfinates was determined using the shift reagent, Eu(fod)$_3$-d_{27} and methyl peak heights as before. This distribution of thiolsulfinates A–D is given in Table I.

Oxidation of Methyl α-Lipoate with *tert*-Butyl Hydroperoxide. A solution of 0.102 g (0.463 mmol) of methyl α-lipoate in 2.5 ml of diethyl ether was added to 8 ml of methanol. To this solution was added a solution of 0.0416 g (0.463 mmol) of *tert*-butyl hydroperoxide in 2 ml of methanol. The resulting solution was allowed to stand overnight at room temperature. The volume of solution was reduced to *ca.* 2 ml and then analyzed by preparative tlc as before. Total thiolsulfinate product was 75.7 mg (69%). The distribution of thiolsulfinates A–D was determined as before and is reported in Table I.

Oxidation of Methyl α-Lipoate with Peracetic Acid. To a solution of 0.102 g (0.463 mmol) of methyl α-lipoate in 2.5 ml of diethyl ether cooled to 0° was added slowly 74 μl (0.46 mmol) of 40% aqueous peracetic acid. The solution was allowed to warm to room temperature and stand for 17 hr. It was then analyzed by preparative tlc as before. Total thiolsulfinate product was 45.6 mg (42%). The distribution of thiolsulfinates A–D was determined as before and is reported in Table I. This reaction was repeated except using 10 ml of methanol in addition to 2.5 ml of diethyl ether as solvent for the methyl α-lipoate. The yield of thiolsulfinates in this case was 57.3 mg (52%). Distribution of thiolsulfinates A–D in this case are also shown in Table I.

Oxidation of Methyl α-Lipoate with Triphenyl Phosphite Ozonide. To 50 ml of methylene chloride at −78° saturated with ozone was added a solution of 0.310 g (1 mmol) of triphenyl phosphite in 10 ml of methylene chloride over a period of *ca.* 30 min. Ozone was always present in excess as indicated by the blue color of the solution. After addition of the triphenyl phosphite the reaction mixture was flushed with nitrogen to remove excess ozone. A solution of 0.22 g (1 mmol) of methyl α-lipoate in 5.4 ml of diethyl ether was added to the phosphite ozonide solution over a period of 2 min and in the dark. A portion (32 ml) of the resulting solution was withdrawn with a syringe and allowed to warm to room temperature, and the solvent was evaporated. The residue was analyzed by tlc and the thiolsulfinate distribution determined as before. Total yield of thiolsulfinates was 60.6 mg (26%). The distribution of thiolsulfinates is given in Table I under fast warm up. The remainder of the reaction solution was allowed to stand at −78° for an additional 48 hr. It was then warmed up and analyzed in the same fashion. Yield of thiolsulfinates in this portion was 50.3 mg (21%). Thus the total yield of thiolsulfinates from the phosphite ozonide oxidation was 47%. The distribution of thiolsulfinates obtained in the latter procedure is reported in Table I under slow warmup.

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Registry No.—, **1**, 62-46-4; **3**, 46236-19-5; **4a**, 53142-12-4; **4a'**, 53142-13-5; **4b**, 53142-14-6; **4b'**, 53142-15-7; **5a**, 53142-16-8; **5b**, 53142-17-9; **6a**, 53178-58-8; **6b**, 53142-18-0; O_2, 7782-44-7; ammonium persulfate, 7727-54-0; *tert*-butyl hydroperoxide, 75-91-2; peracetic acid, 79-21-0; triphenyl phosphite ozonide, 12568-76-2.

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Anodic Oxidations. VII.[1] Nuclear Cyanation of Methylanisoles

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Electrochemical oxidation of methylanisoles in methanol containing sodium cyanide was investigated. In the cases of ortho- and meta-substituted methylanisoles, nuclear cyanation took place preferentially. With *p*-methylanisole, side-chain methoxylation surpassed nuclear cyanation. The data obtained are compared with those of other electron-transfer reactions such as the anodic acetoxylation and the acetoxylation and chlorination by metal oxidizing agents. Factors controlling the competition between nuclear and side-chain substitution in alkyl aromatic compounds are ascribable to the degree of positive charge on the aromatic carbon atoms in the cation radicals as well as the nucleophilicity of attacking agents.

The electrochemical oxidation of alkyl aromatics has attracted considerable attention.[2] It is common to observe products resulting from substitution on both the aliphatic side chain and the aromatic nucleus. There appear to be at least two distinct mechanisms, one in which the substrate is oxidized in the primary electrode reaction, while the other in which the primary electron transfer is from either an anion or the solvent. If electron-donating groups such as methoxy are introduced on the aromatic ring, then the oxidation potential of substrates goes down and the former type of mechanism becomes predominant.[2g]

The oxidation of alkyl aromatic compounds by means of metal salts has also been studied extensively. Application of strong oxidants such as cobalt(III) or manganese(III) to substrates having relatively low oxidation potential causes a charge-transfer reaction involving aromatic cation radical intermediates, which gives side chain substitution products.[3] In the presence of relatively reactive nucleophiles such as chloride ion, nuclear substitution is observed together with side chain substitution.[3b]

The anodic cyanations of alkyl aromatic hydrocarbons such as toluene and tetralin were previously tried in methanol.[4] Side-chain methoxylation was the main reaction and small amounts of nuclear cyanation products were by-produced. The primary electrode process of this reaction is the oxidation of aromatic compounds to cationic species which subsequently react with nucleophiles.[5] There appear to be two essentially important means for favoring anodic cyanation: one is to lower the oxidation potential of organic compounds and the other is to increase the positive charge on any of the aromatic carbon atoms in anodically generated cationic species. If a suitable substituent is put on the aromatic ring, these two favorable factors will be satisfied and cyanation may well become the main reaction. We expected a methoxy group to be such a substituent. In the cases of *o*- and *m*-methylanisoles, aromatic cyanation became the main reaction. With *p*-methylanisole, side chain methoxylation was still predominant. In this article, factors controlling the relative prevalence of the two pathways leading to the nuclear cyanation and the side chain methoxylation are discussed.

Results

The anodic oxidation of o-methylanisole in methanol containing sodium cyanide was carried out under a nitrogen atmosphere at 25 ± 1°, with a constant current of 0.1 A. Four aromatic cyanation products, 4-methoxy-3-methyl-, 3-methoxy-4-methyl-, and 2-methoxy-3-methylbenzonitriles, and o-methylbenzonitrile, were formed together with a substantial amount of aromatic methoxylation product, 2,5-dimethoxytoluene. Table I summarizes the results of electrochemical reaction. It also contains the results of anodic cyanation in the acetonitrile solution of tetraethylammonium cyanide.

The electrochemical oxidation of *m*-methylanisole gave four ring cyanation products, 2-methoxy-6-methyl-, 4-methoxy-2-methyl-, and 2-methoxy-4-methylbenzonitriles, and *m*-methylbenzonitrile. Very small amounts of unidentified methoxylation products were by-produced. The reaction in acetonitrile gave the same type of products in poor yield.

Under the above conditions, *p*-methylanisole gave mono- and di-side-chain methoxylation products, *p*-methoxymethylanisole and *p*-methoxybenzaldehyde dimethyl acetal, together with three aromatic cyanation products, 2-methoxy-5-methyl- and 5-methoxy-2-methyl-benzonitriles and *p*-methylbenzonitrile, and a very small amount of side chain cyanation product, *p*-methoxybenzyl cyanide. The reaction in acetonitrile solution of tetraethylammonium cyanide yielded the same cyanation products. Methoxyl displacement by nitrile did not occur.

The current efficiency for these reactions was 60% or so and the remainder of the current would be consumed with the oxidation of cyanide ion. Cyanide ion discharges at the potentials used probably to produce a cyano radical, which might attack the coexisting cyanide ion to form cyanogen anion radical or dimerize to cyanogen.[5b]

Discussion

The cyanation reaction was first attributed to an ion discharge mechanism.[4a,6] However, as a result of recent investigations, there is general agreement so far as the aromatic compound is concerned. Several types of experimental evidence in favor of direct anodic oxidation of the substrate have been presented; they include voltammetric data, controlled potential electrolysis experiments, and results from product analyses.[5,7-9]

The nuclear cyanation and side chain oxidation of alkyl aromatic compounds are formally a 2-equiv change. Controlled potential coulometric data of the anodic cyanation of 2,5-dimethylfuran, 2,5-dimethylthiophene, and diphenylamines support this experimentally,[5c,8,9] although in the case of methylanisoles we were unable to use this technique because of increasing contamination of the anode surface by the electrolysis product. At least two types of cationic intermediates are conceivable: a cation radical produced by an initial one-electron oxidation[10] and a dication formed by either a single two-electron transfer[2a,c] or a disproportionation of initially produced cation radicals.[11,12] By analogy with the anodic pyridination of 9,10-diphenylanthracene[13] and the anodic hydroxylation of thianthrene,[11] a mechanism involving a cation radical intermediate is reasonable.[14] It is difficult to detect directly the cation radical as the intermediate under the strongly basic environments

Table I
Anodic Cyanation of Methylanisoles

Reactant (Registry no.)	Product	Current efficiency,[a] % NaCN in MeOH[b]	Current efficiency,[a] % Et_4NCN in MeCN[b]	Position substd
o-Methylanisole (578-58-5)	*o*-Methylbenzonitrile	0.4	9.1	1
	4-Methoxy-3-methylbenzonitrile	47.2	7.1	4
	3-Methoxy-4-methylbenzonitrile	2.1	0.6	5
	2-Methoxy-3-methylbenzonitrile	7.3	6.3	6
	2,5-Dimethoxytoluene	4.0		4
m-Methylanisole (100-84-5)	*m*-Methylbenzonitrile	0.7	0.9	1
	2-Methoxy-6-methylbenzonitrile	11.4	3.2	2
	4-Methoxy-2-methylbenzonitrile	35.2	9.4	4
	2-Methoxy-4-methylbenzonitrile	15.8	6.2	6
p-Methylanisole (104-93-8)	*p*-Methylbenzonitrile	5.4	8.2	1
	2-Methoxy-5-methylbenzonitrile	17.4	13.0	2, 6
	5-Methoxy-2-methylbenzonitrile	1.8	1.9	3, 5
	p-Methoxybenzyl cyanide	Trace	Trace	Me
	p-Methoxymethylanisole	12.0		Me
	p-Anisaldehyde dimethyl acetal	24.0[c]		Me

[a] Based on 2e process. [b] Temperature, 25°; electricity, 1 F/mol. [c] Based on 4e process.

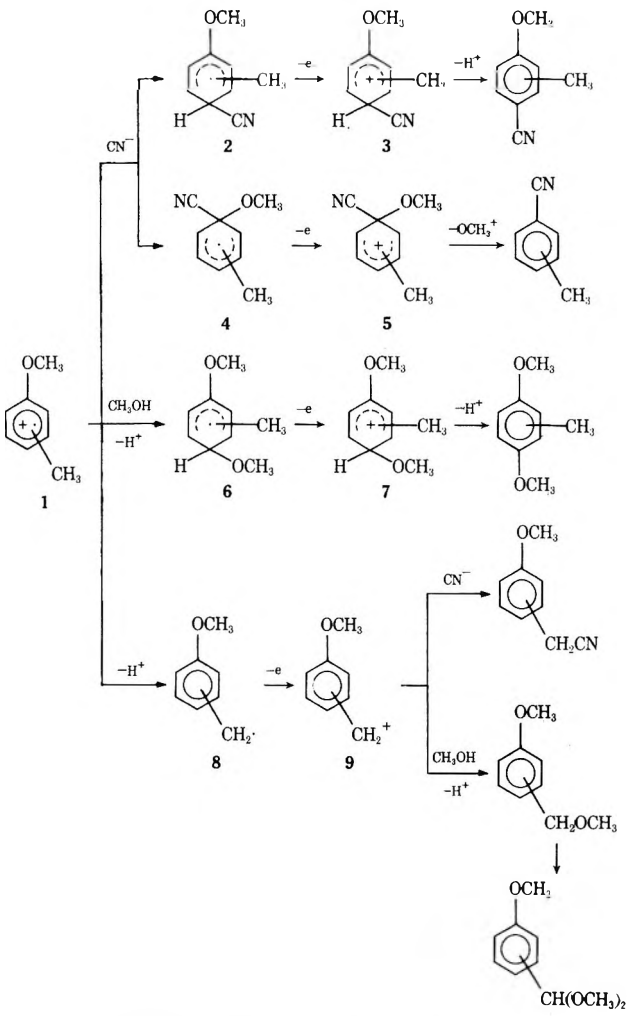
such as methanolic sodium cyanide. Even in weakly basic media such as acetonitrile–perchlorate, the cyclic polarogram of *p*-methylanisole does not give two oxidation peaks separately but gives a peak which corresponds to the transfer of two electrons; a proton peak is observed on the cathodic sweep.[17] The esr measurement of cobaltic acetate oxidation in trifluoroacetic acid, a very weakly basic medium, has shown the presence of the cation radical of *p*-methylanisole.[3b]

The mechanism shown in Scheme I would, therefore, be reasonable to account for the electrochemical oxidation of alkyl aromatics. The principal part of this mechanism is what we previously proposed for the anodic oxidation of 2,5-dimethylfuran[5c] and 2,5-dimethylthiophene[8] and is closely related to that proposed for the oxidation of toluene by cobaltic acetate.[3b] The anodically generated cation radical 1 is attacked by the cyanide ion (or methanol) to produce the radical 2 (or 6), followed by further anodic oxidation and successive proton release, thus leading to the aromatic cyanation (in part methoxylation) products. Part of 1 should also undergo deprotonation to afford the usual radical intermediate 8, which should eventually give rise to side-chain oxidation products.

An alternative mechanism for side-chain oxidation is the ion discharge mechanism. Cyanide ion unquestionably discharges at the potentials used probably to produce a cyano radical, which might abstract a hydrogen atom from the side chain. However, cyanide ion oxidation would not relate directly with the side-chain methoxylation: if the anodically generated radicals abstract a hydrogen atom from the side chain of methylanisole, *o*- and *m*-methylanisoles as well as *p*-methylanisole should produce the side-chain methoxylation products.

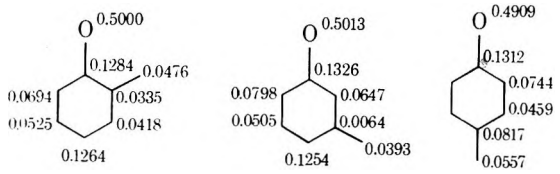
In a previous paper of this series,[1] we demonstrated unambiguously that there are two essentially important stages for anodic cyanation of aromatic compounds: the first stage is the electrochemical oxidation of organic compounds to cation radicals and the second step is the combination reaction of the anodically generated cation radicals with cyanide anion. One can facilitate the former stage by lowering the oxidation potential of substrates by introducing the electron-donating groups such as methoxy on the aromatic nucleus. The second stage is apparently assisted by larger positive charge localized on the carbon atoms in the cation radicals formed. This latter stage is in fact essential; although both *o*- and *m*-methylanisoles have a higher oxidation potential than *p*-methylanisole,[18] their current efficiency in aromatic cyanation is even greater than that of the *p*-methyl isomer.

Scheme I



Nuclear Substitution. The remarkable reaction of cation radicals in the present electrolyte system is the attack

of a nucleophile on the aromatic nucleus. This type of reaction is especially important with o- and *m*-methylanisole cation radicals. According to the proposed mechanism in Scheme I, it is to be expected that the carbon atoms of a higher positive charge in the cation radicals I would react more readily with a nucleophile. Net charge distributions calculated for methylanisole cation radicals by the ω technique[22] show much the same distribution pattern as that of displacement products of aromatic hydrogen by cyanide ion.[23]



An another possible reaction of alkyl aromatic cation radicals is a loss of an α proton, which competes with an attack of a nucleophile on the aromatic nucleus. This competitive reaction was indeed found to be important in the case of *p*-methylanisole. The relative extent of nuclear oxidation is directly related to the degree of positive charge on the carbon atom with an aromatic hydrogen relative to that in the other positions of the cation radical. The relative degree of positive charge on the carbon atoms with an aromatic hydrogen in *p*-methylanisole cation radical is less than that in o- and *m*-methylanisole cation radicals. Therefore, the anodic oxidation of o- and *m*-methylanisoles occurs almost exclusively on the aromatic nucleus, whereas in *p*-methylanisole cation radical, a proton loss competes with a nuclear attack.

The nuclear attack is important when the relatively reactive nucleophiles such as cyanide or chloride ion are used. Thus, while the oxidation of *p*-methylanisole gave only small amounts of nuclear acetoxylation products in the presence of acetate ion,[2c,24] it gave nuclear cyanation products in considerable yields in the presence of cyanide ion. Similarly, the oxidation of toluene with cobaltic acetate gave no measurable nuclear acetoxylation in the presence of acetate ion, whereas it gave substantial yields of nuclear chlorination products in the presence of high chloride ion concentrations.[3b] Analogous results were also obtained with 2-methylnaphthalene. The anodic acetoxylation of toluene is interpreted in the same manner. The relative ratio of nuclear acetoxylation to side-chain acetoxylation was 2.5 in acetic acid containing acetate ion,[2a] whereas it decreased to 0.1 in acetic acid containing nitrate ion.[2d] For anisole, ethylbenzene, and tert-butylbenzene, this tendency is more remarkable. It has been found that the presence of acetate ion is essential for nuclear acetoxylation to occur; no reaction occurs if tosylate or perchlorate is substituted, even with acetic acid as the solvent.[2c]

To check the possibility that methoxymethylbenzonitrile may be produced by anodic cyanation of dimethoxytoluene initially obtained by anodic methoxylation of methylanisole, the anodic cyanation of 3,4-dimethoxytoluene was investigated. The reaction product was not 2-methoxy-5-methylbenzonitrile but 2-methoxy-4-methylbenzonitrile. It is, therefore, concluded that 2-methoxy-5-methylbenzonitrile is produced by the direct substitution of aromatic hydrogen of *p*-methylanisole by cyanide ion.

Side-Chain Substitution. A possible reaction of alkyl aromatic cation radicals is the proton expulsion from the side chain alkyl group.[3b,8] The benzylic radical formed is then rapidly oxidized to the corresponding benzylic cation.[2f] *p*-Methoxybenzyl cation combined predominantly with the solvent methanol to give *p*-methoxymethylanisole; the side-chain cyanation product, *p*-methoxybenzyl cyanide, was formed only in trace amounts. To ascertain this preference of the cation for methanol, the competitive reactions of solvent methanol and sodium cyanide with *p*-chloromethylanisole were investigated. it is known that this chloride readily produces the *p*-methoxybenzyl cation.[25] Product analysis showed that *p*-methoxymethylanisole was the major product, in agreement with the results of anodic oxidation.

p-Anisaldehyde dimethyl acetal is produced by the further oxidation of methoxymethylanisole.[26]

Experimental Section

The electrochemical and spectroscopic instrumentation and techniques were as previously described.[5c]

Materials. Methanol was purified as previously described.[5c] Reagent grade sodium cyanide was used with no purification other than drying. Methylanisoles and tolunitriles were obtained commercially and were purified by distillation before use.

Tetraethylammonium cyanide was prepared according to the method given by Andreades and Zahnow.[5b]

The following reference materials were prepared according to the literature: 2-methoxy-3-methylbenzonitrile,[27] 2-methoxy-4-methylbenzonitrile,[28] 2-methoxy-5-methylbenzonitrile,[30] 2-methoxy-6-methylbenzonitrile,[31] 3-methoxy-2-methylbenzonitrile,[32] 3-methoxy-4-methylbenzonitrile,[33] 4-methoxy-2-methylbenzonitrile,[34] 4-methoxy-3-methylbenzonitrile,[35] 5-methoxy-2-methylbenzonitrile,[36] *p*-methoxybenzyl cyanide,[37] 2,3-,[38] 2,4-,[39] 2,5-,[40] 2,6-,[41] 3,4-,[42] and 3,5-dimethoxytoluenes,[43] *p*-methoxymethylanisole,[44] *p*-anisaldehyde dimethyl acetal,[45] 2- and 3-acetoxy-4-methylanisoles,[3a] and *p*-methoxybenzyl acetate.[46]

Anodic Cyanation. A methanolic solution (200 ml) of methylanisole (14.6 g, 0.12 mol) and sodium cyanide (5.9 g, 0.12 mol) was electrolyzed at 25°, with a constant current of 0.1 A at 13–19 V, until 1 F/mol of charge was passed through the solution. The catholyte was a methanol solution of sodium cyanide. The electrolyzed mixture was treated as usual.[5c] The products were analyzed by vpc, the column packing being PEG 6000.

Each product was separated in pure form by preparative vpc and the ir, nmr, and mass spectra of the products were compared with those of the corresponding authentic sample.

Anodic Acetoxylation of *p*-Methylanisole in Methanol. The anolyte was made up of 19.5 g (0.16 mol) of *p*-methylanisole and 13.1 g (0.16 mol) of sodium acetate in 200 ml of methanol. The catholyte was a methanolic solution of sodium acetate (0.8 *M*). The electrolysis was carried out at 25°, with a constant current of 0.1 A until 1 F/mol had passed through the electrolyte. The solution was then dropped into a vigorously stirred slurry of sodium bicarbonate in water. The organic product was taken up in ether, dried over sodium sulfate, filtered, and stripped on a rotary evaporator. The residue was then analyzed by glc using PEG 6000 column. The following materials were obtained: *p*-methylanisole recovered (8.53 g, 0.070 mol), 2-acetoxy-4-methylanisole (0.36 g, 0.002 mol; current efficiency, 2.5% based on 2e process), *p*-methoxybenzyl acetate (0.25 g, 0.001 mol; current efficiency, 1.3%), *p*-methoxymethylanisole (3.94 g, 0.026 mol; current efficiency, 32.5%), and anisaldehyde dimethyl acetal (1.01 g, 0.006 mol; current efficiency, 15.0% based on 4e process).

Registry No.—*o*-Methylbenzonitrile, 529-19-1; *m*-methylbenzonitrile, 620-22-4; *p*-methylbenzonitrile, 104-85-8; *p*-methoxybenzyl cyanide, 104-47-2; 2-methoxy-3-methylbenzonitrile, 53078-68-5; 2-methoxy-4-methylbenzonitrile, 53078-69-6; 2-methoxy-5-methylbenzonitrile, 53078-70-9; 2-methoxy-6-methylbenzonitrile, 53005-44-0; 3-methoxy-4-methylbenzonitrile, 3556-60-3; 4-methoxy-2-methylbenzonitrile, 21883-13-6; 4-methoxy-3-methylbenzonitrile, 53078-71-0; 5-methoxy-2-methylbenzonitrile, 22246-19-1; *p*-methoxymethylanisole, 1515-81-7; 2,3-dimethoxytoluene, 4463-33-6; 2,4-dimethoxytoluene, 38064-90-3; 2,5-dimethoxytoluene, 24599-58-4; 2,6-dimethoxytoluene, 5673-07-4; 3,4-dimetholytoluene, 494-99-5; 3,5-dimethoxytoluene, 4179-19-5; *p*-methoxybenzaldehyde dimethyl acetal, 2186-91-7; sodium cyanide, 143-33-9.

Supplementary Material Available. The ir, nmr, and mass spectra of the products will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 ×

148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-63.

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Reaction of Isocyanides with Thio Acids[1]

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Reaction of isocyanides, **1**, with thiocarboxylic acids, **2**, have been found to give novel *N*-thioformyl-*N*-acylamides, **3**, and in certain instances, thioformamide **4**. The formation of **3** thus represents a departure from the usual reaction of mercaptans or carboxylic acids with **1**. The former usually give simple alkylthio α adducts, while formamide and acid anhydride formation results from reaction of the latter with **1**. When phosphorus thio acids are herein substituted for **2**, simple α adducts **5** are first formed which, *via* measurable first-order kinetics, are transformed to novel, stable *N*-thioformyl-*N*-phosphoramides, **6**. The reaction rates are shown to depend on the nature of both the phosphorus thio acid and the isocyanide, with no **6** evident from reaction of phosphinodithioic acid with **1**. Finally, reaction of dithiocarbamic acids (*via* their salts) with **1**, is shown to give the α adduct **7** in a reaction that is largely reversible at high temperatures.

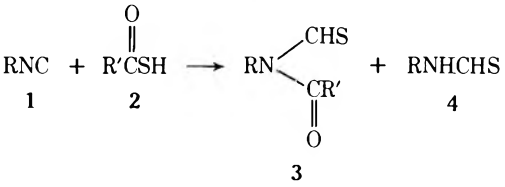
The reaction of mercaptans with organic isocyanides has been shown to give α adducts or isothiocyanates, depending upon the reactants, catalyst, and reaction systems.[2] On the other hand, α adducts arising from carboxylic acids are unstable, with formamide and acid anhydrides as the products isolated.[3]

It was therefore of interest to study the reaction of isocyanides with thio acids. These latter materials have chemi-

cal properties akin to those of both mercaptans and carboxylic acids and consequently could form either the respective analogous α adducts or thioformamides; alternatively, possessing unique features of their own, thio acids might be expected to react *via* a singular reaction mode with isocyanides.

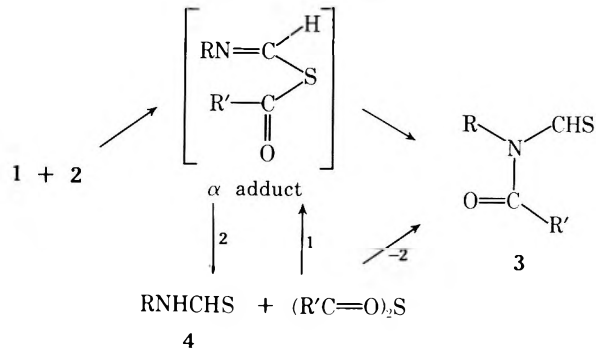
Combination of isocyanide **1** and thiocarboxylic acids, **2**, in inert solvents such as ether or benzene, produced an exotherm with quick disappearance of **1** (as observed by monitoring the diminishing isocyanide ir absorption maximum at 4.7 μ). Depending upon the thio acid and isocyanide employed, *N*-alkyl-*N*-acylthioformamide, **3**, is formed, along with varying amounts of *N*-alkylthioformamide **4** (Scheme I).

Scheme I



By-product **4** most likely arises *via* cleavage of the initial but unstable α adduct, with formation of anhydrosulfide. This pathway is similar to that suggested for the reaction of carboxylic acids with isocyanides. Moreover, it is entirely possible that this route facilitates the formation of **3** *via* acylation of **4** by the anhydrosulfide. In fact, it has been demonstrated (see Experimental Section) that these latter two reagents, in the presence of added base, give appreciable amounts of **3**. Of course, this acylation may well occur initially at the thiono sulfur (with isocyanide behaving as a base), giving rise to the identical α adduct intermediate derived from simple α addition of thio acid **2** to isocyanide **1**. Less likely would be direct acylation of nitrogen in **4** to form **3**. These various pathways are set forth in Scheme II.

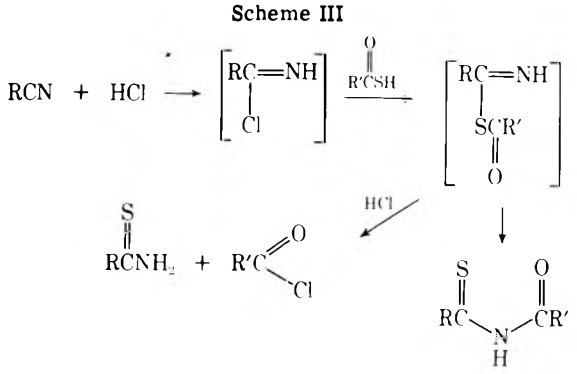
Scheme II



Formation of **3** *via* the α adduct shows a similarity to the acid-catalyzed conversion of nitriles to thioamides. In this classical synthesis,[4] hydrogen chloride both promotes the addition of thio acid to nitrile and serves to cleave the adduct to thioamide and acid chloride. However, if the adduct contains an acyl group with a fair degree of migratory aptitude (such as chloroacetyl), *N*-acylthioamides can be exclusively formed[5] (Scheme III).

Due partly to this undesirable migration when preparing primary thioamides from nitriles, the readily available phosphorodithioic acids $[(RO)_2PS_2H]$ can be successfully substituted in place of thiocarboxylic acids.[6] The thiophosphoryl group apparently is slow to migrate to nitrogen and hence is completely cleaved to $(RO)_2PSCl$ and primary thioamide.

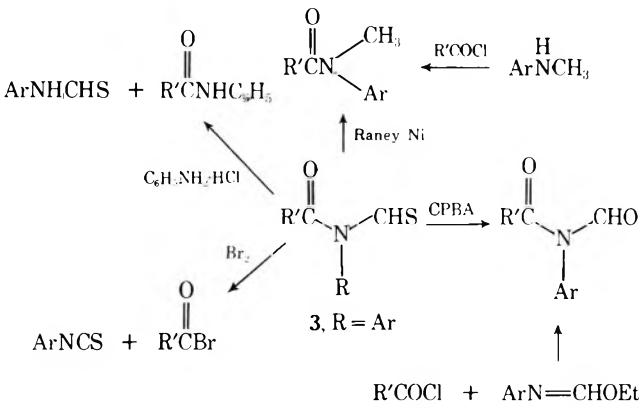
Scheme III



The contrasting properties of different thio acids are also apparent in their reaction with isocyanides. While thioacetic and thiopropionic acids gave about 10–20% thioformamide **4** with aryl isocyanides and *ca.* 50% thioformamide with α-methylbenzyl isocyanide, both thiobenzoic and chlorothioacetic acids gave wholly **3** with aryl isocyanides.

Structure proof for the *N*-acylthioformanilides rests on both chemical transformations and spectral evidence. Raney nickel reduction of **3** reduced the thioformyl group to *N*-methyl, while oxidation with *m*-chloroperbenzoic acid (CPBA) gave the *N*-formyl analog. These degradation products had been prepared previously by other methods[7] as shown in Scheme IV. Finally, bromination of **3** gave carbon–nitrogen cleavage with formation of isothiocyanate and acyl bromide, while this same bond was cleaved by aniline to anilide and thioformanilide.

Scheme IV



The yellow *N*-formyl-*N*-acylamides, **3**, are characterized spectrally by a carbonyl absorption at 5.8–5.9 μ. This of course is at higher frequency than found for the normal amide carbonyl absorption, undoubtedly due to the shortened carbonyl bond (more sp^2 character) which results from greater nitrogen lone-pair interaction with the thiono group. The thioformyl proton is also quite explicit as recorded *via* nmr. The sharp singlet appears at *ca.* δ 10.5, downfield by about 60–100 Hz from the thioformyl proton in the by-product thioformamides, **4**.

The facile reaction of thiocarboxylic acids and isocyanides to form **3** prompted an investigation of this reaction with thiophosphoric acids. These easily derived materials are generally more stable than thiocarboxylic acids. Furthermore, excellent synthetic methods also exist for some of the analogous phosphono- and phosphinodithioic acids.[8]

Mixing any of the phosphorus thio acids with isocyanide produced an immediate reaction, with nearly, but not complete, disappearance of the isocyanide band at 4.7 μ. Simultaneously, there was noted the appearance of a medium to

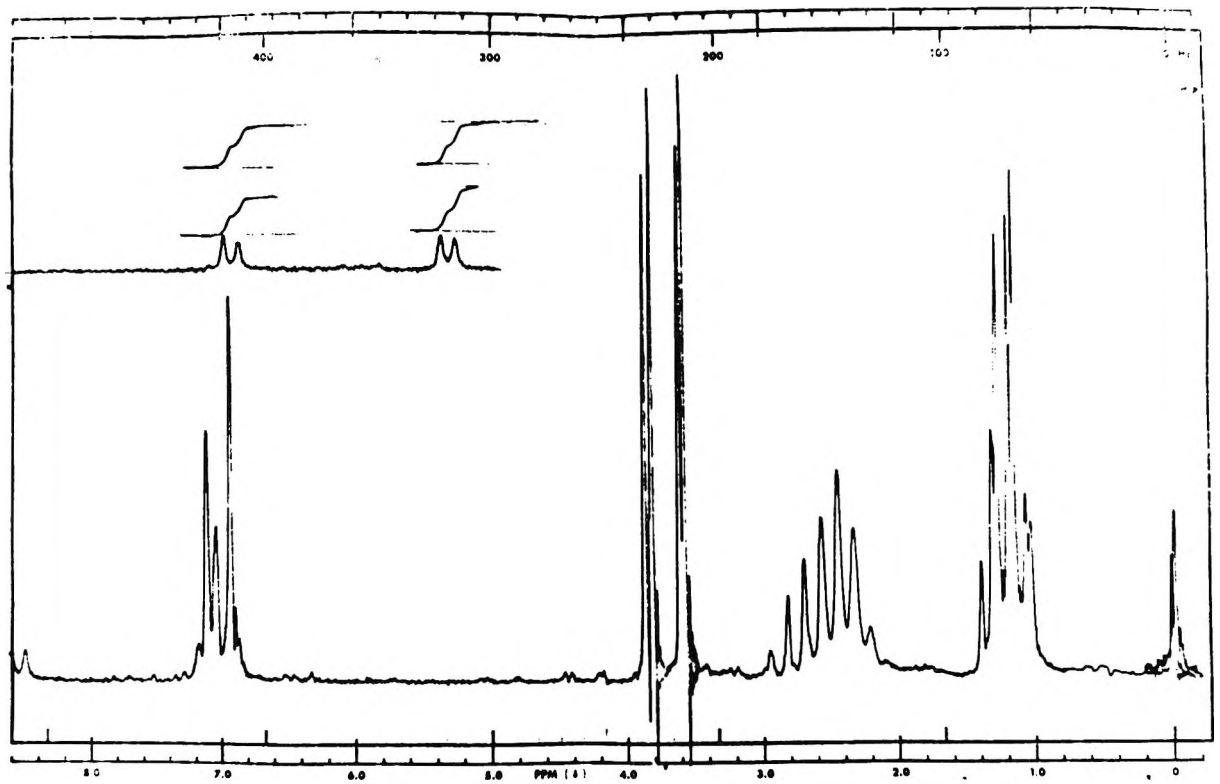


Figure 1. Nmr (CCl_4) at *ca.* 1 half-life of **5**, derived from 2,6-diethylphenyl isocyanide and $(CH_3O)_2PS_2H$, in its conversion to **6c**.

intense C=N band at 6.1–6.2 μ. Nmr spectra of the reaction mixtures usually revealed a doublet at *ca.* δ 8.7 (J = 6 Hz), resulting from coupling with phosphorus. These properties would indicate the initial product to be the α adduct. Both the nmr and ir absorptions agree well with those observed for a similar moiety (–S–CH=N) in α adducts of mercaptans to isocyanide.[2] There are however, some sharply delineating distinctions of these α adducts, **5**, that differentiate them from earlier mercaptan α adducts.

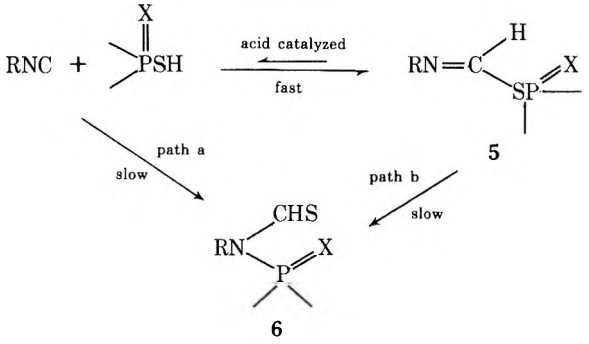
First, no pairs of syn and anti adducts are clearly distinguishable in **5**. In favorable circumstances, only one sharp low-field doublet is observed with no other absorption in that region. In other instances, small, minor peaks, some broadened, are seen in this region, but this is interpreted as arising from side reaction (thioformamide formation) rather than evidence of syn–anti isomerism.

Second, the α adducts from phosphorus thio acids appear to exist in equilibrium with small amounts of isocyanide and thio acid. Indeed, even with excess thio acid present, a small but distinguishable isocyanide ir absorption is still evident. Moreover, the presence of small amounts of excess thio acid invariably causes the low-field doublet to collapse to a singlet. This is interpreted as an acid-catalyzed dissociation of the α adduct (at least breakage of one bond between phosphorus and the α proton).

Finally the most distinguishing characteristic of the α adducts from phosphorus thio acids and isocyanide, **5**, are their measurable rearrangement to *N*-thioformylphosphoramides, **6**. The new materials are characterized by a downfield nmr absorption greater than δ 10, which invariably appears as a doublet (J = 7 Hz) regardless of the acid concentration. The C=N absorption at 6.2 μ is no longer present in **6**. Figure 1 shows an nmr spectrum of **5c** partially converted to **6c**.

The facile but slightly reversible α addition of phosphorus thio acids to isocyanide, followed by a slow irreversible rearrangement to the *N*-thioformylphosphoramide, is shown in Scheme V.

Scheme V



It is apparent from examination of Scheme V that at least two possible alternative mechanisms exist for formation of the final product. Path Va represents a direct attack on the isocyanide nitrogen, while path Vb involves an intramolecular migration of the phosphorus group with cleavage of the P–S bond. If the latter is correct, the migration must necessarily be slower than that observed in reaction of thiocarboxylic acids with isocyanides, to allow **5** to be observed at all. This lesser migratory aptitude is in accord with the reaction of phosphorus thio acids with nitriles, discussed earlier.

Rate data were compiled by measuring, as a function of time, the area under the nmr peaks (1) for the α proton from the initially formed α adduct and (2) for the *N*-thioformyl proton. The measurements show that the formation of **6** is first order with respect to [**5**] and independent (within limits) of thio acid concentration. Unfortunately the observed kinetics do not serve to distinguish between path a and path b, as rates *via* either mechanism would be independent of thio acid concentration. The measured rates do however distinguish between rearrangement proclivities of the original adducts from the various phosphorus thio acids, and these are plotted in Figure 2.

It is apparent that phosphorodithioic acids rearrange

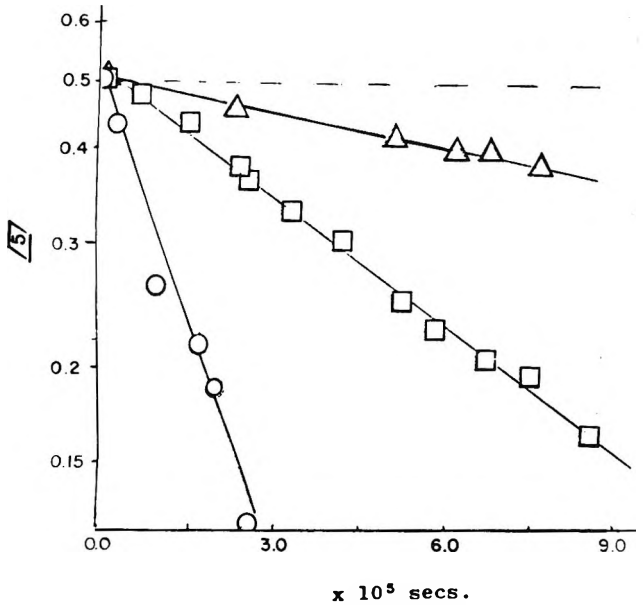


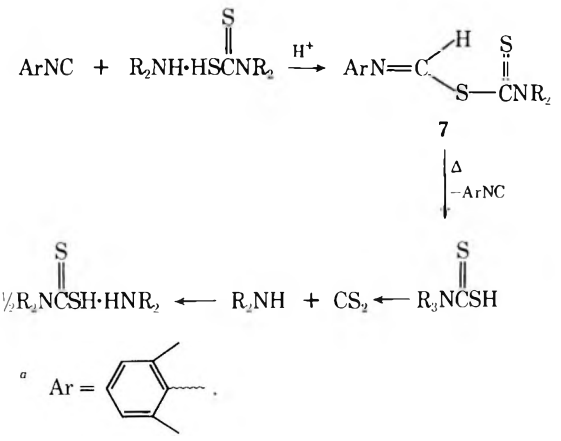
Figure 2. Rearrangement rates of α adducts **5** to thioformylphosphorus amides **6**. Material **5** was derived from 2,6-diethylphenyl isocyanide and phosphorus acids as follows: (○) $(CH_3O)_2PS_2H$; (□) $(C_2H_5O)_2PS_2H$; (△), $C_2H_5OP(CH_3)S_2H$; (– – –) $(C_6H_5)_2PS_2H$.

faster than the analogous phosphonic acids, while α adducts from phosphinodithioic acids do not measurably convert to **6**, even at elevated temperatures. Rationales for the observed order would at present be necessarily speculative without further concrete evidence regarding the mechanism.

Although dithiocarbamic acids are particularly unstable,[9] an isocyanide adduct can be isolated from such acids. One method which met with some success was to neutralize the dithiocarbamate salt formed from carbon disulfide and morpholine in the presence of isocyanide. Reaction could be effected by placing the salt in tetrahydrofuran with 2,6-xylyl isocyanide, cooling to 0–5° and slowly adding 85% phosphoric acid.

The reaction mixture, as monitored by ir methods, displayed a much diminished isocyanide absorption. This absorption did not entirely disappear, even when small additional amounts of phosphoric acid or morpholine dithiocarbamate were added. The reaction mixture was then poured into ice water and the insoluble solid separated and recrystallized. The product so derived displayed spectral properties entirely consistent with that of the α adduct **7** (Scheme VI), including a single resonance at δ 9.6 (–S—CH=N, 1 proton), while the ir spectrum shows prominent C=N absorption at 6.1 μ.

Scheme VI[a]



The α adduct, **7**, could be recrystallized from methylcyclohexane, without change, but with no improvement in melting point. This observation indicated a decomposition mode upon heating. In view of the formation of acylthioformamide **3** and *N*-thioformylphosphoramide **6**, a similar transformation was looked for upon heating **7**. Instead, upon treatment in an inert solvent, a precipitate was formed which was shown to be the morpholine salt of the dithiocarbamate, while 2,6-xylyl isocyanide was recovered in the filtrate (Scheme VI).

Extensions of the thiocarbamic acid addition to isocyanide were disappointing, and the scope and utility of the reaction appear limited. Acidification of the morpholine salt of morpholine thiolcarbamate failed to give an α adduct. Instead, a strong ir absorption for carbonyl sulfide was observed, with no diminution of the isocyanide band. Upon treatment with water only isocyanide was recovered. Obviously, the thiolcarbamic acid from neutralization of the salt decomposes faster than its addition to isocyanide. The same results were obtained even at −40 to −50°.

Even employing dithiocarbamate salts of amines other than morpholine, poor yields and low-quality adducts were obtained. Presumably morpholine with carbon disulfide forms one of the more stable dithiocarbamic acids, while others decompose faster than their addition to isocyanides.

Experimental Section

***N*-Thioformyl-2′,6′-diethylpropionanilide (3a).** 2,6-Diethylphenyl isocyanide[10] (**1a**) (5.1 g, 0.032 mol) was placed in ether and 2.9 g (0.032 mol) of thiopropionic acid was added. After standing overnight, ir analysis indicated (4.7 μ) some unreacted isocyanide present. The material was heated for 2 hr, with no change in isocyanide concentration. To the reaction mixture was then added 20% excess thiopropionic acid and the material was refluxed 1 additional hr. All isocyanide had reacted, and the ether solution was washed with sodium bicarbonate solution, followed by a water wash, drying over magnesium sulfate, and filtering. The ether was removed under vacuum and the residual oil taken up in pentane. A small amount of white solid (1.2 g) insoluble in pentane was isolated as 2,6-diethylthioformanilide, **4a**, mp 98–101°.[11] The clear pentane solution on cooling gave 5 g (63% yield) of yellow crystals, mp 34–36°: pertinent nmr ($CDCl_3$) δ 10.8 (s, 1, NCHS); ir ($CHCl_3$) 5.8 μ (C=O).

Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.59; H, 7.72; N, 5.81.

***N*-Thioformyl-2′,6′-diethylacetanilide (3b). A.** A 10% molar excess of thioacetic acid was refluxed with 4.2 g of **1a** in ether for 2 hr. The cooled ether solution was washed with sodium bicarbonate solution followed by a water wash. The dried (magnesium sulfate) ether solution was evaporated, and the residue taken up in pentane. From this, **4a** was isolated in small amounts, while **3b** was isolated upon cooling as crystals, mp 40–42°, in 83% yield: nmr ($CDCl_3$) δ 1.92 (s, 3, CH_3CO), 10.8 (s, 1, NCHS); ir ($HCCl_3$) 5.8 μ (C=O).

Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95. Found: C, 67.00; H, 7.62; N, 5.72.

B. In *ca.* 50 ml of dry ether, 1.2 g (0.01 mol) of acetyl sulfide,[12] 1.9 g (0.01 mol) of 2,6-diethylthioformanilide, and 0.8 g (0.01 mol) of pyridine were mixed and refluxed for 18 hr. The ether solution on cooling was washed successively with sodium carbonate solution and water and then dried over $MgSO_4$. After removal of the drying agent and distillation of the solvent, the residue was recrystallized from pentane to give 0.7 g of starting 2,6-diethylthioformanilide and 0.95 g of **3b** assaying by nmr at 86% (42% yield).

2′,6′-Diethyl-*N*-thioformylbenzanilide (3c). In 100 ml of ether, 4.5 g (0.029 mol) of **1a** was mixed with 3.8 g (0.029 mol) of thiobenzoic acid **2c**. A slight exotherm was noted. After the mixture stood at ambient temperature for 16 hr, a small amount of isocyanide was detected, which still remained after adding an additional 1 g of **2c** and refluxing for 3 hr. The ether solution was washed with sodium bicarbonate, followed by a water wash. After drying over magnesium sulfate and solvent evaporation, the resi-

due could be recrystallized from cold hexane to give 5.2 g (62% yield) of yellow crystals, mp 64–65°: nmr ($CDCl_3$) δ 10.6 (s, 1, NCHS); ir ($CHCl_3$) 5.82 μ (C=O).

Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.64; H, 6.48; N, 4.87.

2′,6′-Diethyl-*N*-thioformyl-2-chloroacetanilide (3d). To 100 ml of ether were added **1a** (6.4 g, 0.04 mol) and 0.045 mol of freshly distilled chlorothioacetic acid. An exotherm was noted, and the solution was allowed to stand 16 hr. Inspection of the reaction mixture by ir after this time revealed complete reaction of **1a**. The ether solution was washed once with dilute sodium bicarbonate, followed by water. After drying over magnesium sulfate, the filtered ether solution was evaporated, and the resulting residue recrystallized from cold heptane to give 9.1 g (84% yield) of yellow crystals, mp 93–94°: nmr ($CDCl_3$) δ 3.98 (s, 2, $ClCH_2CO$), 10.9 (s, 1, NCHS); ir ($CHCl_3$) 5.8 μ (C=O).

Anal. Calcd for $C_{13}H_{16}ClNOS$: Cl, 13.14; N, 5.19; S, 11.89. Found: Cl, 13.25; N, 5.23; S, 12.18.

2,2′,6′-Trichloro-*N*-thioformylacetanilide (3e). In ether solvent, 3.4 g (0.02 mol) of 2,6-dichlorophenyl isocyanide,[10] **1b**, was mixed with 2.5 g of α-chlorothioacetic acid. An exotherm was noted; then the resulting solution was heated at reflux for 3 hr. During this time yellow solid was deposited. After standing at room temperature overnight, the solution was filtered to give 4.9 g (83%) of **3e**, mp 164–165°: nmr ($CDCl_3$) δ 3.98 (s, 2, $ClCH_2CO$), 7.4–7.6 (m, 3, Ar H), 10.7 (s, 1, NCHS); ir ($CHCl_3$) 5.8 μ (C=O).

Anal. Calcd for $C_9H_6Cl_3NOS$: Cl, 37.64; N, 4.96; S, 11.35. Found: Cl, 38.20; N, 5.23; S, 11.27.

2′,6′-Dichloro-*N*-thioformylacetanilide (3f). Following the procedure given for **3e**, 3 g of thioacetic acid combined with 5.1 g (0.03 mol) of **1b** gave, after recrystallization from methylcyclohexane, 5.1 g of **3f**, mp 91–92°: nmr ($CDCl_3$) δ 2.02 (s, 3, CH_3CO), 7.3–7.6 (m, 3, Ar H), 10.5 (s, 1, NCHS); ir ($CDCl_3$) 5.8 μ (C=O).

Anal. Calcd for $C_9H_7Cl_2NOS$: C, 43.56; H, 2.84; N, 5.67. Found: C, 43.14; H, 2.95; N, 6.17.

6′-*tert*-Butyl-2-chloro-*N*-thioformyl-*o*-acetotoluidide (3g). In 100 ml of ether solvent were dissolved 5.2 g (0.03 mol) of 6-*tert*-butyl-*o*-tolyl isocyanide (mp 63–65°) and 3.9 g of α-chlorothioacetic acid. The mixture was heated at reflux for 1 hr, cooled, and washed once with sodium bicarbonate solution, followed by a water wash. After drying over magnesium sulfate, the ether solution was filtered and then evaporated to give, after trituration with pentane–ether, 5.9 g of **3g**, mp 115°: nmr ($CDCl_3$) δ 1.4 (s, 9, $(CH_3)_3C$), 2.2 (s, 3, Ar CH_3), 4.02 (AB quartet, 2, J = 15 Hz, $ClCH_2CO$, 7.2–7.8 (m, 3, Ar H), 10.9 (s, 1, NCHS); ir ($CHCl_3$) 5.8 μ (C=O).

Anal. Calcd for $C_{14}H_{18}ClNOS$: Cl, 12.49; N, 4.94; S, 11.30. Found: Cl, 12.91; N, 5.05; S, 11.51.

2′-*tert*-Butyl-6′-ethyl-*N*-thioformylacetanilide (3h). In ether, 2-*tert*-butyl-6-ethylphenyl isocyanide [bp 81–87° (0.7 mm), $n^{25}D$ 1.5165)] (5.4 g) was mixed with 3.0 g of thioacetic acid, and the mixture was refluxed until the isocyanide band (ir 4.7 μ) had vanished. The material was washed with sodium bicarbonate, followed by water. After ether drying ($MgSO_4$) and solvent removal the residual oil was allowed to deposit crystals of 2-*tert*-butyl-6-ethylthioformanilide, **4b**, mp 98–100° (identified by spectra and mixture melting point with authentic material obtained from the formanilide and P_2S_5). The residual oil was identified as **3h** (containing traces of **4b**), but it was suitable for the transformation described below: pertinent nmr ($CDCl_3$) δ 10.4 (s, 1, NCHS); ir ($CDCl_3$) 5.8 μ (C=O).

Anal. Calcd for $C_{15}H_{21}NOS$: N, 5.32. Found: N, 5.30.

Mixture of *N*-(α-Methylbenzyl)-*N*-thioformylacetamide (3i) and *N*-(α-Methylbenzyl)thioformamide (4c). In ether, α-methylbenzyl isocyanide (0.04 mol, 5.2 g) was mixed with 5 g (0.045 mol) of thioacetic acid; the material was refluxed 3 hr and then permitted to stand overnight at room temperature. After treatment with sodium bicarbonate solution, followed by a water wash, the ether solution was dried over magnesium sulfate, filtered, and vacuum treated to remove solvent. The residual oil consisted of a *ca.* 50:50 mixture of **3i** and **4c**, as determined by ir and nmr spectra. **3i** could be obtained pure by taking the residue up in hot pentane, decanting the solution from residual oil, and permitting **3i** to crystallize from pentane with scratching, mp 68–71°: nmr ($CDCl_3$) δ 1.75 (d, 3, J = 7 Hz, $CHCH_3$), 2.2 (s, 3, CH_3CO), 6.85 (q, 1, J = 7 Hz, $CHCH_3$), 10.5 (s, 1 CHS); ir (CCl_4) 5.8 μ (C=O).

Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76; S, 15.47. Found: C, 64.04; H, 6.48; N, 6.79; S, 15.75.

Transformations of 3. A. Oxidation of 3 with *m*-Chloroperbenzoic Acid. Several of the thioformyl materials, **3**, were converted to their oxygen analogs (Scheme IV). The conversion of **3g** is illustrative. In 25 ml of dichloromethane was charged 1.4 g (0.005 mol) of 6-*tert*-butyl-2-chloro-*N*-thioformyl-*o*-acetotoluidide and 3.1 g of 85% *m*-chloroperbenzoic acid. There was a noticeable exotherm, after which the mixture was stirred at ambient temperature for 2 hr. The slurry of *m*-chlorobenzoic acid was filtered off and the filtrate washed with a solution of combined sodium carbonate and sodium sulfite, followed by a separate water wash. The organic layer was then dried over magnesium sulfate, filtered, and vacuum treated to remove solvent, not permitting the contents of the flask to warm above room temperature. The solid residue was washed with pentane and recrystallized from methylcyclohexane, mp (sealed capillary) 128–129°: nmr ($CDCl_3$ plus deuteriodimethyl sulfoxide) δ 1.1 (s, 9, $(CH_3)_3C$), 2.02 (s, 3, Ar CH_3), 4.1 (br s, 2, $ClCH_2CO$), 7.05–7.6 (m, 3, Ar H), 9.4 (br s, 1, CHO); ir (chloroform) 5.75 and 5.86 μ (HC=O and CC=O, respectively). The melting point is identical with that previously reported for 6′-*tert*-butyl-2-chloro-*N*-formyl-o-acetotoluidide[13] and the spectral results were entirely consistent with those previously discussed for the respective α-bromo derivative.[7]

B. Raney Nickel Treatment. To 5 g of freshly prepared Raney nickel in 100 ml of ethanol was added 1 g of **3h**. The mixture was refluxed 3 hr, cooled, and filtered. The filtrate was vacuum treated and the resulting residue recrystallized from heptane to give a product entirely identical (melting point, mixture melting point, ir, nmr) with authentic *N*-methyl-2′-*tert*-butyl-6′-ethylacetanilide, mp 58–59°, prepared from *N*-methyl-2′-*tert*-butyl-6′-ethylaniline[7] and acetyl chloride.

Anal. Calcd for $C_{15}H_{23}NO$: N, 6.00. Found: N, 6.05.

C. Reaction with Aniline Hydrochloride. In 50 ml of toluene, 3.0 g (0.01 mol) of **3c** was mixed with 1.4 g of aniline hydrochloride and the whole was refluxed for *ca.* 20 hr. Hydrogen chloride rather than hydrogen sulfide evolution was observed during this time. Upon cooling, 1.3 g of crystals, mp 159–160°, was deposited. These were identified as benzanilide. Solvent evaporation gave crystals of 2′,6′-diethylthioformanilide, **4a**.

D. Reaction with Bromine. In 75 ml of CCl_4 was dissolved 3.0 g (0.011 mol) of **3d** and to this solution, with stirring, was added 1.8 g (0.011 mol) of bromine, contained in *ca.* 20 ml of the same solvent. The reaction was monitored by nmr. It showed ready disappearance of the thioformyl proton, and a shift of the chloromethylene group. After solvent had been removed, the residue was distilled, with chloroacetyl bromide collected at bp 53° (50 mm) and 2,6-diethylphenyl isothiocyanate at bp 139° (10 mm). The 2,6-diethylphenyl isothiocyanate thus prepared possessed ir and nmr spectra identical with those of authentic material prepared from 2,6-diethylaniline and thiophosgene. The chloroacetyl bromide, which possessed consistent ir (C=O at 5.52 μ) and nmr spectra ($ClCH_2$, δ 4.50, s), could be further converted to α-chloroacetanilide upon reaction with aniline.

***N*-(2,6-Diethylphenyl)thiolformimidic Acid–*O,O*-Diethylphosphorodithioic Acid Mixed Anhydrosulfide (5a).** 2,6-Diethylphenyl isocyanide (8.0 g, 0.05 mol) was dissolved in ether and 10 g (0.054 mol) of *O,O*-diethylphosphorodithoic acid was added dropwise. The isocyanide ir band at 4.7 μ had nearly completely disappeared after 0.5 hr at room temperature. The solution was washed with sodium carbonate solution and then dried over magnesium sulfate. After solvent evaporation under high vacuum, the residual oil (which would not crystallize) was filtered through clay to give 13 g of a light amber oil: nmr ($CDCl_3$) δ 1.2 and 1.4 (two t, 12, J = 7 Hz, CH_2CH_3), 2.5 (4, J = 7 Hz, Ar CH_2CH_3), 4.2 (m, 4, $POCH_2CH_3$), 7.0 (3, Ar H), 8.8 (d, 1, J = 6 Hz, =CH); ir (film) trace at 4.7 (Ar NC), 6.2 μ (C=N).

Anal. Calcd for $C_{15}H_{24}NO_2PS_2$: N, 4.05; P, 8.97; S, 18.56. Found: N, 4.01; P, 8.69; S, 18.43.

***O,O*-Diethyl *N*-(2,6-Diethylphenyl)-*N*-thioformylphosphoramidothioate (6a).** Material **5a** (12.5 g) was allowed to stand for 2 weeks at room temperature, after which time it had completely solidified. Spectral analyses were recorded on this solid and found identical with those recorded after the material had been recrystallized from cold hexane to give 9.1 g of yellow crystals, mp 42–43°: nmr ($CDCl_3$) δ 1.2 and 1.25 (2 t, 12, J = 7 Hz, CH_2CH_3), 2.60 (q, 4, J = 7 Hz, Ar CH_2CH_3), 4.2 (m, 4, $POCH_2CH_3$), 7.1 (3, Ar H), 10.4 (d, 1, J = 7 Hz, NCHS); ir ($CDCl_3$), no absorption at 6.0–6.2 μ (no C=N).

Anal. Calcd for $C_{15}H_{24}NO_2PS_2$: N, 4.05; P, 8.97; S, 18.56. Found: N, 4.05; P, 8.88; S, 18.38.

***O,O*-Diethyl *N*-(2,6-Xylyl)-*N*-thioformylphosphoramidothioate (6b).** 2,6-Xylyl isocyanide (3.3 g, 0.025 mol) was dissolved in 50 ml of CCl_4 and 4.65 g (0.025 mol) of *O,O*-diethylphos-

phorodithioic acid was added dropwise. After addition, inspection by ir and nmr spectra revealed the α adduct, **5b:** nmr (CCl_4) δ 1.38 (t, 6, J = 7 Hz, OCH_2CH_3), 2.05 (s, 6, Ar CH_3), 4.2 (m, 4, $POCH_2CH_3$), 6.8 (3, Ar H), 8.63 (s or d (J = 6 Hz) depending on acid concentration, =CH); ir (CCl_4) 6.1 μ (C=N). After sufficient time had elapsed, the α adduct rearranged. The CCl_4 solution was removed under vacuum and the residue crystallized by scratching, with recrystallization from hexane to give 4.0 g of yellow solid, mp 53–56°: nmr ($CDCl_3$) δ 1.3 (t, 6, J = 7 Hz, OCH_2CH_3), 2.21 (s, 6, Ar CH_3), 4.15 (m, 4, $POCH_2CH_3$), 7.1 (3, Ar H), 10.4 (d, 1, J = 6 Hz, PNCHS); ir ($CHCl_3$), no absorption at 6.0–6.2 μ (no C=N).

Anal. Calcd for $C_{13}H_{20}NO_2PS_2$: C, 49.19; H, 6.35; N, 4.41. Found: C, 49.61; H, 6.11; N, 4.32.

***O,O*-Dimethyl *N*-(2,6-Diethylphenyl)-*N*-thioformylphosphoramidothioate (6c).** 2,6-Diethylphenyl isocyanide (4.0 g, 0.025 mol) was mixed in 50 ml of CCl_4 with 3.95 g of *O,O*-dimethylphosphorodithioic acid. The initial nmr and ir spectra were consistent for the α adduct (d (J = 17 Hz) at δ 3.70 for $(OCH_3)_2$ and d (J = 6 Hz) at δ 8.52 for =CH; ir 6.2 μ (C=N)), although the nmr spectra also showed the presence of **6c.** After standing, the carbon tetrachloride solution was washed with 5% sodium carbonate solution, followed by water; it was then allowed to dry over $MgSO_4$. After solvent removal under vacuum, the residual oil **6c,** which did not crystallize, possessed an nmr spectrum consistent with that of the assigned structure: d (J = 18 Hz) at δ 3.75 for $P(OCH_3)_2$ and d (J = 6 Hz) at δ 10.27 for CHS.

Anal. Calcd for $C_{13}H_{20}NO_2PS_2$: N, 4.41; P, 9.76; S, 20.20. Found: N, 4.22; P, 9.54; S, 19.64.

***O*-Ethyl *N*-(2,6-Diethylphenyl)-*N*-thioformylmethylphosphonamidothioate (6d).** *O*-Ethylmethylphosphonodithioic acid[14] (3.9 g, 0.025 mol) was dissolved in carbon tetrachloride and the isocyanide was added dropwise. The reaction was immediate, and the nmr and ir spectra of the organic solution were consistent with the formation of the α adduct: d (J = 15 Hz) at δ 8.63, =CHS; ir 6.2 μ (C=N). The rate of conversion to **6d** was sufficiently slow that, to obtain the latter material, the organic solution was subsequently heated at reflux for 2 hr. The solvent was then removed under vacuum, ether added to the residue, and the solution washed with aqueous sodium bicarbonate, followed by water. After drying over magnesium sulfate, the solvent was removed to give 4.8 g of oil, which failed to crystallize: nmr ($CDCl_3$) δ 1.2 (t, 9 protons, CH_2CH_3), 1.84 (d, J = 15 Hz, 3 protons, CH_3P), 2.53 (m, 6 protons, Ar CH_2CH_3), 4.21 (m, 4 protons, $POCH_2CH_3$), 7.2 (m, 3, Ar H), 10.40 (d, J = 6 Hz, 1, CHS).

Anal. Calcd for $C_{14}H_{22}NOPS_2$: N, 4.44; P, 9.82; S, 20.33. Found: N, 4.43; P, 9.56; S, 19.92.

***N*-(2,6-Diethylphenyl)thiolformimidic Acid–Diphenylphosphinodithioic Acid Mixed Anhydrosulfide (5e).** Diphenylphosphinodithioic acid[8] (3.0 g, 0.0125 mol) was mixed in 25 ml of CCl_4 with 2.0 g (0.0125 mol) of 2,6-diethylphenyl isocyanide and the material permitted to stand. The α adduct appeared to form immediately as discerned by ir and nmr spectra. On prolonged standing, even with heating, the material failed to rearrange. The solvent was removed under vacuum, and the oily residue taken up in ether and washed with aqueous sodium bicarbonate, followed by water. After drying over magnesium sulfate and ether evaporation, the product obtained was an oil that would not crystallize: nmr (CCl_4) δ 1.02 (t, J = 7 Hz, 6, Ar CH_2CH_3), 2.5 (q, J = 7 Hz, 4, Ar CH_2CH_3), 6.8–8.0 (m, 13, Ar H) 8.77 (d, J = 7 Hz, 1, =CH); ir (CCl_4) 6.25 μ (C=N).

Anal. Calcd for $C_{23}H_{24}NPS_2$: N, 3.42; P, 7.56; S, 15.66. Found: N, 3.41; P, 7.36; S, 15.50.

Rate Measurements for Rearrangement of α Adducts 5, to 6. As described above, the requisite phosphorus thiol acid and aryl isocyanide were placed in CCl_4, usually in equimolar quantities, at an initial concentration of 0.5 *M*. An aliquot was withdrawn and placed in a sealed nmr tube. The tubes were stored at 25 ± 0.5°. Periodically their nmr spectra were examined and the concentrations of the initially formed α adduct **5** and *N*-thioformyl rearrangement product **6** were calculated from the ratio of the olefinic proton (doublet) at 510–525 Hz (*ca.* δ 8.10) to that of the thioformyl proton (doublet) (*ca.* δ 10.4). The rearrangement was followed kinetically until at least 60% of **5** had been converted. As described above, the final rearrangement products, **6,** were isolated upon completion of the reaction. The kinetic results were plotted as log [**5**] *vs.* time and first-order rate constants were obtained from the slope of the straight lines thus obtained. An average linear correlation coefficient of 0.9966 was obtained for all plots.

4-Morpholinecarbodithioic Acid–*N*-(2,6-Xylyl)thiolformimidic Acid Mixed Anhydrosulfide (7a). 2,6-Xylyl isocyanide (3.23 g, 0.025 mol) was dissolved in a THF slurry of an equimolar amount of morpholine salt of morpholine dithiocarbamate. The mixture was allowed to stir at room temperature over a period of *ca.* 54 hr. There was no apparent change in density of the slurry, so the mixture was heated to reflux. After 1.5 hr there was no apparent change, so 4 drops of methanesulfonic acid was added and the mixture refluxed an additional 2.5 hr. Again, there was no apparent decrease in morpholine salt slurry, so the mixture was cooled to 0–5° and 2.9 g (0.025 mol) of 85% phosphoric acid was added dropwise in THF solution. The ir spectrum after this addition was complete showed a small isocyanide band (4.7 μ) still present. An additional 1 g of morpholine salt was added, without diminishing isocyanide concentration. Therefore, several additional drops of phosphoric acid was added, without further reducing the isocyanide absorption. The reaction mixture was then poured into 500 ml of ice water and the insoluble material was filtered and air-dried to give a 3.8-g yield, mp 93–95°. Recrystallization from methylcyclohexane gave mp 94–97°. There was no change in nmr when the material was aged at room temperature for several days. Upon heating **7a** in refluxing methylcyclohexane, the morpholine salt of dithiocarbamate was again formed, with appreciable quantities of isocyanide present (ir 4.7 μ) in the mother liquors: **7a,** nmr ($CDCl_3$) δ 2.1 (s, 6, Ar CH_3), 3.6–4.5 (m, 8, morpholine protons), 7.0 (3 protons, Ar H), 9.6 (s, 1, N=CH); ir ($CHCl_3$) 6.2 μ (C=N).

Anal. Calcd for $C_{14}H_{18}N_2OS_2$: C, 57.11; H, 6.16; N, 9.51. Found: C, 57.03; H, 6.15; N, 9.17.

Registry No.—**1a,** 2980-92-9; **1b,** 6697-95-6; **1** (R = 6-*tert*-butyl-*o*-tolyl), 52559-62-3; **1** (R = 2-*tert*-butyl-6-ethylphenyl), 53042-88-9; **1** (R = α-methylbenzyl), 17329-20-3; **1** (R = 2,6-xylyl), 2769-71-3; **2c,** 98-91-9; **2** (R′ = CH_3CH_2), 1892-31-5; **2** (R′ = CH_3), 507-09-5; **2** (R′ = $ClCH_2$), 867-49-2; **3a,** 53042-89-0; **3b,** 53042-90-3; **3c,** 53042-91-4; **3d,** 53042-92-5; **3e,** 53042-93-6; **3f,** 53042-94-7; **3g,** 53042-95-8; **3h,** 53042-96-9; **3i,** 53042-97-0; **4a,** 53042-98-1; **4b,** 53042-99-2; **4c,** 20278-33-5; **5a,** 53043-00-8; **5b,** 53043-01-9; **5c,** 53043-02-0; **5d,** 53043-03-1; **5e,** 53043-04-2; **6a,** 53043-05-3; **6b,** 53043-06-4; **6c,** 53043-07-5; **6d,** 53043-08-6; **7a,** 53043-09-7; acetyl sulfide, 3232-39-1; 2,6-diethylthioformanilide, 53042-98-1; *m*-chloroperbenzoic acid, 937-14-4; 6′-*tert*-butyl-2-chloro-*N*-formyl-*o*-acetotoluidide, 4655-12-3; *N*-methyl-2′-*tert*-butyl-6′-ethylacetanilide, 53043-10-0; 2′-*tert*-butyl-6′-ethylaniline, 13117-97-0; acetyl chloride, 75-36-5; aniline hydrochloride, 142-04-1; bromine, 7726-95-6; chloroacetyl bromide, 15108-06-1; 2,6-diethylphenylisothiocyanate, 25343-69-5; *O,O*-diethylphosphorodithioic acid, 298-06-6; *O,O*-dimethylphosphorodithioic acid, 756-80-9; *O*-ethylmethylphosphonodithioic acid, 999-83-7; diphenylphosphinothioic acid, 1015-38-9; morpholinedithiocarbamic acid morpholine salt, 5327-10-6.

References and Notes

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Nonclassical Condensed Thiophenes. VI. Isothianaphthene 2,2-Dioxides

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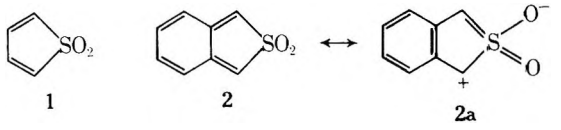
The synthesis and reactions of some derivatives of isothianaphthene 2,2-dioxide (2), including its 1-bromo derivative (3), its 1,3-dibromo derivative (4), and its 1,3-diphenyl derivative (5), are described. Of these compounds, only the 1,3-diphenyl derivative 5 was sufficiently stable to be observed directly in solution as an unstable, deep purple substance. The possible role of sulfur d orbitals *vs.* sulfonyl oxygen spiro conjugation in the electronic structure of the isothianaphthene 2,2-dioxide system is discussed. Desulfonylation reactions of some substituted 1,3-dihydroisothianaphthene 2,2-dioxides are also described in the context of this study.

Conjugation of a sulfonyl group with an olefinic or aromatic system has been well documented by many workers. The electronic nature of this effect is not obvious, however, and more than one type of sulfonyl conjugation effect may be invoked, depending upon the structural factors involved. The major complication in sulfonyl conjugation is the possible use of d orbitals by the sulfur atom.[2]

In view of the high instability of thiophene 1,1-dioxide (1) as compared to thiophene,[3] it seemed of interest to attempt the synthesis of some derivatives of isothianaphthene 2,2-dioxide (2), a system which was unreported at the inception of our work except in the form of reduced derivatives. It was thought that sulfur d orbital participation might be much more important in 2 than in 1, since nonclassical canonical forms such as 2a would be stabilized Kekulé structures, in contrast to the classical 4-π *o*-quinonoid structure 2.



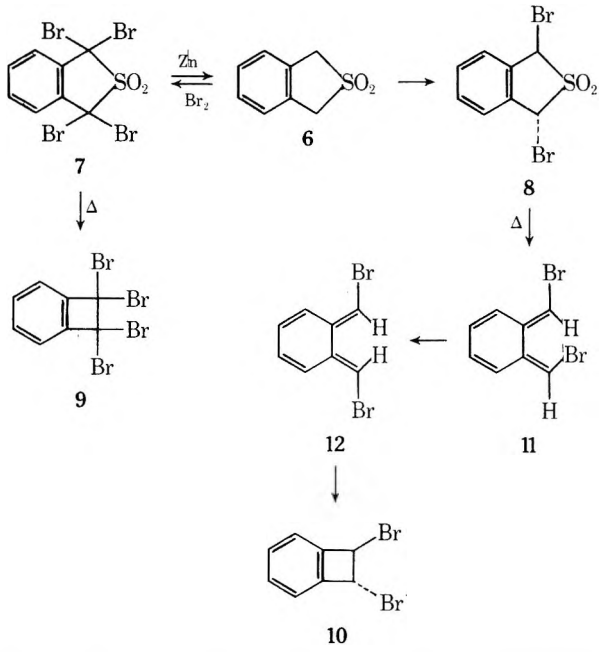
1 2 2a

This paper describes the generation and some reactions of the 1-bromo derivative (3), the 1,3-dibromo derivative (4), and the 1,3-diphenyl derivative (5) of 2, as well as some aspects of the chemistry of their chemical precursors.[4]

Results

Bromo Derivatives 3 and 4 of Isothianaphthene 2,2-Dioxide (2). The light-catalyzed benzylic bromination of 1,3-dihydroisothianaphthene 2,2-dioxide (6)[5] was found to take place smoothly in hot dilute carbon tetrachloride solution. A monobrominated product could not be obtained, but either the tetrabromo sulfone (7) or a single dibromo sulfone, presumably the trans isomer 8, could be prepared. Since gas phase pyrolysis of the parent sulfone 6 affords benzocyclobutene,[6] it was of interest to examine a similar pyrolysis of its brominated derivatives. Indeed, pyrolysis of 7 gave 1,1,2,2-tetrabromobenzocyclobutene, (9), while pyrolysis of 8 gave *trans*-1,2-dibromobenzocyclobutene (10); yields were modest (<25%), although the reactions were not studied from a preparative point of view. At first glance, application of electrocyclic reaction theory[7] to the formation of the benzocyclobutene 10 would seem to imply that 8 must be the cis isomer rather than the trans. However, pyrolysis of *trans*-8 would initially produce the less stable *o*-quinodimethane 11, which at 400° would be expected to rearrange to the more stable isomer 12 before closing on cooling to the observed product 10.

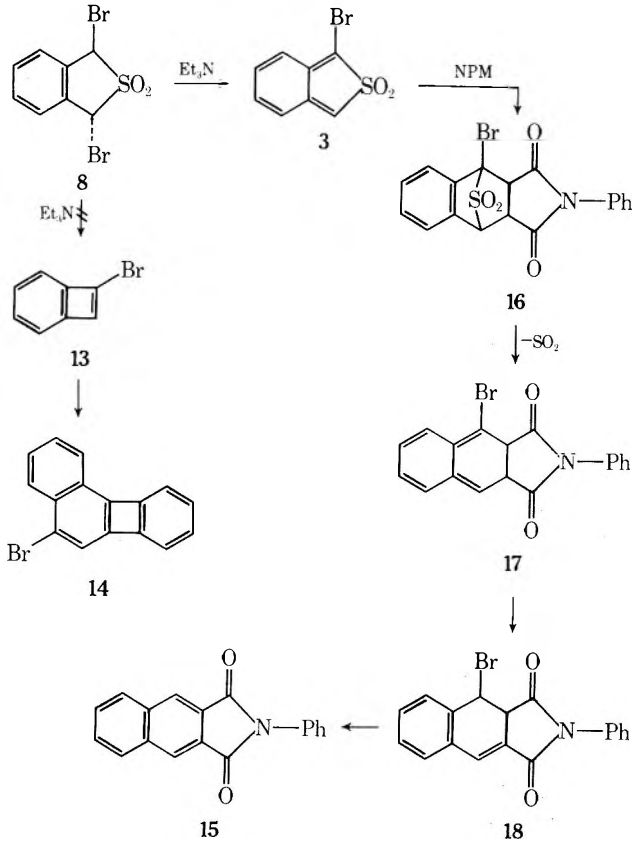
All four bromine atoms of 7 could be removed reductively. Thus, the unhalogenated sulfone 6 was obtained from 7 in good yield after long refluxing with zinc in ethanol.

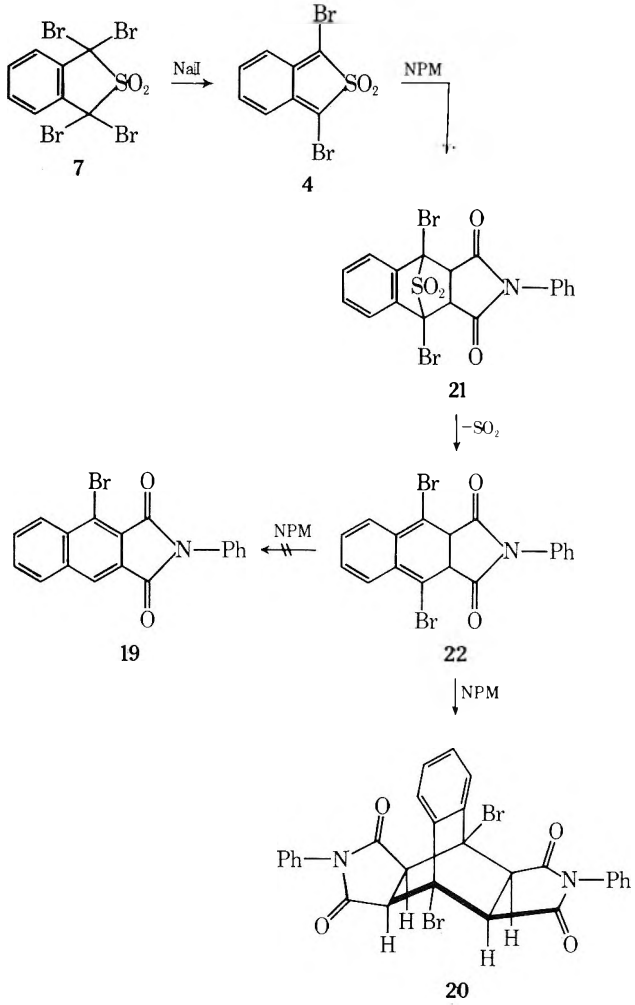


7 6 8 9 12 11 10

Treatment of dibromo sulfone 8 with triethylamine at room temperature led to the formation of a brown color with destruction of the starting material; no crystalline reaction product was isolated. In theory, sulfone 8 might have undergone a Ramberg–Backlund reaction to give 1-bromobenzocyclobutadiene (13) which, under the basic reaction conditions, would have been transformed into 5-bromobenzo[*a*]biphenylene (14).[8] However, thin-layer chromatography revealed no detectible amount of 14. The fact that base treatment of 8 had instead generated 1-bromoisothianaphthene 2,2-dioxide (3) was apparent by running the dehydrobromination reaction in the presence of excess *N*-phenylmaleimide (NPM). The reaction product, isolated in 88% yield, was the known *N*-phenyl-2,3-naphthalimide (15).[8] The formation of 15 may be explained by assuming that 3 undergoes a Diels–Alder addition of the dienophile to give the bridged sulfone 16, which then loses sulfur dioxide to give the *o*-quinodimethane 17. A 1,5-prototropic shift would convert the latter to the stable benzenoid isomer 18, which then could lose hydrogen bromide to give the naphthalene derivative 15.

The reaction of tetrabromo sulfone 7 with sodium iodide generated iodine, but no organic reaction product could be isolated. When the debromination was carried out in the presence of excess NPM, however, a white crystalline product, mp 360°, was formed in high yield (93%). This product was not the expected naphthalimide 19; its mass spectrum and elemental analysis indicated the composition $C_{28}H_{18}Br_2N_2O_4$, and it was assigned the diimide structure 20. The endo,endo configuration for 20 is supported by its





nmr spectrum, which shows four equivalent protons α to the carbonyls at δ 4.08, as well as four shielded aromatic protons in the region δ 6.38–6.55. The latter represent the ortho protons of the *N*-phenyl substituents, which are shielded by the bridged benzene ring. An analogous effect has been observed with the endo (but not the exo) NPM adduct of isothianaphthene.[9] The formation of **20** may be explained by assuming that tetrabromide **7** is first debrominated to give 1,3-dibromoisothianaphthene 2,2-dioxide (**4**), which is then trapped by NPM to give the bridged sulfone **21.** Loss of sulfur dioxide from **21** generates the *o*-quinodimethane **22,** which adds a second molecule of NPM stereoselectively to give the observed product **20.** It is interesting to note that the quinonoid intermediate **22** apparently adds NPM faster than it undergoes a 1,5-prototropic shift, a situation in contrast to the related intermediate **17.** The difference may simply be a matter of base catalysis, since **17** (but not **22**) was generated in the presence of triethylamine.

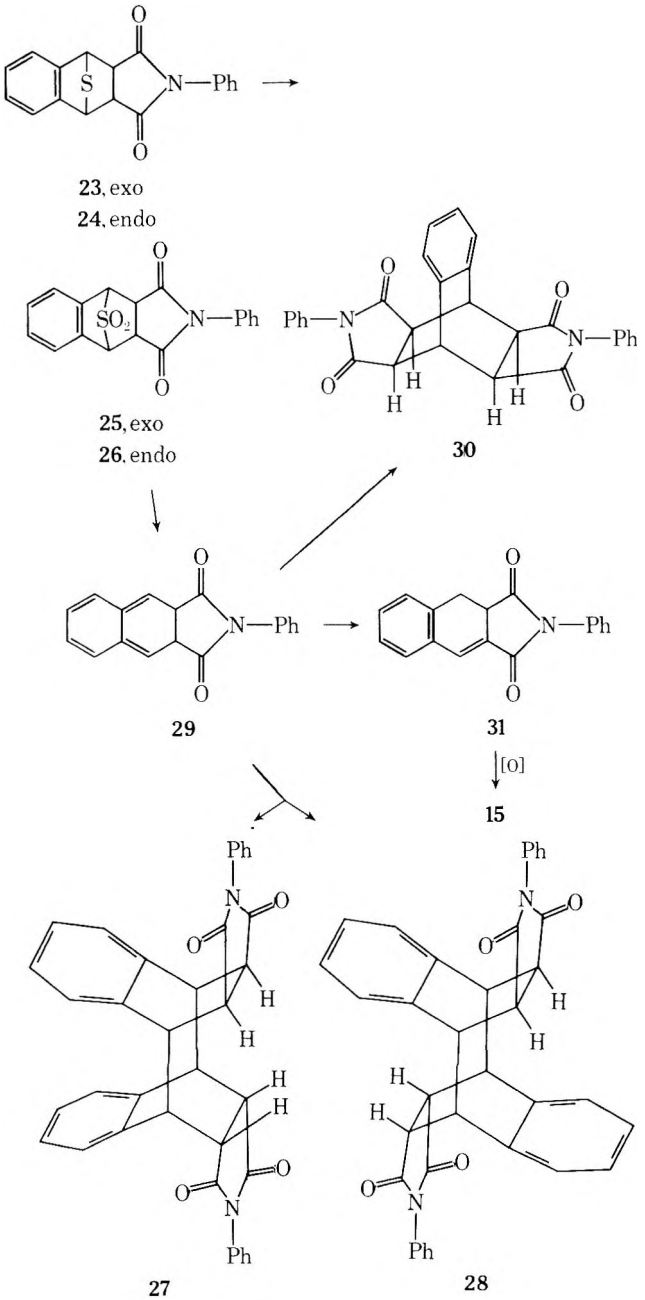
The *N*-Phenylmaleimide (NPM) Adducts of Isothianaphthene 2,2-Dioxide (2). In the chemistry outlined above, NPM adducts (**16** and **21**) of the brominated isothianaphthene 2,2-dioxides **3** and **4** were assumed to be nonisolable intermediates in the formation of compounds **15** and **20** from bromo sulfones **8** and **7,** respectively. Although we were unable to generate and trap the parent isothianaphthene 2,2-dioxide (**2**) in a similar manner, it proved to be quite simple to synthesize both the exo and endo NPM adducts of **2** indirectly and to study some of their reactions. Thus, peracetic acid oxidation of the known NPM-isothianaphthene adducts **23** and **24**[9] afforded the corresponding crystalline exo and endo sulfone adducts **25** and **26.**

The bridged sulfones **25** and **26** were considerably less stable thermally than the parent sulfone **6** of this series; they lost sulfur dioxide readily in a neutral solvent at 150–170° to give a white crystalline dimeric product, mp 360°. On the basis of its composition and its nmr spectrum, this material was assumed to be a 1:1 mixture of the endo,endo head-to-head and endo,endo head-to-tail dimers (**27** and **28**) of the *o*-quinodimethane **29.** In accord with this formulation, the nmr of the product (in CF_3CO_2D) showed singlets at δ 2.78, 3.32, and 3.88 and multiplets at 5.80–6.00 and 6.69–7.00, in a ratio of 1:1:4:4:14. The protons α to the carbonyls in the head-to-head dimer **27** appear at δ 3.32, while the corresponding protons in the dimer **28** are shielded by aromatic rings and appear at δ 2.78. In both dimers, the bridgehead protons are seen at δ 3.88. Evidence that both dimers are endo,endo structures is found in the shielded position (δ 5.80–6.00) of the ortho protons of all the *N*-phenyl groups. Although **27** and **28** were virtually inseparable, several crystallizations effected an enrichment of **27** as shown by nmr.

Thermal decomposition of either sulfone **25** or **26** in the presence of excess NPM led to the formation of an adduct of the intermediary *o*-quinodimethane **29.** This adduct (**30**), like its previously described dibromo analog **20,** was assigned the endo,endo configuration on the basis of its nmr.

In the conversion of dibromo sulfone **8** to imide **15** by NPM and triethylamine, the bridged sulfone **16** was assumed to be an intermediate but could not be isolated. In order to determine if this type of sulfone would be attacked by triethylamine, the model sulfones **25** and **26** were subjected to this reagent at room temperature. Attack did indeed occur, and the naphthalimide **15,** presumably formed *via* the dihydro derivative **31,** was isolated after work-up. A transient yellow fluorescent intermediate, presumably the *o*-quinodimethane **29,** was visible during the reaction. Indeed, when the reaction was run in the presence of NPM, intermediate **29** was effectively intercepted with the formation of the diimide adduct **30** in good yield.

The mechanism of the triethylamine desulfonylation is not entirely clear, but it appears to involve an unusual direct attack of the amine on the strained sulfonyl bridge; elimination of the bridge *via* removal of a proton α to an imide carbonyl would not lead to formation of o-quinodimethane **29**. Finally, it is interesting to note that the bicyclic parent sulfone **6** is quite unaffected by long heating with triethylamine, thus attesting to the importance of the strain factor in this desulfonylation reaction.



1,3-Diphenylisothianaphthene 2,2-Dioxide (5). The addition of sulfur dioxide to *trans*-1,2-diphenylbenzocyclobutene (**32**) readily affords a 1,3-dihydro-1,3-diphenylisothianaphthene 2,2-dioxide;[10] the latter sulfone can now be assigned the cis stereochemistry **33** on the basis of the application of electrocyclic reaction theory to the addition of dienophiles to **32**.[11,12] Light-catalyzed bromination of **33** could be controlled to give a single monobromo sulfone **34**, mp 198–200°; the stereochemistry of this bromide is uncertain, but it is probably the *cis*-diphenyl isomer; the latter would result by bromine addition to the less hindered side of the benzylic radical derived from **33**. Dibromination of **33** could also be achieved in a similar manner to give a dibromo sulfone **35**, mp 225–227°; the mother liquors contained a lower melting stereoisomer of **35** which was not further examined. Gas phase pyrolysis of **34** and **35** did not give benzocyclobutene derivatives, but instead gave 9-phenylanthracene (**36**) and 9-bromo-10-phenylanthracene (**37**), respectively.[13]

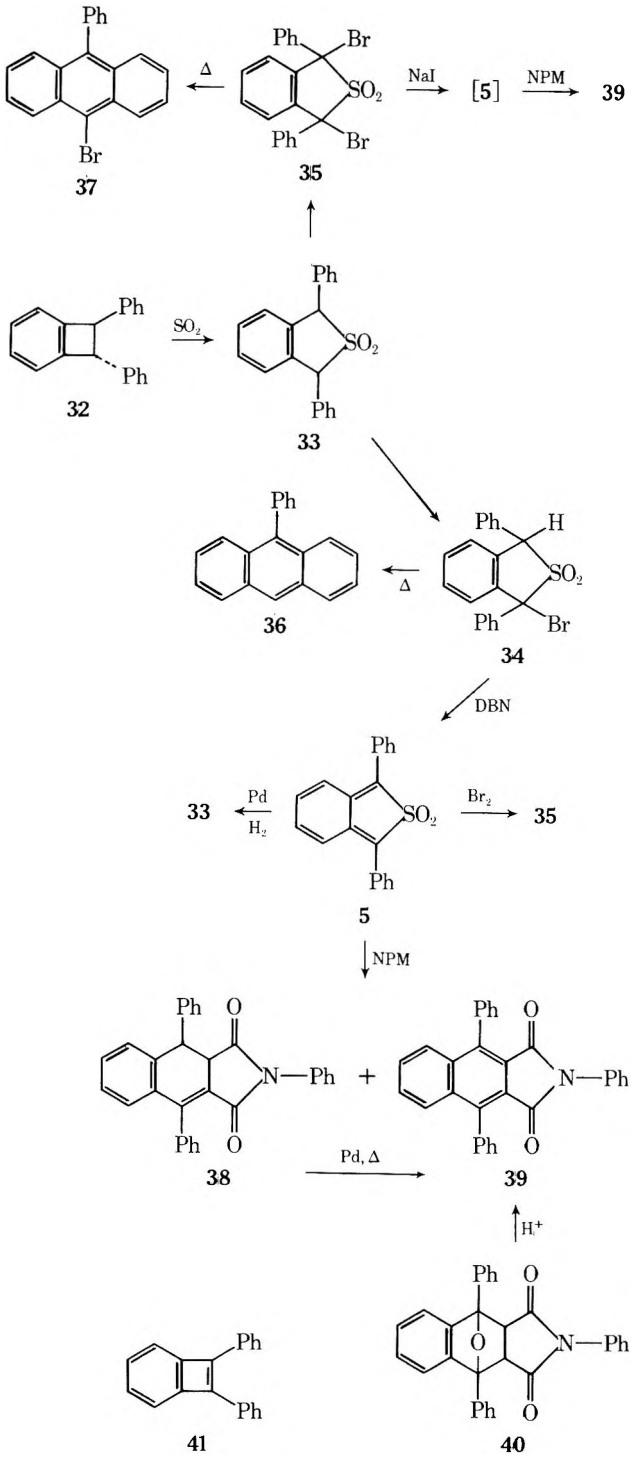
Treatment of monobromo sulfone **34** with a wide variety of bases (*i.e.*, alumina, triethylamine, potassium *tert*-butoxide) produced a purple coloration reminiscent of permanganate; this purple color was attributed to 1,3-diphenylisothianaphthene 2,2-dioxide (**5**) on the basis of the evidence outlined below. Preparatively, the best procedure for preparing **5** involved treatment of bromide **34** with diazabicyclononene (DBN), followed by immediate chromatographic purification on a cooled alumina column. The resulting purple solutions faded after several hours at room temperature, but benzene solutions were essentially unchanged in the frozen state after 1 week. All attempts to isolate the purple sulfone by solvent evaporation caused discharge of the purple color with the formation of a yellow-orange residue, from which characterizable constituents were not isolated.

The purple sulfone **5** reacted instantly with *N*-phenylmaleimide (NPM); because of the color change this reaction could be used as a visual titration method for the estimation of the concentration of **5** in a chromatographed solution. In this way also, a value of log ϵ = 2.65 was determined for the broad visual absorption band of **5** which was centered at 550 nm. A preparative reaction of **5** with NPM gave a difficulty separable mixture of two products. The minor product, $C_{30}H_{21}NO_2$, was assigned the dihydro imide structure **38**; on heating with palladium, it was dehydrogenated to give the major product, $C_{30}H_{19}NO_2$, assigned the structure *N*-1,4-triphenylnaphthalimide (**39**). Imide **39** was identical with material synthesized by the acid dehydration of the adduct (**40**) of NPM and 1,3-diphenylisobenzofuran. The reaction of dibromo sulfone **35** with NPM and sodium iodide also resulted in the formation of imide **39**. The purple color of **5** could be detected when **35** was heated with copper powder in benzene, but this was not a useful method for generating **5** due to the relatively high temperature required.

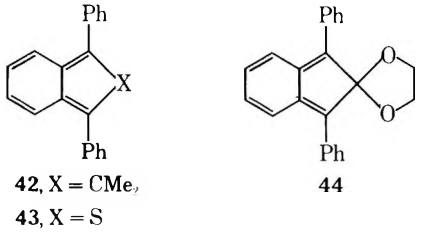
The evidence presented above does not exclude the possibility that the labile purple intermediate from sulfones **34** and **35** may have been the unknown 1,2-diphenylbenzocyclobutadiene (**41**) instead of the unsaturated sulfone **5**. This possibility was eliminated on the basis of two reactions carried out with NPM-analyzed solutions of **5**. In the first reaction, rapid catalytic hydrogenation afforded the parent *cis*-dihydro sulfone **33** in 88% yield. In the second reaction, low temperature addition of bromine afforded the dibromo sulfone **35** in 74% yield.

Discussion

It is clear from the chemistry described above that the isothianaphthene 2,2-dioxide system is highly reactive, like that of thiophene 1,1-dioxide.[3] Direct observation of the long wavelength absorption band of the diphenyl derivative **5** at 550 nm is indicative of some type of sulfonyl conjugation, since the electronically insulated isoindene **42** and the related sulfide **43** have corresponding bands at 444[14] and 388 nm,[4] respectively. At the time of our preliminary report of the generation of **5**,[4] this bathochromic effect in **5** seemed to be an indication of at least a modest degree of d-orbital participation by the sulfonyl sulfur. Subsequently, however, the unstable o-quinonoid ketal **44** has been generated and found to have an absorption maximum at



537 nm,[14] a value close to that (550 nm) of **5**. Since the observed conjugation in **44** can only be an example of spiroconjugation,[15] we must revise our earlier opinion[4] and agree with Holland and Jones[14] that spiroconjugation is operative in both **44** and **5**.[16]



In conclusion, it appears that sulfonyl conjugation does exist in the isothianaphthene 2,2-dioxide system but that this effect involves spiroconjugation with the sulfonyl oxygens rather than sulfur d orbital participation. The observed high reactivity of the system is consistent with a spiroconjugation effect.[14,15]

Experimental Section

Melting points are uncorrected. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. The visible spectrum of **5** was determined in benzene solution with a Perkin-Elmer Model 202 spectrophotometer. Nmr spectra were recorded in the indicated solvent (TMS standard) with a Varian A60A spectrometer. Mass spectra and ir spectra (KBr disks) were run using an Atlas CH4 instrument and a Perkin-Elmer Infracord, respectively.

1,3-Dihydro-1,3-dibromoisothianaphthene 2,2-Dioxide (8). A solution of bromine (58 ml of a 0.208 *M* solution) in carbon tetrachloride (150 ml) was added dropwise over 90 min to a refluxing and irradiated (200-W tungsten bulb) solution of 1,3-dihydroisothianaphthene 2,2-dioxide (**6**, 1.0 g)[5,6] in carbon tetrachloride (150 ml). After an additional 30 min of refluxing and irradiation, the solvent was removed *in vacuo* and the product (2.2 g) was crystallized by the addition of 15 ml of 1:1 benzene–cyclohexane. Recrystallization from the same solvent gave pure **8** (1.7 g, 89%): mp 137–138°; nmr ($CDCl_3$) δ 4.42 (s, 2 H).

Anal. Calcd for $C_8H_6Br_2SO_2$: C, 29.45; H, 1.84; Br, 49.15. Found: C, 29.49; H, 1.94; Br, 49.45.

Pyrolysis of 1,3-Dihydro-1,3-dibromoisothianaphthene 2,2-Dioxide (8). Sulfone **8** (0.500 g) was slowly sublimed from a warm flask by a slow nitrogen stream (5 mm pressure), the gas stream being led over a Nichrome wire heated to 400°. The pyrolysate was trapped on a Dry Ice cold finger and purified by ptlc (silica; 1:3 benzene–cyclohexane). White crystals of *trans*-1,2-dibromobenzocyclobutene (**10**, 0.085 g, 22%), mp 52–54° (lit.[17] mp 52–53°), were obtained, which were identical (ir, mixture melting point) with authentic material.

Reaction of 1,3-Dihydro-1,3-dibromoisothianaphthene 2,2-Dioxide (8) with *N*-Phenylmaleimide and Triethylamine. A solution of sulfone **8** (0.050 g) and *N*-phenylmaleimide (0.052 g) in benzene (50 ml) and triethylamine (10 ml) was stirred for 1 day at room temperature under nitrogen. Evaporation of the filtered solution and chromatography of the residue on silica (3:1 benzene–chloroform) afforded *N*-phenyl-2,3-naphthalimide (**15**, 0.036 g, 88%), mp 270–275°, identical (ir, mixture melting point) with authentic material.[8]

1,1,3,3-Tetrabromoisothianaphthene 2,2-Dioxide (7). A solution of bromine (24 g) in carbon tetrachloride (150 ml) was added over 3 hr to a refluxing and irradiated (200-W tungsten bulb) suspension of 1,2-dihydroisothianaphthene 2,2-dioxide (**6**, 5.0 g) in carbon tetrachloride (150 ml). After an additional 3 days of irradiation and refluxing, the solution was evaporated *in vacuo* and the residue was taken up in benzene and decolorized with charcoal. Crystallization from benzene–cyclohexane gave the tetrabromo sulfone **7** (8.5 g, 69%), mp 177–179°.

Anal. Calcd for $C_8H_4Br_4O_2S$: C, 19.72; H, 0.83; Br, 66.20. Found: C, 20.15; H, 0.91; Br, 65.93.

Pyrolysis of 1,1,3,3-Tetrabromoisothianaphthene 2,2-Dioxide (7). Tetrabromo sulfone **7** (0.500 g) was pyrolyzed as described for the dibromo sulfone **8**. Purification of the pyrolysate by ptlc (neutral alumina; benzene–cyclohexane 1:1) gave, after crystallization from methanol, 1,1,2,2-tetrabromobenzocyclobutene (**9**, 0.110 g, 24%), mp 117–119° (lit.[18] mp 117–118°), identical (ir) with authentic material.

Reaction of 1,1,3,3-Tetrabromoisothianaphthene 2,2-Dioxide (7) with *N*-Phenylmaleimide and Sodium Iodide. A solution of sodium iodide (7.0 g) in dry dimethylformamide (100 ml) was added dropwise at room temperature (nitrogen atmosphere) to a stirred solution of tetrabromo sulfone **7** (3.0 g) and *N*-phenylmaleimide (2.0 g) in dimethyl sulfoxide (10 ml) and dimethylformamide (150 ml). After stirring for an additional 3 days, the mixture was poured into cold water (150 ml) and the free iodine was reduced by adding sodium sulfite. The precipitated solid was recrystallized from chloroform to give white crystals of adduct **20** (3.5 g, 93%), mp 360°: mass spectrum *m/e* 606 (M^+); nmr (DMSO-d_6) δ 4.08 (s, 4 H), 6.38–6.55 (m, 4 H), 7.25–7.55 (m, 10 H).

Anal. Calcd for $C_{28}H_{18}Br_2N_2O_4$: C, 55.45; H, 2.97; Br, 26.41. Found: C, 55.13; H, 2.91; Br, 25.07.

Zinc Reduction of 1,1,3,3-Tetrabromoisothianaphthene 2,2-Dioxide (7). A mixture of tetrabromo sulfone **7** (1.00 g), activated zinc dust (5 g), and ethanol (150 ml) was refluxed (nitrogen) until tlc showed the disappearance of starting material (2 days). Evaporation of the filtered solution, followed by crystallization from methanol and recrystallization from benzene–cyclohexane, gave the debrominated sulfone **6** (0.285 g, 82%), mp 148–150°.

Exo and Endo Sulfones 25 and 26. The exo and endo isothianaphthene adducts **23** and **24** were prepared as described earlier.[9] A mixture of exo adduct **23** (3.0 g) and 40% peracetic acid (100 ml) was stirred for 15 hr at room temperature. The precipitated solid was recrystallized from benzene–hexane to give, in two crops, exo sulfone **25** (3.2 g, 97%): mp 169–171°; nmr (CF_3CO_2D) δ 3.60 (s, 2 H), 5.40 (s, 2 H), and 7.15–7.80 (m, 9 H).

Anal. Calcd for $C_{18}H_{13}NO_4S$: C, 63.75; H, 3.83; N, 4.13. Found: C, 63.57; H, 3.96; N, 4.12.

By an identical procedure, endo adduct **24** (0.60 g) gave pure endo sulfone **26** (0.60 g, 91%): mp 178–181°; nmr (CF_3CO_2D) δ 4.02 (d of d, 2 H), 5.35 (d of d, 2 H), 6.22 (m, 2 H), and 7.10–7.40 (m, 7 H).

Anal. Calcd for $C_{18}H_{13}NO_4S$: C, 63.75; H, 3.83; N, 4.13. Found: C, 63.75; H, 3.96; N, 4.12.

Pyrolysis of Exo and Endo Sulfones 25 and 26. A mixture of exo sulfone **25** (0.150 g) and triethylene glycol dimethyl ether (10 ml) was heated for 30 min at 120° and then at 150–180° for 15 min. The solid which separated on cooling was crystallized from benzene–chloroform to give a mixture of dimers **27** and **28** (0.080 g, 66%), mp 360°. (See Discussion for nmr.)

The identical mixture of **27** and **28** was obtained from endo sulfone **26** in 63% yield under similar conditions.

Anal. Calcd for $C_{36}H_{26}N_2O_4$: C, 78.50; H, 4.73; N, 5.09. Found: C, 78.22; H, 4.81; N, 5.03.

Pyrolysis of Exo and Endo Sulfones 25 and 26 in the Presence of *N*-Phenylmaleimide. A mixture of exo sulfone **25** (0.300 g), *N*-phenylmaleimide (0.600 g), and triethylene glycol dimethyl ether (100 ml) was heated to 180° for 30 min. The cooled solution was poured into water (100 ml) and extracted with chloroform (2 × 100 ml). Evaporation of the dried extract, followed by trituration with pentane, gave a precipitate which was purified by ptlc (silica; benzene–chloroform 1:2), giving white crystalline adduct **30** (0.120 g, 40%): mp 328–330°; nmr (CF_3CO_2H) δ 3.35 (s, 4 H), 3.88 (s, 2 H), 5.8–6.0 (m, 4 H), and 6.6–6.9 (m, 10 H).

The same adduct **30** was obtained in similar yield from endo sulfone **26** under the same conditions.

Anal. Calcd for $C_{28}H_{20}N_2O_4$: C, 75.00; H, 4.46; N, 6.25. Found: C, 74.92; H, 4.62; N, 6.29.

Reaction of Exo and Endo Sulfones 25 and 26 with Triethylamine. Exo sulfone **25** (0.150 g) was stirred under nitrogen with degassed benzene (50 ml), and triethylamine (3 ml) was added through a serum cap; addition of the amine produced an immediate greenish-yellow color and a strong fluorescence. After stirring for 24 hr at room temperature, the product was worked up in the usual manner, followed by ptlc purification (silica; benzene–chloroform 3:1) to give *N*-phenyl-2,3-naphthalimide (**15**, 0.040 g, 33%), mp 275–278° (lit.[8] mp 284–285°), identical with an authentic sample. The same imide **15** was obtained in similar yield from endo sulfone **26** under the same conditions.

Ultraviolet irradiation did not alter the course of this reaction. Thus, when the above experiment was repeated with either exo sulfone **25** or endo sulfone **26** under irradiation conditions (Hanovia high pressure lamp, Pyrex filter), imide **15** was isolated in 67 and 80% yield, respectively.

The reaction of the exo sulfone **25** (0.150 g) with triethylamine (4 ml) in benzene (50 ml) was repeated (30 hr, nitrogen) in the presence of *N*-phenylmaleimide (0.080 g). Direct crystallization of the reaction product from chloroform gave the diimide adduct **30** (0.045 g, 66%), mp 328–330°.

Attempted Reaction of 1,3-Dihydroisothianaphthene 2,2-Dioxide (6) with Triethylamine. A mixture of sulfone **6** (0.300 g), *N*-phenylmaleimide (0.320 g), triethylamine (5 ml), and benzene (75 ml) was refluxed for 4 days. Solvent evaporation, followed by silica chromatography (benzene–cyclohexane 1:1), gave only recovered *N*-phenylmaleimide (0.302 g, 94%) and recovered sulfone **6** (0.285 g, 95%).

***cis*-1,3-Dihydro-1,3-diphenylisothianaphthene 2,2-Dioxide (33).** This compound was prepared by the following modification of the literature method.[10] A stream of sulfur dioxide was passed through a solution of *trans*-1,2-diphenylbenzocyclobutene (4.80 g) in ether (50 ml) at room temperature for a period of 1 hr. The precipitated solid was recrystallized from methylene chloride–petroleum ether to give, in two crops, sulfone **33** (4.80 g, 82%), mp 233–235° (lit.[10] mp 232–234°).

1,3-Dihydro-1-bromo-1,3-diphenylisothianaphthene 2,2-Dioxide (34). A solution of bromine (0.513 g) in carbon tetrachloride (100 ml) was added dropwise over 2 hr to a refluxing and irradiated (200-W tungsten bulb) solution of *cis*-sulfone **33** (1.00 g) in carbon tetrachloride (150 ml). After an additional 30 min of refluxing and irradiation, the solvent was removed *in vacuo* and the product was crystallized by the addition of 1:2 benzene–cyclohexane. Two recrystallizations from benzene gave pure bromo sulfone **34** (0.700 g, 58%): mp 198–200°; nmr ($CDCl_3$) δ 5.23 (s, 1 H), 7.2–7.8 (m, 14 H).

Anal. Calcd for $C_{20}H_{15}BrO_2S$: C, 60.15; H, 3.76; Br, 20.05. Found: C, 59.95; H, 3.81; Br, 20.16.

Pyrolysis of 1,3-Dihydro-1-bromo-1,3-diphenylisothianaphthene 2,2-Dioxide (34). Sulfone **34** (0.300 g) was slowly sublimed from a warm flask by a slow stream of nitrogen (8 mm pressure), the gas stream being led over a Nichrome wire heated to 350°. The pyrolysate, which was collected on a Dry Ice–acetone cold finger, was purified by ptlc (neutral alumina, benzene) to give 9-phenylanthracene (**36**, 0.100 g, 53%), mp 151–152° (lit.[13] mp 154–156°), identical (ir, mixture melting point) with an authentic sample.

1,4-*N*-Triphenyl-2,3-naphthalimide (39). A mixture of 1,3-diphenylisobenzofuran (0.300 g), *N*-phenylmaleimide (0.200 g), and benzene (25 ml) was refluxed for 1 hr at room temperature. Evaporation of the solvent, followed by chromatography (silica; benzene–chloroform 1:1), afforded adduct **40** as white crystals (0.400 g, 91%), mp 205–207°.

Anal. Calcd for $C_{30}H_{21}NO_3$: C, 81.25; H, 4.74; N, 3.16. Found: C, 81.06; H, 4.99; N, 3.19.

Adduct **40** (0.100 g) was added to concentrated sulfuric acid (10 ml) at 0°. After 10 min, the yellow solution was poured into ice water (100 ml) and the precipitate was crystallized from benzene–chloroform 1:1 to give imide **39** (0.90 g, 92%), mp 292–293°.

Anal. Calcd for $C_{30}H_{21}NO_3$: C, 84.75; H, 4.48; N, 3.29. Found: C, 84.80; H, 4.50; N, 3.19.

Generation and Reactions of 1,3-Diphenylisothianaphthene 2,2-Dioxide (5). (a) Reaction of 5 with *N*-Phenylmaleimide. A solution of diazabicyclononene (DBN, 1.92 g) in benzene (50 ml) was added dropwise under nitrogen to a stirred solution of bromo sulfone **34** (2.00 g) and *N*-phenylmaleimide (1.92 g) in degassed benzene (100 ml). Each drop of base produced a purple color which was discharged almost immediately. After an additional 1 hr of stirring, the mixture was acidified by adding 10% sulfuric acid (75 ml). The usual work-up of the organic phase, followed by crystallization from benzene–methylene chloride, gave a crystalline mixture (1.11 g, 52%) of adducts **38** and **39**. An aliquot was separated by ptlc (silica; benzene–chloroform 1:1) to give the two crystalline components. The first component, mp 292–293°, was identical (ir, mp) with the naphthalimide **39** prepared from 1,3-diphenylisobenzofuran (see above). The second component, mp 180–185°, was the dihydro imide **38**.

Anal. Calcd for $C_{30}H_{21}NO_2$: C, 84.29; H, 4.92. Found: C, 84.32; H, 4.83.

Dehydrogenation of dihydro imide **38** was accomplished by heating a sample (0.050 g) with an equal weight of 10% palladium–charcoal for 1 hr at 250–290° under nitrogen. Sublimation of the product, followed by crystallization from benzene, afforded the naphthalimide **39** (0.035 g, 70%), mp 292–293°, identical (ir, mp) with an authentic sample.

(b) Hydrogenation of 5. Diazabicyclononene (0.340 g) was added in one portion to a degassed mixture of bromo sulfone **34** (0.519 g), benzene (10 ml), and chloroform (3 ml). After 3 min, the deep purple solution was chromatographed on a column prepared from neutral alumina and deoxygenated cold benzene. The column was eluted rapidly with benzene under pressure, the purple band being collected and made up to 100 ml with benzene. One quarter of the purple solution was removed and titrated visually with *N*-phenylmaleimide in benzene, indicating formation of the purple sulfone in about 64% yield. The remainder of the purple solution was hydrogenated at once (hydrogen at 40 psi) using 200 mg of 5% palladium–charcoal as catalyst. After 10 min, the colorless solution was worked up and purified by silica chromatography (benzene–chloroform 1:1 eluent) to give white crystals of *cis*-1,3-dihydro-1,3-diphenylisothianaphthene 2,2-dioxide (**33**, 0.175 g, 88%), mp 234–236°, identical (ir, mp) with an authentic sample.

(c) Addition of Bromine to 5. A solution of chromatographed purple sulfone **5** was prepared from bromo sulfone **34** (0.400 g) and DBN (0.248 g) in the general manner described in the above hy-

drogenation experiment; *N*-phenylmaleimide titration of one quarter of the solution indicated a 50% yield of **5** from bromo sulfone **34**. The remainder of the purple solution was cooled quickly to −67° (Dry Ice–methylene chloride) and bromine (0.16 g) was added. After warming to room temperature, the usual work-up, followed by ptlc (silica; benzene–chloroform 1:1) afforded white crystals (0.179 g, 74%) of the high melting isomer of dibromo sulfone **35**, mp 225–227°, identical with material prepared by the bromination of *cis*-1,3-dihydro-1,3-diphenylisothianaphthene 2,2-dioxide (**33**).

Anal. Calcd for $C_{20}H_{14}Br_2O_2S$: C, 50.20; H, 2.92; Br, 33.47. Found: C, 50.41; H, 3.08; Br, 33.19.

1,3-Dibromo-1,3-diphenylisothianaphthene 2,2-Dioxide (35). A solution of bromine (0.50 g) in carbon tetrachloride (100 ml) was added dropwise over 2 hr to a refluxing and irradiated (200-W tungsten bulb) solution of *cis*-sulfone **33** (0.50 g) in carbon tetrachloride (150 ml). After an additional 1 hr of refluxing and irradiation, solvent removal, chromatography on alumina (benzene), and repeated crystallization from benzene gave 0.300 g (41%) of dibromo sulfone **35**, mp 225–227°, identical with the bromine addition product of purple sulfone **5** (see above). The benzene mother liquors gave a further 200 mg (27%) of crystals, mp 215–217°; this material was slightly different spectrally (ir, nmr) and appeared to be an impure stereoisomer of the 225° dibromide.

Reactions of 1,3-Dibromo-1,3-diphenylisothianaphthene 2,2-Dioxide (35). (a) With Sodium Iodide. Sodium iodide (0.4 g) in dry dimethylformamide (15 ml) was added to a solution of dibromo sulfone **35** (1.00 g) and *N*-phenylmaleimide (0.40 g) in dry dimethylformamide (30 ml) under nitrogen at room temperature. After 10 hr, the reddish solution was poured into water and the product was worked up in the usual manner, iodine being removed by a sodium sulfite wash. After silica chromatography (benzene–chloroform 1:1), crystallization from benzene–pentane gave, as white crystals (0.325 g, 37%), triphenylnaphthalimide **39**, mp 292–293°, identical (ir, mp) with material prepared (see above) from 1,3-diphenylisobenzofuran.

(b) Pyrolysis. Dibromo sulfone **35** (0.500 g) was pyrolyzed as described for monobromo sulfone **34**; the hot wire temperature was 400°. Purification by ptlc (silica, benzene) gave, after crystallization from benzene, yellow crystals (0.075 g) of 9-bromo-10-phenylanthracene (**37**), mp 145–147°.

Anal. Calcd for $C_{20}H_{13}Br$: C, 72.01; H, 4.13; Br, 23.61. Found: C, 72.58; H, 4.36; Br, 23.96.

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Registry No.—**5**, 23398-54-1; **6**, 2471-91-2; **7**, 53092-82-3; **8**, 53092-83-4; **9**, 26448-34-0; **10**, 14420-75-8; **15**, 21815-18-9; **20**, 53092-60-7; **23**, 13129-12-9; **24**, 13129-13-0; **25**, 53092-61-8; **26**, 53152-37-7; **27**, 53092-62-9; **28**, 5312-38-8; **30**, 53092-63-0; **33**, 53152-39-9; **34**, 21815-15-6; **35**, 21815-16-7; **36**, 602-55-1; **37**, 23674-20-6; **38**, 21815-17-8; **39**, 4209-87-4; **40**, 27594-00-9; *N*-phenylmaleimide, 941-69-5; triethylamine, 121-44-8; sodium iodide, 7681-82-5.

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Preparation and Basicities of Substituted *N,N*-Diethyl- and *N,N*-Dimethylaniline Oxides[1]

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Twelve *meta*- and *para*-substituted *N,N*-dimethylanilines and eleven similar *N,N*-diethylanilines and the corresponding *N*-oxides have been prepared. pK_a values of the amine oxides in water have been determined. They were very well correlated in the Hammett equation *vs.* σ^n, indicating that there is little or no conjugation from the ring through the nitrogen to the oxygen. The ρ values are entirely consistent with a reaction center one atom removed from the benzene ring (ρ = 0.907 for the dimethyl case and ρ = 0.91 for the diethyl case).

In contrast with heterocyclic amine oxides the chemistry of *N,N*-dialkylated aniline oxides has remained largely undeveloped since the original studies of Bamberger,[3] with the exception of the Polonovski reaction[4-7] (*N,N*-dimethylaniline oxide plus acetic anhydride).

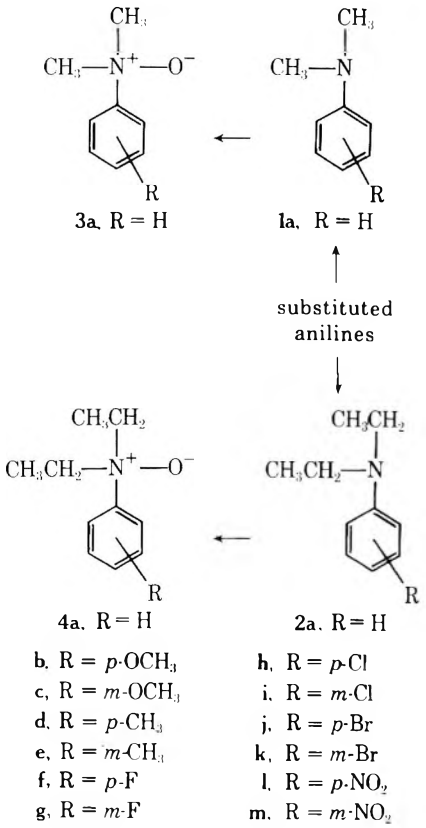
Amine oxides are unusual both in their physical properties and in the variety of chemical reactions they can undergo. The reactions of dialkylaniline oxides that have been observed, but for which there are no modern, published mechanistic studies, are the Cope elimination,[8] the rearrangements observed upon treatment with nitrous[2,9] or sulfurous acids,[2,10,11] the deoxygenations and/or rearrangements resulting from treatment with various nonmetal oxides[12] and chlorides,[13] and deoxygenation with alkyl halides.[14,15] The rates of reaction of substituted *N,N*-dialkylaniline oxides can be used to obtain information about the mechanistic nature of these reactions. Since the kinetic behavior of *N*-oxides in protic solvents must involve acid–base ionization, the values of the K_a's must be known before actual rate constants can be determined.

A continuing interest in these compounds, their reactions, and the mechanics of their reactions led to the syntheses and pK_a studies of *N,N*-dimethylaniline oxides (**3**) and *N,N*-diethylaniline oxides (**4**) described here.

Table I
Synthesis of *N,N*-Dimethylanilines with Dimethyl Sulfate

Compd	Yield, %	Bp or Mp, °C	Bp or Mp, °C
1c (*m*-OCH_3)	76	66–68 (0.1 mm)	204–205 (740 mm)[a]
1k (*m*-Br)	81	74–76 (0.3 mm)	100–104 (2.0 mm)[b]
1g (*m*-F)	48	72–73 (6.0 mm)	82 (15 mm)[c]
1i (*m*-Cl)	43	124 (9.3 mm)	232 (760 mm)[d]
1f (*p*-F)	71	24	25[e]
1b (*p*-OCH_3)	68	47.5–48	47[c]

[a] Reference 27. [b] E. Schmidt and R. Schumacher, *Chem. Ber.*, 54, 1414 (1921). [c] H. P. Crocker and B. Jones, *J. Chem. Soc.*, 1808 (1959). [d] H. Goldschmidt and H. Keller, *Chem. Ber.*, **35**, 3542 (1902). [e] G. Schiemann and W. Winkelmuller, *Chem. Ber.*, 36, 731 (1933).



Results

The commercially unavailable tertiary amines were prepared from the appropriately substituted anilines by exhaustive alkylation with methyl sulfate for 1(a-R,M) and with ethyl bromide or ethyl sulfate for 2(a-R,M). Excellent yields were obtained in most cases in accord with the previous reports for similar reactions[15] (Tables I and II).

The amine oxides were all synthesized by reaction of the tertiary amine with peracetic acid in chloroform. Reaction times varied for differently substituted anilines. Work-up for *N,N*-dimethylaniline oxides involved isolation and purification of the hydrochloride salts. The yields and selected physical properties of compounds prepared by this method are shown in Table III. Acceptable elemental analyses were obtained for the hydrochloric acid salts.

The substituted *N,N*-diethylaniline oxides were prepared using the conditions described for the dimethyl compounds, but the isolation procedure which yielded amine oxide hydrates was different and varied with the nature of the substituent. All of the substituted *N,N*-diethylaniline oxides were isolated as crystalline solids and all but one of these contained water of hydration, usually with a simple whole number ratio of water molecules to oxide. The presence of water and the amount of water per sample was measured by nmr, elemental analysis, and molecular weight calculated from acid–base titrations. The properties of these compounds are summarized in Table IV.

Table II
Properties of *N,N*-Diethylanilines

Compd	Mp, °C or Bp, °C (mm)	Lit. Mp, °C or Bp, °C (mm)	pK_a[a]	Yield, %[b] Method 1	Yield, %[b] Method 2
2a		216[c]	6.58	87.4	
2b (*p*-OCH_3)	147–149 (21)	246–247[d]	7.22	71.5	90[f]
2c (*m*-OCH_3)	149 (22)		6.29	98	
2d (*p*-CH_3)	123–125 (21)	229[g]	6.92	80.6	90[f]
2e (*m*-CH_3)	83 (4)	231–231.5[h]	6.72	84.3	57.7
2h (*p*-Cl)	39	39[g]		83.4	55.9
2i (*m*-Cl)	106 (5)	248–249[g]		92.3	43.4
2j (*p*-Br)	32	33[i]		79	65.6
2k (*m*-Br)	109 (3.3)	139.5–142[j] (9–10)			24.6
2m (*m*-NO_2)	140 (5)	288–290[k]		79.8	10.6

[a] These values were determined from the half-neutralization points of titration curves of dilute solutions (<0.05 *M*). [b] In method 1 amine is heated with EtBr and base in an autoclave. In method 2 amine is reacted with Et_2SO_4 in aqueous base at reflux. [c] Commercially available — Aldrich no. D-8990-5. [d] D. G. Thomas, J. H. Billman, and C. E. Davis, *J. Amer. Chem. Soc.*, **68**, 895 (1946). [e] These pK_a's were determined in 10::90 v/v alcohol-water solution. [f] These yields were determined by glpc of the ether extract of the reaction solution. Less than 1% of secondary amine was present. [g] R. Reinhardt and W. Staedel, *Chem. Ber.*, **16**, 29 (1883). [h] A. J. Hill and J. J. Donleavy, *J. Ind. Eng. Chem.*, 13, 50 (1921). [i] A. Claus and H. Howitz, *Chem. Ber.*, **17**, 1327 (1884). [j] W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 127 (1915). [k] A. Groll, *Chem. Ber.*, **19**, 198 (1886).

It was possible to isolate acetate or sulfate salts of the oxides. Analysis by nmr allowed a quick test for the absence of acetate salt that resulted if either too little base or water was used in the neutralization of the reaction mixture.

Discussion

Yields of alkylated amine are affected by the nature of the alkylating reagent and by the reaction temperature. The fact that methylation occurs readily at lower temperature whereas ethylation gave good yields of tertiary amine only when heated above 100° is in keeping with the known dependence of S_N2 reaction on the nature of the alkyl group. The syntheses were most convenient when the amounts of secondary amine remaining were minimized. Purification involved separation of tertiary amine from secondary amine and from the inevitable black tar.

The methylations could be driven completely to quaternary salt formation and the extra methyl group removed by steam distillation from strongly basic medium with no detectable amount of secondary amine contamination. It was, however, difficult to carry the diethyl sulfate alkylations beyond the point of mixtures of tertiary amine, quaternary salt, and unacceptably large amounts of secondary amine. Separation was accomplished by conversion of the secondary amine to amide with acetic anhydride. Ethylation in an autoclave with ethyl bromide usually gave good yields of tertiary amine without secondary amine contamination

Table III
Substituted *N,N*-Dimethylaniline Oxide Hydrochlorides

Compd	Yield, %	Mp, °C (expt)	Mp, °C (lit.)	pK_a	$10^5 K_a$
3a (H)	44	124–125	124–125[b]	4.26[c]	5.52 ± 0.11
3b (*p*-OCH_3)	37	144–145	146[b]	4.34	4.58 ± 0.11
3c (*m*-OCH_3)	20	109–111	112–113[b]	4.16	6.89 ± 0.01
3d (*p*-CH_3)	52	124–125	138[b]	4.34[c]	4.52 ± 0.11
3e (*m*-CH_3)	39	115–117		4.26	5.55 ± 0.05
3f (*p*-F)	20	155–157		4.09	8.11 ± 0.04
3g (*m*-F)	15	117–120		3.95	11.2[f]
3h (*p*-Cl)	64	149–151	142–143[b]	4.02	9.96 ± 0.21[e]
3i (*m*-Cl)	50	141–142		3.89	13.0 ± 0.1
3j (*p*-Br)	35	155–158	165–166[d]	3.97	10.7 ± 0.8[e]
3k (*m*-Br)	48	142–144		3.86	13.88 ± 0.05
3l (*p*-NO_2)	28	149–152	168–169[d]	3.50	31.3 ± 2.1
3m (*m*-NO_2)	45	146–148	157–158[d]	3.47	31.9 ± 1.4

[a] All compounds melted with decomposition. [b] R. Huisgen, F. Bayerlein, and W. Heydkamp, *Chem. Ber.*, **92**, 3223, (1959). [c] Reference 18 lists 4.21 for **1a** and 4.32 for **1d**. [d] L. W. Jones and E. B. Hartshorn, *J. Amer. Chem. Soc.*, **46**, 1845 (1924). [e] Average error in nine pH values from a single titration curve. [f] Single titration curve value of the half-neutralization point.

even for amines with deactivating substituents (*i.e.*, *m*-NO_2) and must be considered the preferable method.

Analysis for purity was most conveniently carried out by examination of the 3300-cm^{-1} region of the ir spectra, although glpc and nmr gave equally unambiguous indications of the amounts of primary, secondary, and tertiary amines.

The synthesis of amine oxides using peracetic acid in chloroform provides good yield in a rapid reaction. This is consistent with the experience of Craig and coworkers[16] using *m*-chloroperbenzoic acid. Diminished yields of crystalline products are caused by the extreme solubility of the oxide in water. An acceptable procedure involves extracting the oxide from aqueous base with chloroform. The distribution coefficient strongly favors water and is affected by the substituent. The first extract in chloroform contains a variety of organic impurities including starting amine and its other oxidation products. These can be removed from the solid amine oxide with ether or ether–hexane mixtures.

The white crystalline *N,N*-diethylaniline oxides were, with the exception of **2j**, all isolated as hydrates. The degree of hydration for each was determined by (1) titration of a known weight of amine oxide, (2) nmr in $CDCl_3$ (a broad singlet between δ 4 and 5) and (3) by elemental analyses which gave acceptable values only when calculated with water of hydration. The presence of the acetate salt, with the hydrate or instead of it, was easily ascertained by the characteristic nmr signal at δ 2.

The nature of the hydrate has an effect on the physical properties of the amine oxide and on the rates of reaction of the oxide function in nonhydroxylic solvents. We have observed, for example, that the acetate salts are more soluble in nonpolar solvents, *i.e.*, benzene or chloroform than the hydrates. The hydrochlorides are insoluble in nonpolar solvents, may be crystallized from chloroform or low molecular weight ketones, and are soluble in all proportions in water or alcohols. The water of hydration can be removed at −70° in THF with molecular sieves, as found by Cram and coworkers.[17] Once the water of hydration is removed, Cope elimination occurs even at room temperature.

Table IV
Properties of *N,N*-Diethylaniline Oxides

Compound	Yield, %	Mp, °C[a]	pK_a[b]	H_2O of hydration	λ(N–O), cm^{-1} infrared
4a	70	88–89[c]	4.50[d]	1.5	961
4b (*p*-OCH_3)	36.0	80–82	4.66	0.5	945
4c (*m*-OCH_3)	24.5	86–87	4.46	0.5	950
4d (*p*-CH_3)	84.5	101	4.67	0.5	950
4e (*m*-CH_3)	68.5	99–100	4.64	1	957
4h (*p*-Cl)	71.4	91–92	4.28	0.5	949
4i (*m*-Cl)	13.8	105–106	4.21	1	955
4j (*p*-Br)	65.6	104	4.27	0.5	946
4k (*m*-Br)	51.6	82	4.14	*e*	984
4l (*p*-NO_2)	26.4	91–92	3.80	2	949
4m (*m*-NO_2)	69.5	81–82	3.79	1	945

[a] Compounds melted with decomposition. [b] All values were determined from the half-neutralization points of titration curves. All are averages of three runs except **2m** and **2e** (2 titrations) and **2h**, **2i**, and **2j** (1 titration). [c] Reference 4 reports of 96° for the monohydrate. [d] Reference 18 reports a value of 4.53 for this compound. [e] Contains one acetic acid molecule rather than one water molecule per product molecule.

The pK_a's of the amine oxides correlate very nicely. The average deviation in each case was less than 7% of the K_a value. In most cases the average error is less than 3% which is of the same order of magnitude as the accepted errors in pH standard solutions and glass electrode potentials. The values of the pK_a's also agree with those of Nylen,[18] who

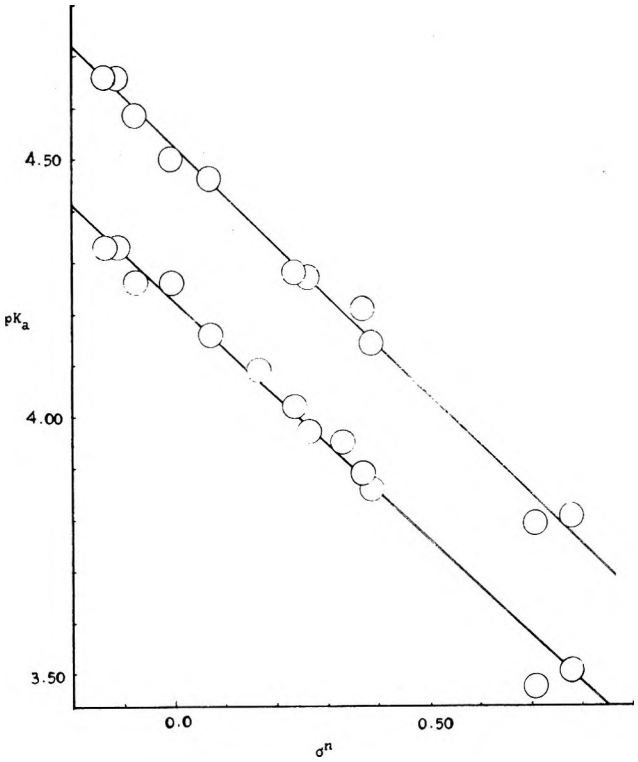


Figure 1. Hammett plot of the pK_a values of **3** and **4** *vs.* σ^n.

obtained values of 4.21 for **3a**, 4.32 for **3d**, and 4.53 for **4a**. The substituted *N,N*-dimethylaniline oxides were titrated as the hydrochlorides with sodium hydroxide. The titration curves were analyzed by computer program in a manner suggested by Albert and Sargeant[19] to give the pK_a values listed in Table III.

The substituted *N,N*-diethylaniline oxides were dissolved in water to give ~0.05 *M* solutions which were titrated with 0.1 *M* hydrochloric acid solution. The pK_a's of these compounds were determined from the half-neutralization points. Although the latter pK_a's were determined with a minimum of data analysis, the spread of values and correlation of them appears to be as good as that for the more rigorously analyzed data.

The pK_a's of **3** and **4** correlated very well with the σ^n of van Bekkum, Verkade, and Wepster[20] and even better with each other (Figure 1). This is exactly what would be expected of a basic atom insulated from the benzene ring by a second period tetravalent atom. The σ^n value for *p*-F is somewhat suspect as it is based on fewer and less applicable data than the values of the other substituents.[20] The magnitude of the ρ values for the correlations is very close to those observed for the similarly affected substituted benzenearsonic acids (ρ = 0.95) and substituted benzenephosphonic acids (ρ = 0.76) pK_a values.[20,21]

Experimental Section

Nuclear magnetic resonance (nmr) data were obtained from a Varian Model T-60 spectrometer with Permalok accessory. The samples were run in $CDCl_3$ solution using tetramethylsilane as an internal standard. Infrared (ir) spectra were obtained from films for liquid samples or KBr pellets for solids using a Beckman IR-10 spectrophotometer. Gas–liquid phase chromatography (glpc) was carried out on a Varian Aerograph Model A-90P.

Anilines and solvents were used as obtained commercially. The peracetic acid and 98% hydrogen peroxide were obtained from FMC Corporation. Melting points and boiling points were uncorrected and obtained at atmospheric pressure unless otherwise indicated. Analyses were carried out by Galbraith Labs, Knoxville, Tenn. The compounds *N,N*-dimethylaniline, *m*- and *p*-*N,N*-dimethyltoluidines, *m*- and *p*-nitro-*N,N*-dimethylanilines, and *N,N*-diethylaniline were purchased from Eastman Organic Chemicals.

General Procedure for Preparation of *N,N*-Dimethylanilines (1). The compounds **1c, 1k, 1g, 1i, 1f,** and **1b** were prepared by the following method. See Table I for physical properties and yields.

***N,N*-Dimethyl-*m*-anisidine (1c).** A mixture of 12.3 g (0.1 mol) of *m*-anisidine, 30 g (0.3 mol) of sodium carbonate, and 100 ml of water was treated repeatedly with 12.6-g (0.1 mol) portions of dimethyl sulfate with stirring until the reaction mixture became homogeneous. The reaction temperature was maintained below 40°. The solution was made strongly basic and steam distilled (excess base is necessary to hydrolyze the quaternary salt). The oily layer was separated, combined with ether extracts of the aqueous layer, dried, concentrated, and vacuum distilled to give a colorless oil, bp 66–68° (0.1 mm) [lit.[22] bp 204–205° (740 mm)].

***p*-Bromo-*N,N*-dimethylaniline (1j).** A 57% yield of **1j** was obtained by the method of Wurster and Beran.[23]

***p*-Chloro-*N,N*-dimethylaniline (1h).** A 60% yield of **1h** was obtained from the appropriate diazonium salt by the method of Ayling and coworkers.[24]

Substituted *N,N*-Dimethylaniline Oxide Hydrochlorides (3). A solution of 3 ml (0.1 mol) of 90% hydrogen peroxide and one drop of concentrated HCl in 30 ml of chloroform was allowed to warm to reflux while 12 ml (0.1 mol) of acetic anhydride was added over 15 min. After the mixture was stirred for 1 hr, 0.1 mol of substituted *N,N*-dimethylaniline was added dropwise while the temperature was maintained below 10°. After the product warmed to room temperature it was extracted with several portions of water. The aqueous extracts were combined and washed twice with ether, and the water was removed from the product on a rotary evaporator. When most of the water was gone, 15 ml of concentrated HCl was added. Crystals of the salt appeared after further evaporation. The products were recrystallized from butanone or mixtures of butanone and chloroform. The products gave acceptable analyses for C, H, N, and Cl. Yields and melting points (with decomposition) are given in Table III.

General Procedures for the Preparation of *N,N*-Diethylanilines (2). All of the diethylanilines used in this study except *p*-nitro-*N,N*-diethylaniline were synthesized by one of two general methods; either the autoclave method or the diethyl sulfate method.

***m*-Nitro-*N,N*-diethylaniline (2m) (Method 1).** A mixture of 0.3 mol of ethyl bromide, 0.33 mol of sodium acetate, 20 ml of water, and 0.1 mol of *m*-nitroaniline was put in an autoclave. The mixture was heated at 160° for 4 hr then cooled to room temperature, added to 1 l. of water, and made basic to litmus with 10% KOH. The product was steam distilled and the distillate was extracted with ether. The ether solution was dried ($MgSO_4$), filtered, and evaporated to leave an oil, which was vacuum distilled to give a 79.8% yield of product, bp 140° (5 mm) (lit.[25] bp 288–290°).

***N,N*-Diethyl-*m*-toluidine (2e) (Method 2).** Diethyl sulfate (1 mol), Na_2CO_3 (1 mol), *m*-toluidine (1 mol), and 150 ml of water were combined with stirring. Heat and CO_2 evolution accompanied the addition of 200 ml of diethyl sulfate. The rate of addition was adjusted to moderate the reaction. After the initial reaction subsided, more Na_2CO_3 (0.5 mol) was added and the mixture heated to reflux for 24 hr. The mixture was treated with another 50 ml of diethyl sulfate and heated at reflux for another 24-hr period. The organic phase was separated and combined with three further ether extracts of the aqueous phase. The aqueous phase was basified and steam distilled. The ether extracts of the steam distillate were combined with the previous ether extracts and dried (Na_2CO_3). The ether was evaporated, and glpc analysis was used to determine the amount of secondary amine remaining. If the product was free of secondary amine it was vacuum distilled. When secondary amine was present an ether solution of product was treated with excess acetic anhydride and a few drops of concentrated H_2SO_4. After 3 hr the mixture was washed with excess 10% HCl. The combined acid washings were made basic, separated from the tertiary amine, and extracted with ether. The combined amine and extracts were dried (Na_2CO_3) and filtered, and the ether was evaporated. The product was vacuum distilled. The physical properties and yields are listed in Table II.

***p*-Nitro-*N,N*-diethylaniline (2b).** The method of Behr and coworkers[26] was used to prepare this compound in 95% yield, mp 70° (lit. 77–78°).

Preparation of Dialkylaniline Oxides (4). Amine (0.1 mol) was dissolved in 150 ml of $CHCl_3$ and cooled to −70°. After 40 ml of 40% peracetic acid was added slowly, the reaction was allowed to warm to room temperature. The acid was neutralized with saturated Na_2CO_3. The phases were separated and the aqueous layer was washed three times with chloroform. The washings were combined with the organic layer, the solution was dried (Na_2CO_3), and the $CHCl_3$ was rotoevaporated, leaving a hygroscopic solid. White crystals were obtained by trituration of the solid with ether. The product was filtered from the ether and quickly stored in a desiccator. The nmr spectra of all the products except **4k** showed a peak for water of hydration between δ 3.5 and 5.0. A listing of physical properties, yields, and degree of hydration are listed in Table IV.

Determination of the pK_a's. All measurements were carried out at 25.0 ± 0.2° and in dilute (0.5 *M*) solution.

The pK_a's of Substituted *N,N*-Dimethylaniline Oxide Hydrochlorides (3). Dilute solutions of **3** were placed in a water-jacketed flask containing a stirring bar and situated over a magnetic stirrer to allow for complete mixing. Water from a constant temperature bath was circulated around the flask allowing the temperature to be maintained at 25.0 ± 0.2°. A Heathkit recording pH meter fitted with Beckman glass and calomel electrodes was used to monitor the titrations. A 1 rpm synchronous motor which had been adapted to drive a vernier microburet was connected so that it started simultaneously with the recorder chart drive. In this way known amounts of base per unit time could be added to the solutions of **3** while the resulting change in pH was being recorded.

The method for calculating the pK_a values from the neutralization curves was taken from Albert and Sargeant and modified so that it could be carried out by computer. The data were the pH's of the solution at various degrees of neutralization (*i.e.*, 10%, 20%, etc.). Then the pK_a's were calculated at each of the points by means of simple pH *vs.* pK_a relationship. The average values of the resulting pK_a's and their average errors are given in Table III.

The pK_a's of *N,N*-Diethylaniline Oxides (4). Solutions (0.05 *M*) or less of amine oxide were titrated with standard 0.1 *M* HCl. The pH values were determined on a Sargent Welch Model NX

digital pH meter fitted with a combination electrode. The pK_a was taken to be equal to neutralization point. The results are listed in Table IV. Three or more titrations were used except where indicated. The precision of the results appears to equal the accuracy normally accepted for glass electrodes, pH meters, and commercial pH standards.

The pK_a's of *N,N*-Diethylanilines (2). These values were obtained from titration curves of 0.001 *M* solutions of the aniline in a slight excess of HCl titrated with 0.001 *M* NaOH solution. If the amines were insoluble in water (less than 0.001 *M*), but soluble in a 10% (v/v) ethanol–water solution, then the same concentrations were used in that medium. The results are summarized in Table II.

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Registry No.—**1a**, 121-69-7; **1b**, 701-56-4; **1c**, 15799-79-8; **1d**, 99-97-8; **1e**, 121-72-2; **1f**, 403-46-3; **1g**, 2107-43-9; **1h**, 698-69-1; **1i**, 6848-13-1; **1j**, 586-77-6; **1k**, 168-62-0; **1l**, 100-23-2; **1m**, 619-31-8; **2a**, 91-66-7; **2b**, 15144-80-6; **2c**, 92-18-2; **2d**, 613-48-9; **2e**, 606-46-2; **2h**, 2873-89-4; **2i**, 6375-75-3; **2j**, 2052-06-4; **2k**, 53142-19-1; **2m**, 2216-16-2; **3a**, 5882-46-2; **3b**, 13330-09-1; **3c**, 53142-20-4; **3d**, 13330-17-1; **3e**, 53247-79-3; **3f**, 53142-21-5; **3g**, 53142-22-6; **3h**, 16657-26-4; **3i**, 53142-23-7; **3j**, 16657-27-5; **3k**, 53142-24-8; **3l**, 13330-12-6; **3m**, 53142-25-9; **4a**, 826-42-6; **4b**, 53142-26-0; **4c**, 53142-27-1; **4d**, 53142-28-2; **4e**, 53142-29-3; **4h**, 22480-56-4; **4i**, 53142-30-6; **4j**, 53142-31-7; **4k**, 53142-32-8; **4l**, 24429-84-3; **4m**, 53142-33-9; dimethyl sulfate, 77-78-1; diethyl sulfate, 64-67-5; *m*-anisidine, 536-90-3; *m*-nitroaniline, 99-09-2; *m*-toluidine, 108-44-1; *m*-bromoaniline, 591-19-5; *m*-fluoroaniline, 372-19-0; *m*-chloroaniline, 108-42-9; *p*-fluoroaniline, 371-40-4; *p*-anisidine, 104-94-9; aniline, 62-53-3; *p*-toluidine, 106-49-0; *p*-chloroaniline, 106-47-8; *p*-bromoaniline, 106-40-1.

References and Notes

(1) Supported in part by National Science Foundation Grants No. G-7345 and GP-1970 at the University of Vermont and GY-7674 at Ball State University and a Ball State Faculty Research Grant.
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Reactions of Dichlorine Heptoxide and of Acyl Perchlorates with Ethers[1]

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Spectral and solubility properties of acyl perchlorates, prepared from silver perchlorate and acid chlorides, are consistent with covalent mixed anhydride structures and not with acylium salts. Acetyl perchlorate in carbon tetrachloride reacted with tetrahydrofuran to give 4-perchloratobutyl acetate and with epoxides to give vicinal acetoxy perchlorates. Isopropyl ether gave isopropyl perchlorate and isopropyl acetate whereas isopropyl pentyl ether gave isopropyl perchlorate and pentyl acetate. Dimethoxymethane gave methyl acetate and methoxymethyl perchlorate. Benzoyl perchlorate and *N,N*-diethylcarbamoyl perchlorate reacted with tetrahydrofuran to give the corresponding 4-perchloratobutyl esters. Dichlorine heptoxide in carbon tetrachloride reacted with tetrahydrofuran, trimethylene oxide, and 2,3-butene oxide to give 1,4-butane diperchlorate, 1,3-propane diperchlorate, and 2,3-butane diperchlorate, respectively. Ethyl ether gave ethyl perchlorate and a trace of ethyl acetate. Propyl ether gave propyl perchlorate and isopropyl perchlorate, whereas isopropyl ether gave isopropyl perchlorate and 2,2-diperchloratopropane. Dimethoxymethane and dichlorine heptoxide gave methyl perchlorate and methoxymethyl perchlorate.

Dichlorine heptoxide in carbon tetrachloride was shown recently to be an effective perchlorylating agent for alcohols[2] and for amines.[3] The present paper deals with reactions of this little explored reagent and of related acyl perchlorates with ethers.

Acyl perchlorates[4–6] have been used as acylating agents and are generally assumed[7] to be perchlorate salts of acylium cations, $RCO^+ClO_4^-$. Solubilities in nonpolar solvents and spectral properties, which should readily differentiate between the salt structures and the corresponding covalent mixed anhydrides, $RC(O)–OClO_3$, have not been reported. The present work includes the characterization of acyl perchlorates and their utilization in ether cleavages to prepare alkyl perchlorate derivatives.

Acetyl chloride was found to react on mixing with a suspension of silver perchlorate in carbon tetrachloride to give a solution of acetyl perchlorate. The yield, determined by nmr, was essentially quantitative. The nmr chemical shift of the compound, δ 2.27, is close to those of acetyl halides and anhydrides, whereas values reported for CH_3CO^+ salts[8] are approximately δ 4.0. The infrared spectrum of acetyl perchlorate shows a normal carbonyl peak at 1825

cm^{-1} rather than the peak at 2300 cm^{-1} assigned to CH_3CO^+ salts.[8] Solutions of acetyl perchlorate in methylene chloride, chloroform, and ethylene chloride were also prepared by adding acetyl chloride to suspensions of silver perchlorate in these solvents. The solubility properties and spectra of acetyl perchlorate are thus clearly consistent with the covalent mixed anhydride structure $CH_3C(O)$–$OClO_3$ and not with the salt structure.

Electron-supplying substituents would increase the likelihood for an acyl perchlorate to exist as an acylium salt. Benzoyl perchlorate and *N,N*-diethylcarbamoyl perchlorate were therefore prepared from the corresponding acid chlorides and silver perchlorate in carbon tetrachloride. The compounds were soluble in carbon tetrachloride, and their spectral properties, described in the Experimental Section, are similar to those of acetyl perchlorate. Thus even an adjacent phenyl or amino group to stabilize positive charge is not sufficient to impart salt-like properties to an acyl perchlorate.

$$CH_3COCl + AgClO_4 \longrightarrow CH_3C(O)OClO_3$$

$$C_6H_5COCl + AgClO_4 \longrightarrow C_6H_5C(O)OClO_3$$

$$(C_2H_5)_2NCOCl + AgClO_4 \longrightarrow (C_2H_5)_2NC(O)OClO_3$$

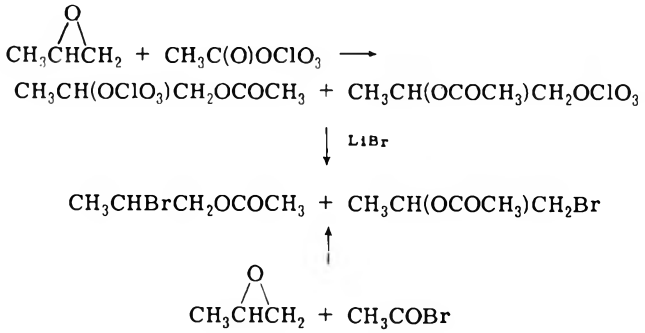
Acyl perchlorates in carbon tetrachloride reacted cleanly with cyclic ethers to give α,ω-acetoxy perchlorates. Thus, acetyl perchlorate in carbon tetrachloride reacted rapidly with tetrahydrofuran at 0° to give a 78% yield of 4-perchloratobutyl acetate, identified by ir and nmr spectra and by conversion to 4-bromobutyl acetate with lithium bromide in acetone. No 1,4-butane diperchlorate or 1,4-diacetoxybutane was formed, which would be expected if acetyl perchlorate equilibrates to dichlorine heptoxide and acetic anhydride.

$$CH_3C(O)OClO_3 + (CH_2)_4O \longrightarrow CH_3CO_2(CH_2)_4OClO_3 \xrightarrow[(CH_3)_2CO]{LiBr} CH_3CO_2(CH_2)_4Br$$

Epoxides readily added acetyl perchlorate to give vicinal acetoxy perchlorates. Thus, ethylene oxide gave an 89% yield of 2-perchloratoethyl acetate, identified by spectra and by conversion to 2-bromoethyl acetate. Propylene

$$+ CH_3C(O)OClO_3 \longrightarrow CH_3CO_2CH_2CH_2OClO_3 \xrightarrow{LiBr} CH_3CO_2CH_2CH_2Br$$

oxide gave an 80% yield of 2-perchlorato-1-propyl acetate and an 8% yield of 1-perchlorato-2-propyl acetate. This mixture reacted with lithium bromide in acetone to give the corresponding acetoxy bromides, which were also prepared independently from acetyl bromide and propylene oxide. Epichlorohydrin similarly gave a mixture of 1-per-



$$CH_3CHCH_2 + CH_3C(O)OClO_3 \longrightarrow CH_3CH(OClO_3)CH_2OCOCH_3 + CH_3CH(OCOCH_3)CH_2OClO_3$$

$$\downarrow LiBr$$

$$CH_3CHBrCH_2OCOCH_3 + CH_3CH(OCOCH_3)CH_2Br$$

$$\uparrow$$

$$CH_3CHCH_2 + CH_3COBr$$

chlorato-3-chloro-2-propyl acetate and 2-perchlorato-3-chloro-1-propyl acetate. 2-Butene oxide gave 3-perchlorato-2-butyl acetate.

Secondary alkyl ethers were also cleaved readily. Thus, isopropyl ether reacted with acetyl perchlorate in carbon tetrachloride to give essentially quantitative yields of isopropyl perchlorate and isopropyl acetate. Similarly, isopropyl pentyl ether gave isopropyl perchlorate and pentyl acetate, with no detectable trace of pentyl perchlorate or isopropyl acetate. Simple primary dialkyl ethers were less readily cleaved by acetyl perchlorate. Ethyl ether, propyl ether, and pentyl ether gave ethyl acetate, propyl acetate, and pentyl acetate, respectively, in yields of 20–25%, but no alkyl perchlorates were detected.

$$(CH_3)_2CHOCH(CH_3)_2 + CH_3C(O)OClO_3 \longrightarrow (CH_3)_2CHOCOCH_3 + (CH_3)_2CHOClO_3$$

$$(CH_3)_2CHO(CH_2)_4CH_3 + CH_3C(O)OClO_3 \longrightarrow CH_3(CH_2)_4OCOCH_3 + (CH_3)_2CHOClO_3$$

Acetals were also cleaved by acetyl perchlorate. Thus, dimethoxymethane gave methyl acetate and methoxymethyl perchlorate. The latter compound was also synthesized independently from silver perchlorate and chloromethyl methyl ether.

$$CH_3OCH_2OCH_3 + CH_3C(O)OClO_3 \longrightarrow CH_3O_2CCH_3 + CH_3OCH_2OClO_3$$

$$ClCH_2OCH_3 + AgClO_4 \longrightarrow CH_3OCH_2OClO_3$$

Benzoyl perchlorate and *N,N*-diethylcarbamoyl perchlorate also reacted with tetrahydrofuran to give 4-perchloratobutyl benzoate and 4-perchloratobutyl *N,N*-diethylcarbamate, respectively. Reaction of these products with lithium bromide gave the corresponding 4-bromobutyl esters. The acyl perchlorates also gave high yields of the corresponding methyl esters on addition of methanol.

Reactions of ethers with dichlorine heptoxide were studied using the standard 0.3 *M* reagent in carbon tetrachloride described previously.[2] Tetrahydrofuran was cleaved rapidly by this reagent to give an 83% yield of 1,4-butane diperchlorate. Trimethylene oxide gave 1,3-propanediperchlorate in 55% yield.

$$+ Cl_2O_7 \longrightarrow ClO_3O(CH_2)_4OClO_3$$

$$+ Cl_2O_7 \longrightarrow ClO_3O(CH_2)_3OClO_3$$

Epoxides also reacted with dichlorine heptoxide. An excess of dichlorine heptoxide reacted with 2-butene oxide to give a 30% yield of 2,3-butane diperchlorate, but stoichiometric mixtures of the reagents gave a mixture of products, which appeared to contain oligomers. Regardless of the ratio of reactants, ethylene oxide, propylene oxide, and epichlorohydrin gave complex mixtures which showed perchlorate bands in their ir spectra.

Simple aliphatic ethers were also cleaved with dichlorine heptoxide. The reaction of ethyl ether, monitored by nmr, was found to be rapid initially, yielding 33% ethyl perchlorate. The formation of ethyl perchlorate then became progressively slower; the yield was 53% in 2 hr, 59% in 18 hr, and 67% in 66 hr. Apparently perchloric acid, formed in a side reaction, reduces the rate by complexing with unreacted ether. An acidic hydrogen appeared at δ 15.5–16.0, accompanied by a downfield shift of 0.28 ppm for the methylene hydrogens of ether. A 2–3% yield of ethyl acetate was also formed.

A similar effect was observed in the reaction of propyl ether with dichlorine heptoxide. In 15 hr, a 49% yield of

propyl perchlorate was obtained, as well as a 13% yield of isopropyl perchlorate.

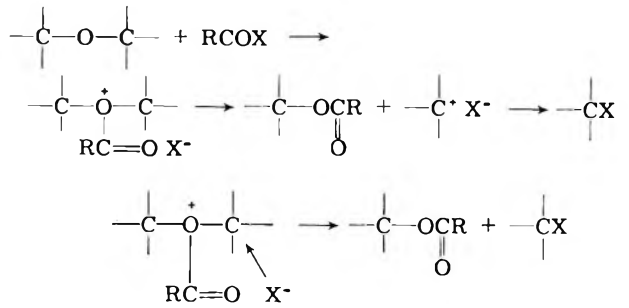
$$CH_3CH_2CH_2OCH_2CH_2CH_3 + Cl_2O_7 \longrightarrow CH_3CH_2CH_2OClO_3 + (CH_3)_2CHOClO_3$$

Isopropyl ether was also cleaved by dichlorine heptoxide in carbon tetrachloride to give a 10% yield of isopropyl perchlorate, but the major product was 2,2-diperchloratopropane, identified spectrally and by conversion to the 2,4-dinitrophenylhydrazone.[9] Isopropyl pentyl ether also gave this compound as well as low yields of isopropyl perchlorate and pentyl perchlorate.

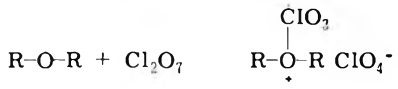
Dimethoxymethane was cleaved by dichlorine heptoxide to give a 78% yield of methoxymethyl perchlorate and an 86% yield of methyl perchlorate in 5 days.

$$CH_3OCH_2OCH_3 + Cl_2O_7 \longrightarrow CH_3OClO_3 + CH_3OCH_2OClO_3$$

Ether cleavages by acylium ions and related species are generally assumed to take place through oxonium ion intermediates.[10-12] Cleavage of the intermediates may take place by a spectrum of mechanisms ranging from SN1 to SN2, depending on the carbonium ion stability of the substrate fragment and the strength of the nucleophile, as well as steric factors.



Lewis acid catalyzed cleavages of secondary and tertiary ethers by acid halides appear to go by an SN1 type mechanism whereas primary ethers give SN2 type products. Mechanisms of cleavages by mixed sulfonic carboxylic anhydrides are shifted toward the SN1 end of the mechanistic spectrum because of the weak nucleophilic properties of sulfonate anions.[12] This shift would be expected to be more pronounced for acyl perchlorates. A similar mechanism for cleavages by dichlorine heptoxide would involve a perchloryloxonium ion intermediate.



This strongly electron-withdrawing group on the oxonium ion should further enhance the tendency toward an SN1-like cleavage. The formation of a significant amount of isopropyl perchlorate from propyl ether and dichlorine heptoxide is thus noteworthy, since isopropyl derivatives were not found in the reaction of propyl ether with acetyl tosylate.[12]

The formation of oxidation products from dichlorine heptoxide, particularly with isopropyl ethers, is also consistent with a perchloryloxonium ion intermediate, which has similarities to intermediates proposed for the oxidation of ethers by bromine[13] and of alcohols by chromic acid.[14] Direct oxidation by dichlorine heptoxide cannot be ruled out, however.

Although alkyl perchlorates are sensitive explosives as neat materials, they are insensitive when sufficiently diluted in an inert solvent and have been shown to function as potent alkylating agents in solution.[2] The acyl perchlorate and dichlorine heptoxide reagents used in this work were prepared as dilute solutions. With reasonable precautions, the methods provide practical means of introducing functionalized alkoxy moieties in synthesis.

Experimental Section

Nmr spectra were recorded with a Varian T-60 spectrometer and ir spectra were recorded with a Perkin-Elmer 700 spectrometer. A Varian 920 gas chromatograph with a 5 ft × 0.25 in. column of 12% QF-1 on chromosorb W was used for glpc separations.

Caution! Neat alkyl perchlorates are sensitive explosives, and the previously noted[2] precautions should be observed. Similar safeguards should be observed with acyl perchlorates.

Acetyl Perchlorate. Acetyl chloride (0.0785 g, 1 mmol) was added in two portions to a stirred suspension of 0.3 g (1.5 mmol) of silver perchlorate in 4 ml of carbon tetrachloride at 0°. The reaction mixture was stirred for 30 min and filtered to give a colorless solution which fumed in moist air. The yield was 96%, determined by nmr using ethylene chloride as internal standard. Solutions of acetyl perchlorate were stable for several days at room temperature. The same procedure was used to prepare acetyl perchlorate solutions in methylene chloride, chloroform, and ethylene chloride. Nmr (CCl_4) δ 2.27 ppm (s); ir (CCl_4) 1825 (vs), 1370 (w), 1285 (vs), 1160 (m), 1040 (s), 1095 cm^{-1} (m).

Reaction of Acetyl Perchlorate with Methanol. Excess methanol (1 ml) was added with stirring to 1 mmol of acetyl perchlorate in 4 ml of carbon tetrachloride at 0°. The mixture was stirred for 30 min, washed with water, and dried. Nmr and ir spectra showed only methyl acetate obtained in 90% yield.

Reaction of Acetyl Perchlorate with Tetrahydrofuran. Tetrahydrofuran (0.072 g, 1 mmol) was added to 1 mmol of acetyl perchlorate in 4 ml of carbon tetrachloride with stirring at 0°. The reaction mixture was stirred for 30 min, washed with water, and dried. The only product in the carbon tetrachloride layer was 4-perchloratobutyl acetate in 78% yield (chlorobenzene as internal nmr standard): nmr (CCl_4) δ 4.52 (t, 2 H, J = 6 Hz, CH_2OClO_3), 4.38 (t, 2 H, J = 6 Hz, CH_2OAc), 2.02 (s, 3 H, CH_3CO), 1.88 ppm (m, 4 H, CH_2CH_2); ir (CCl_4) 1740 (C=O), 1280, 1240, 1040 cm^{-1} ($OClO_3$).

The solution of 4-perchloratobutyl acetate was added dropwise at room tempature to 5 ml of a 10% solution of lithium bromide in acetone. After 30 min, the reaction mixture was washed with water and dried. Evaporation of solvent gave 0.146 g (75%) of 4-bromobutyl acetate: nmr (CCl_4) δ 4.02 (t, 2 H, J = 6 Hz, CH_2OAc), 3.37 (t, 2 H, J = 6 Hz, CH_2Br), 2.00 (s, 3 H, CH_3CO), 1.87 ppm (m, 4 H, CH_2CH_2); ir (CCl_4) 1740, 1240 cm^{-1} (COO).

Anal. Calcd for $C_6H_{11}BrO_2$: C, 36.92; H, 5.64; Br, 40.99. Found: C, 36.69; H, 5.38; Br, 40.88.

Reaction of Acetyl Perchlorate with Isopropyl Ether. Isopropyl ether (0.102 g, 1 mmol) was added to a solution of 1 mmol of acetyl perchlorate in 4 ml of carbon tetrachloride with stirring at 0°. Nmr spectra indicated completion of reaction in less than 10 min. The reaction mixture was washed with water and dried. Isopropyl perchlorate[2] and isopropyl acetate were obtained in 97% yield, identified by comparison with authentic samples by ir and nmr.

Reaction of Acetyl Perchlorate with Isopropyl Pentyl Ether. By the above procedure, acetyl perchlorate and isopropyl pentyl ether gave isopropyl perchlorate and *n*-pentyl acetate in 95 ± 5% yield. Pentyl perchlorate and isopropyl acetate were not observed. Control experiments indicated that 1–2% of these components would have been detected.

Reaction of Acetyl Perchlorate with Primary Ethers. The appropriate primary ether (1 mmol) was added to 1 mmol of acetyl perchlorate in carbon tetrachloride with stirring at 0°. The solution immediately became yellow-orange and some insoluble material was formed. The only products observed either before or after treatment with water were the *n*-alkyl acetate (20–25% yield) and starting material (45–50%). Thus, ethyl acetate, propyl acetate, and pentyl acetate were obtained from ethyl, propyl, and pentyl ethers, respectively. Increasing the reaction time to 48 hr did not improve the yield and a dark tarry residue was deposited. In no case was any alkyl perchlorate detected.

Reaction of Acetyl Perchlorate with Ethylene Oxide. Ethylene oxide (0.088 g, 2 mmol) was added at 0° with stirring to a solution of 2 mmol of acetyl perchlorate in 10 ml of CCl_4. The reaction mixture was stirred for 30 min, washed with water, and dried. The nmr spectrum of the solution showed an 89% yield of 2-perchlora-

toethyl acetate (C_6H_5Cl as quantitative standard): nmr (CCl_4) δ 4.60 (m, 2 H, A_2B_2, CH_2OClO_3), 4.27 (m, 2 H, A_2B_2, CH_2OAc)? 2.10 ppm (s, 3 H, CH_3COO); ir (CCl_4) 1750 (COO), 1285, 1240, 1040 cm^{-1} ($OClO_3$). Treatment of the CCl_4 solution with an excess of 10% lithium bromide in acetone gave 2-bromoethyl acetate (81%): nmr (CCl_4) δ 4.22 (t, 2 H, J = 6.5 Hz, CH_2OAc), 3.37 (t, 2 H, J = 6.5 Hz, CH_2Br), 2.00 ppm (s, 3 H, CH_3COO). The infrared spectrum was identical with that of an authentic sample.

Reaction of Acetyl Perchlorate with Propylene Oxide. Propylene oxide (0.058 g, 1 mmol) was added to a solution of 1 mmol of acetyl perchlorate at 0° with stirring. After 30 min, the reaction mixture was washed with water and dried. Nmr spectra showed two compounds identified as 2-perchlorato-1-propyl acetate (80% yield) and 1-perchlorato-2-propyl acetate (8% yield): nmr (CCl_4) of 2-perchlorato-1-propyl acetate, δ 5.17 (m, 1 H, $CHOClO_3$), 4.13 (m, 2 H, CH_2OAc), 2.07 (s, 3 H, $OCOCH_3$), 1.52 ppm (d, 3 H, J = 7 Hz, CH_3CH); nmr of 1-perchlorato-2-propyl acetate, δ 5.10 (m, CHOAc), 4.48 (m, CH_2OClO_3), 2.07 (s, CH_3COO), 1.33 ppm (d, J = = 6 Hz, CH_3CH). The ir spectrum of the mixture had a strong carbonyl band at 1755 cm^{-1} and perchlorate bands at 1280, 1240, and 1040 cm^{-1}.

The mixture of isomers in carbon tetrachloride was added dropwise to 5 ml of 10% bromide in acetone at room temperature. A mixture of 2-bromopropyl acetate (95%) and 1-bromo-2-propyl acetate (5%) was obtained. The structures were assigned by comparison of nmr and ir spectra with those of an independently prepared mixture described below.

Reaction of Acetyl Bromide with Propylene Oxide. Propylene oxide (2.90 g, 0.05 mol) dissolved in 10 ml of carbon tetrachloride was added dropwise (1 hr) to a solution of 6.15 (0.05 mol) of acetyl bromide in 50 ml of carbon tetrachloride with a catalytic quantity of zinc bromide. The reaction mixture was then stirred for 1 hr, washed with water, and dried. Evaporation of the solvent and distillation of the residual oil gave 6.55 g (72%) of a mixture of bromo acetates, bp 54–58° (10 mm). The ratio of 1-bromo-2-propyl acetate to 2-bromo-1-propyl acetate was 2:1. Nmr (CCl_4) of 1-bromo-2-propyl acetate δ 4.87 (septet, 1 H, CHOAc), 3.32 (d, 2 H, J = 5 Hz, CH_2Br), 1.32 ppm (d, 3 H, J = 6 Hz, CH_3CH); 1-bromo-2-propyl acetate nmr (CCl_4) δ 4.05 (m, 3 H, CHBr, and CH_2OAc), 1.65 ppm (d, 3 H, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_5H_9BrO_2$: C, 33.17; H, 5.01; Br, 44.13. Found: C, 33.11; H, 4.98; Br, 44.16.

Reaction of Acetyl Perchlorate with Epichlorohydrin. Epichlorohydrin (0.0925 g, 1 mmol) was added to a solution of 1 mmol of acetyl perchlorate in carbon tetrachloride with stirring at 0°. After 30 min the reaction mixture was washed with water and dried. The nmr spectrum showed 1-perchlorato-3-chloro-2-propyl acetate and 2-perchlorato-3-chloro-1-propyl acetate in the ratio 1.4:1. The total yield was 93% using chlorobenzene as a quantitative nmr standard: 1-perchlorato-3-chloro-2-propyl acetate nmr (CCl_4) δ 5.10 (m, 1 H, CHOAc), 4.68 (d, 2 H, J = 5 Hz, CH_2OClO_3), 3.65 (d, 2 H, J = 6 Hz, CH_2Cl), 2.13 ppm (s, 3 H, CH_3 COO); 1-perchlorato-2-chloro-1-propyl acetate nmr (CCl_4) δ 5.20 (m, 1 H, $CHOClO_3$), 4.37 (m, 2 H, CH_2OAc), 3.78 (d, 2 H, J = 6 Hz, CH_2Cl), 2.08 ppm (s, 3 H, CH_3COO). The infrared spectrum of the mixture of products showed strong bands at 1755 (C=O) and 1280, 1240, 1050 cm^{-1} ($OClO_3$).

The solution was added dropwise to 5 ml of a 10% solution of lithium bromide in acetone with stirring at room temperature. The reaction mixture was washed with water and dried. Evaporation of solvent gave 0.186 g (87%) of a mixture of 1-bromo-3-chloro-2-propyl acetate and 2-bromo-3-chloro-1-propyl acetate.

Reaction of Acetyl Perchlorate with 2-Butene Oxide. 2-Butene oxide (0.072 g, 1 mmol) was added to a solution of 1 mmol of acetyl perchlorate with stirring at 0°. After 30 min the solution was washed with water and dried to give a carbon tetrachloride solution of 3-perchlorato-2-butyl acetate in 73% yield: nmr (CCl_4) δ 4.92 (m, 2 H, CHOAc, $CHOClO_3$), 2.03 (s, 3 H, CH_3COO), 1.48 (d, 3 H, J = 6.5 Hz, $CH_3CHOClO_3$), 1.28 ppm (d, 3 H, J = 7 Hz, CH_3CHOAc); ir (CCl_4) 1745 (C=O), 1280, 1240, 1040 cm^{-1} ($OClO_3$).

Reaction of Acetyl Perchlorate with Dimethoxymethane. Dimethoxymethane (0.076 g, 1 mmol) was added to a solution of 1 mmol of acetyl perchlorate in carbon tetrachloride with stirring at 0°. After 15 min, nmr showed the disappearance of the starting materials and the formation of methyl acetate (95%) and methoxymethyl perchlorate (83%). The yields were determined by nmr using chloroform as a quantitative standard. Washing with water and filtration of the solution through silica gel to remove formaldehyde polymer gave a solution of methyl acetate (78%) identified by comparison of spectral and gas chromatographic parameters with those of an authentic sample.

Reaction of Chloromethyl Methyl Ether with Silver Perchlorate. Chloromethyl methyl ether (0.0805 g, 1 mmol) was added to a stirred suspension of 0.30 g (1.5 mmol) of silver perchlorate in 4 ml of carbon tetrachloride. After 30 min, nmr spectra indicated that starting material was consumed, and methoxymethyl perchlorate, identical with the material above, was formed in 81% yield. Solutions fumed in moist air: nmr (CCl_4) δ 5.57 (s, 2 H, CH_2), 3.67 ppm (s, 3 H, CH_3); ir (CCl_4) 1280, 1260, 1050 cm^{-1} ($OClO_3$).

Benzoyl Perchlorate. Benzoyl chloride (0.703 g, 5 mmol) in 5 ml of carbon tetrachloride, was added dropwise at 0° with stirring to 1.45 g (7 mmol) of silver perchlorate suspended in 10 ml of carbon tetrachloride. Stirring was continued for 2 hr. Filtration under anhydrous conditions gave a colorless solution of benzoyl perchlorate which fumed in moist air. The yield was 98% using cyclohexane as quantitative internal nmr standard: nmr (CCl_4) δ 7.4–8.1 (m, Ar); ir (CCl_4) 3080 (w), 1780 (vs), 1590 (m), 1450 (m), 1280 (vs), 1225 (s), 1180 (m), 1050 (s), 950 cm^{-1} (vs).

Reaction of Benzoyl Perchlorate with Methanol. Excess methanol (0.96 g, 30 mmol) was added to 5 mmol of benzoyl perchlorate in carbon tetrachloride prepared as above. The reaction mixture was stirred for 10 min, washed with water, and dried. The only product was methyl benzoate (95%).

Reaction of Benzoyl Perchlorate with Isopropyl Ether. Isopropyl ether (0.50 g, 5 mmol) was added to 5 mmol of benzoyl perchlorate in carbon tetrachloride at room temperature. After 3 hr the reaction, monitored by nmr, was complete and gave isopropyl perchlorate and isopropyl benzoate each in 98% yield (ethylene chloride as quantitative internal nmr standard). The structure of the products was confirmed by comparison of nmr and ir spectra with those of authentic isopropyl perchlorate and isopropyl benzoate.

Reaction of Benzoyl Perchlorate with Tetrahydrofuran. A solution of 0.36 g (5 mmol) of tetrahydrofuran in 2 ml of carbon tetrachloride was added dropwise with stirring to 5 mmol of benzoyl perchlorate in carbon tetrachloride at 0°. After 30 min the reaction mixture was washed with water and dried. Nmr spectra of the carbon tetrachloride solution showed 4-perchloratobutyl benzoate (83%) contaminated by a small quantity of polymeric materials showing a broad band in the ether region (3.50 ppm). Filtration through a short column of silica gel removed the latter: nmr (CCl_4) δ 7.2–8 (m, 5 H, Ar), 4.57 (m, 2 H, CH_2OClO_3), 4.32 (m, 2 H, $CH_2OCOC_6H_5$), 1.95 ppm (broad m, 4 H, CH_2CH_2); ir (CCl_4) 1735 (C=O), 195, 1260 cm^{-1} ($OClO_3$).

The carbon tetrachloride solution was added dropwise at room temperature to 20 ml of a 10% solution of lithium bromide in acetone. The reaction mixture was stirred for 30 min, washed with water, and dried. Evaporation of solvent gave 0.905 g (71%) of 4-bromobutyl benzoate: nmr (CCl_4) δ 7.1–7.8 (m, 5 H, Ar), 4.20 (m, 2 H, $CH_2OCOC_6H_5$), 3.33 (m, 2 H, CH_2Br), 1.93 ppm (m, 4 H, CH_2CH_2); ir (CCl_4) 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.40; H, 5.10; Br, 31.10. Found: C, 51.42; H, 4.93; Br, 31.20.

***N,N*-Diethylcarbamoyl Perchlorate.** Diethylcarbamoyl chloride (0.675 g, 5 mmol) dissolved in 5 ml of carbon tetrachloride was added dropwise with stirring, over a 10-min period, to 1.20 g (6 mmol) of silver perchlorate suspended in 15 ml of carbon tetrachloride at 0°. The reaction mixture was stirred for 30 min and 10 ml of carbon tetrachloride was added to give a solution of *N,N*-diethylcarbamoyl perchlorate in 82% yield (ethylene chloride as quantitative nmr standard): nmr (CCl_4) δ 3.33 (q, 4 H, J = 7 Hz, NCH_2), 1.25 ppm (t, 6 H, J = 7 Hz, CH_3); ir (CCl_4) 2960 (m), 1782 (vs), 1480 (m), 1460 (m), 1420 (m), 1390 (m), 1370 (w), 1320 (w), 1280 (vs), 1220 (m), 1140 (s), 1100 (s), 1050 (s), 1020 (m), 960 (w), 900 cm^{-1} (s).

Reaction of *N,N*-Diethylcarbamoyl Perchlorate with Methanol. Excess methanol (0.96 g, 0.03 mol) was added to a solution of *N,N*-diethylcarbamoyl perchlorate in carbon tetrachloride, prepared as above, with stirring at 0°. The reaction mixture was stirred for 30 min, washed with water, and dried. Evaporation of solvent gave 0.517 g (96%) of methyl *N,N*-diethylcarbamate identified by spectral comparison with an authentic sample described below.

Methyl *N,N*-Diethylcarbamate. Methyl chloroformate (9.45 g, 0.1 mol) was added dropwise with stirring at 0–5° to a solution of 7.3 g (0.1 mol of diethylamine and 3.9 g (0.1 mol) of sodium hydroxide in 25 ml of water. The reaction mixture was stirred for 30 min and extracted with methylene chloride and distilled to give 10.3 g (79%) of methyl *N,N*-diethylcarbamate, bp 66–68° (26 mm):

nmr (CCl_4) δ 3.57, (s, 3 H, OCH_3), 3.17 (q, 4 H, J = 7 Hz, NCH_2); 1.10 ppm (t, 6 H, J = 7 Hz, CH_3); ir (CCl_4) 1700, 1280, 1180 cm^{-1} (OCON).

Reaction of *N,N*-Diethylcarbamoyl Perchlorate with Tetrahydrofuran. A solution of 0.36 g (5 mmol) of tetrahydrofuran in 3 ml of carbon tetrachloride was added dropwise with stirring at 0° to a solution of *N,N*-diethylcarbamoyl perchlorate prepared as above. After 30 min the solution was washed with water and dried to give a solution of 4-perchloratobutyl *N,N*-diethylcarbamate (75% yield by nmr, chlorobenzene quantitative standard): nmr (CCl_4) δ 4.52 (t, 2 H, J = 6 Hz, CH_2OClO_3), 4.00 (t, J = 6 Hz, 2 H, CH_2OCON), 3.18 (q, 4 H, J = 6.5 Hz, CH_2N), 1.83 (m, 4 H, CH_2CH_2), 1.12 ppm (t, 6 H, J = 6.5 Hz, CH_3); ir (CCl_4) 1695 (OCON), 1280, 1040 cm^{-1} ($OClO_3$).

The carbon tetrachloride solution of the product was added to 20 ml of a 10% solution of lithium bromide in acetone. After 30 min, the reaction mixture was washed with water and dried. Evaporation of solvent gave 0.176 g (70%) of 4-bromobutyl *N,N*-diethylcarbamate as a pale yellow oil. An analytical sample was collected by glpc using a 6 ft × ¼ in. aluminum column packed with 10% QF-1 on 60–80 mesh chromosorb W at 150°: nmr (CCl_4) δ 3.97 (t, 2 H, J = 6 Hz, CH_2OCON), 3.33 (t, 2 H, J = 6 Hz, CH_2Br), 3.17 (q, 4 H, J = 7 Hz, NCH_2), 1.83 (m, 4 H, CH_2CH_2), 1.10 ppm (t, 6 H, J = 7 Hz, NCH_2CH_3); ir (CCl_4) 1695, 1180 cm^{-1} (OCON).

Anal. Calcd for $C_9H_{18}BrNO_2$: C, 42.86; H, 7.2; Br, 31.69; N, 5.6. Found: C, 42.56; H, 6.87; Br, 31.58; N, 5.74.

Reaction of Ethyl Ether with Dichlorine Heptoxide. Ethyl ether (0.0888 g, 1.2 mmol) was added to 4 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride[2] at room temperature. Aliquots were removed periodically, washed with water, dried, and analyzed by nmr for ethyl perchlorate[2] (per cent yield) and ethyl ether (per cent recovery) respectively as follows: 10 min, 33, 57; 2 hr, 53, 37; 18 hr, 59, 26; 66 hr, 67, 18. Ethyl acetate was also formed, with a yield of 2–3% in 66 hr. A small acid signal also appeared (before water treatment of the aliquots) at δ 15.5–16.0 as the reaction progressed, and its formation was accompanied by a downfield shift of 0.28 ppm for the methylene hydrogens of ethyl ether.

Reaction of Propyl Ether with Dichlorine Heptoxide. Propyl ether (0.1224 g, 1.2 mmol) was added to 4 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride and the reaction was followed by nmr, as in the preceding example. In 15 hr, the spectrum showed propyl perchlorate[2] (49% yield), isopropyl perchlorate[2] (13%), and propyl ether (33%); in 66 hr, no significant further changes took place. An acid signal (δ 15.9) and downfield shift of the α-hydrogen signal of propyl ether were observed before water treatment of the samples. In a control experiment, no reaction was observed between propyl perchlorate and propyl ether under the same conditions.

Reaction of Tetrahydrofuran with Dichlorine Heptoxide. Tetrahydrofuran (0.176 g, 2.4 mmol) in 1 ml of carbon tetrachloride was added dropwise with stirring at 0° to 8 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride. After 15 min, the solution was washed with water and dried over magnesium sulfate to give a solution of 1,4-butane diperchlorate[2] (83% yield using chlorobenzene as quantitative nmr standard). No other products were detected by nmr or ir.

Reaction of Trimethylene Oxide with Dichlorine Heptoxide. A solution of 0.087 g (1.5 mmol) of trimethylene oxide in 2 ml of carbon tetrachloride was added dropwise with stirring to 5 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride at 0°. After 30 min, the solution was washed with water, dried over sodium sulfate, and filtered through silica gel to remove small quantities of polymeric material. The nmr spectrum of the resulting solution showed only 1,3-propane diperchlorate (55% yield using chlorobenzene as quantitative standard): nmr (CCl_4) δ 4.63 (t, 4 H, J = 6 Hz, CH_2OClO_3), 2.28 ppm (quintet, 2 H, J = 6 Hz, $C-CH_2-C$; ir (CCl_4) 1290, 1270, 1230, 1010, 1030 cm^{-1} ($OClO_3$).

Reaction of Isopropyl Pentyl Ether with Dichlorine Heptoxide. Isopropyl pentyl ether (0.078 g, 0.6 mmol) was stirred with 2 ml of 0.3 *M* dichlorine heptoxide solution in carbon tetrachloride for 18 hr at room temperature. A small quantity of a colorless oil separated, soluble in $CDCl_3$, which was identified as 2,2-diperchloratopropane by nmr.[9] The carbon tetrachloride layer was washed with water and dried. Nmr showed a 22% yield of isopropyl perchlorate, 11% pentyl perchlorate, and 18% isopropyl pentyl ether.

Reaction of Dimethoxymethane with Dichlorine Heptoxide. Dimethoxymethane (0.091 g, 1.2 mmol) was added to 4 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride. The reaction, followed by nmr, was complete in 5 days to give methyl perchlorate (86%) and methoxymethyl perchlorate (78%).

Reaction of Isopropyl Ether with Dichlorine Heptoxide. Isopropyl ether (0.061 g, 0.6 mmol) was added to 2 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride with stirring at 0°. In 5 min, the solution became pale yellow-green, and after 10–15 min, a colorless oil separated and the solution became colorless. The solution contained isopropyl perchlorate (10% yield by nmr) and isopropyl ether (25%). The oil was identified as 2,2-diperchloratopropane:[9] nmr ($CDCl_3$) δ 2.60 ppm (s). In another experiment, water and 2,4-dinitrophenylhydrazine reagent were added to the crude product mixture to give 0.086 g (60%) of acetone 2,4-dinitrophenylhydrazone.

Reaction of Epoxides with Dichlorine Heptoxide. 2-Butene oxide (0.0353 g, 0.49 mmol) was added with stirring to 2 ml of 0.3 *M* dichlorine heptoxide in carbon tetrachloride at 0°. The solution was stirred 24 hr at ambient temperature. The solution was separated from a dark insoluble oil, washed with water, and dried over sodium sulfate. Spectra were consistent with the 2,3-butane diperchlorate structure (30% yield by nmr): nmr (CCl_4) δ 1.58 (d, 6 H, J = 6 Hz, CH_3), 5 ppm (m, 2 H, CH); ir (CCl_4) 1280, 1240, 1040 cm^{-1} (ClO_4).

Equimolar amounts of 2-butene oxide and dichlorine heptoxide by this procedure gave a mixture with two additional methyl doublets.

Ethylene oxide, propylene oxide, and epichlorohydrin reacted on mixing with dichlorine heptoxide, but nmr spectra indicated complex mixtures. The ir spectra showed strong perchlorate bands at approximately 1280, 1240, and 1020 cm^{-1}.

Registry No.—Acetyl perchlorate, 2889-74-9; acetyl chloride, 75-36-5; silver perchlorate, 7783-93-9; methanol, 67-56-1; tetrahydrofuran, 109-99-9; 4-perchloratobutyl acetate, 53209-91-9; 4-bromobutyl acetate, 4753-59-7; isopropyl ether, 108-20-3; isopropyl pentyl ether, 5756-37-6; ethylene oxide, 75-21-8; 2-perchloratoethyl acetate, 53209-92-0; 2-bromoethyl acetate, 927-68-4; propylene oxide, 75-56-9; 2-perchlorato-1-propyl acetate, 53209-93-1; 1-perchlorato-2-propyl acetate, 53209-94-2; 1-bromo-2-propyl acetate, 10299-39-5; 2-bromo-1-propyl acetate, 592-19-8; epichlorohydrin, 106-89-8; 1-perchlorato-3-chloro-2-propyl acetate, 53209-95-3; 1-perchlorato-2-chloro-1-propyl acetate, 53209-96-4; 2-butene oxide, 3266-23-7; 3-perchlorato-2-butyl acetate, 53209-97-5; dimethoxymethane, 109-87-5; chloromethyl methyl ether, 107-30-2; methoxymethyl perchlorate, 17810-45-6; benzoyl perchlorate, 53209-98-6; benzoyl chloride, 98-88-4; 4-perchloratobutyl benzoate, 53209-99-7; 4-bromobutyl benzoate, 36978-34-4; *N,N*-diethylcarbamoyl perchlorate, 53210-00-7; diethylcarbamoyl chloride, 88-10-8; *N,N*-diethyl methylcarbamate, 4652-44-2; methyl chloroformate, 79-22-1; diethylamine, 109-89-7; 4-perchloratobutyl *N,N*-diethylcarbamate, 53210-01-8; *N,N*-diethyl 4-bromobutylcarbamate, 53210-02-9; ethyl ether, 60-29-7; dichlorine heptoxide, 10294-48-1; propyl ether, 111-43-3; trimethylene oxide, 503-30-0; 1,3-propane diperchlorate, 53210-03-0; 2,2-diperchloratopropane, 28078-46-8; 2,3-butane diperchlorate, 53210-04-1.

References and Notes

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Some Stereochemical Aspects of the Claisen Rearrangement of Allyl Vinyl Ethers[1]

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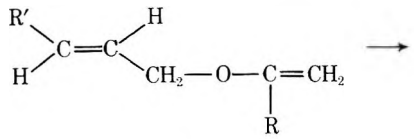
The Claisen rearrangement of the allyl vinyl ethers **9** and **19a** has been used to explore the possibility that reactions proceeding by six-membered cyclic transition states may exhibit a selectivity for either axial or equatorial attack at a double bond exocylic to a cyclohexane ring. In the two cases studied there was a slight preference for attack to form a new equatorial bond, the product ratios being 52% equatorial and 48% axial for enol ether **9** and 75–77% equatorial and 23–25% axial for the enol ether **19a**.

Previous studies of the Claisen rearrangement of allyl vinyl ethers **1** have shown this reaction to be a concerted intramolecular process involving a cyclic six-centered transition state.[2] The stereochemical results[2b-d,3] obtained in studies of this rearrangement have established that a chair conformation **2** is preferred for the cyclic six-centered transition state and that the stereochemically favored path for rearrangement is remarkably sensitive to steric factors in spite of the relatively high reaction temperatures (110–200°) employed. Because of these properties, this rearrangement offered a useful tool with which to explore the question of whether the intervention of a cyclic six-centered transition state **4** in additions to a double bond exocyclic to a cyclohexane ring (*e.g.*, **3**) offered any inherent stereoselectivity for either axial (*e.g.* **5a**) or equatorial (*e.g.*, **5b**) attack. Such cyclic transition states have frequently been invoked in additions of organometallic reagents or metal hydrides to cyclohexanone derivatives (**3**, X = O), and yet it is presently unclear whether or not there is a clear energetic preference for one of the transition states **4a** or **4b**.



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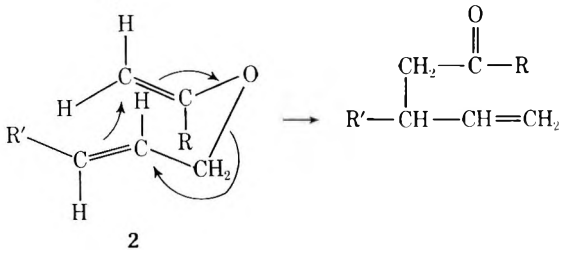

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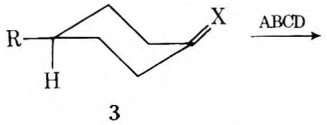

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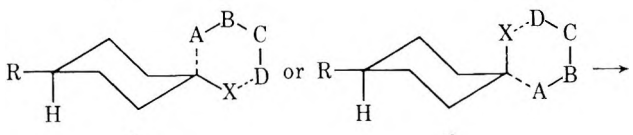
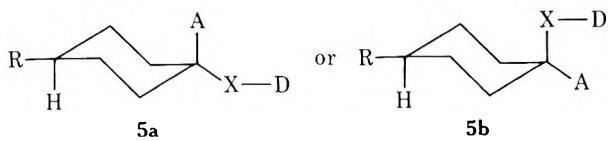
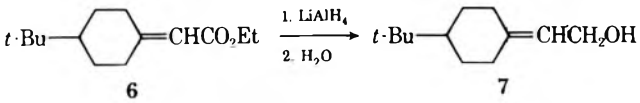


4a **4b**

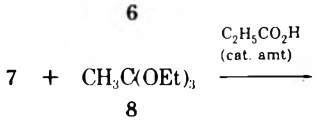


5a **5b**

Scheme I



6 **7**



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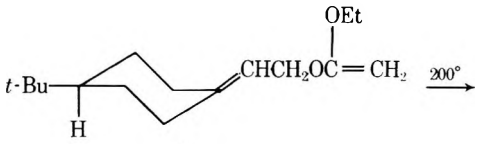

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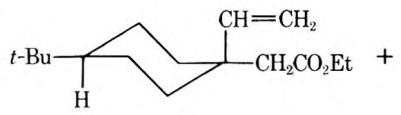

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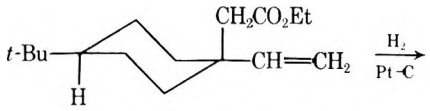

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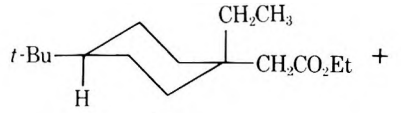

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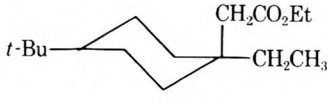
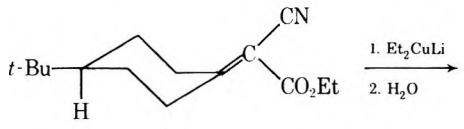


13a



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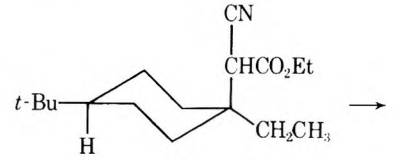

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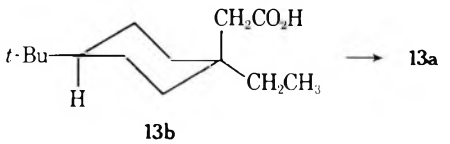


13b

We have selected two systems with which to study this question. In the first study, the known[4] ester **6** (Scheme I) was reduced to the allylic alcohol **7** and then treated with ethyl orthoacetate (**8**) in the presence of an acid catalyst to form the enol ether **9**. Thermal rearrangement produced a mixture of the stereoisomeric esters **10** and **11** that we were unable to resolve by a variety of chromatographic techniques. However, nmr analysis indicated the composition of the mixture to be 52% **10** and 48% **11**. Hydrogenation of the mixture of esters **10** and **11** afforded the saturated esters **12** (52% of the mixture) and **13a** (48% of the mixture) that were separable by gas chromatography. To establish the configuration of these esters **12** and **13a**, we used the known[4,5] stereospecificity of the addition of lithium dialkylcuprates to the alkylidene derivative **14** to form the cyano ester **15** with an equatorial ethyl group. Hydrolysis, decarboxylation, and reesterification converted the cyano ester **15** to the ester **13a**.

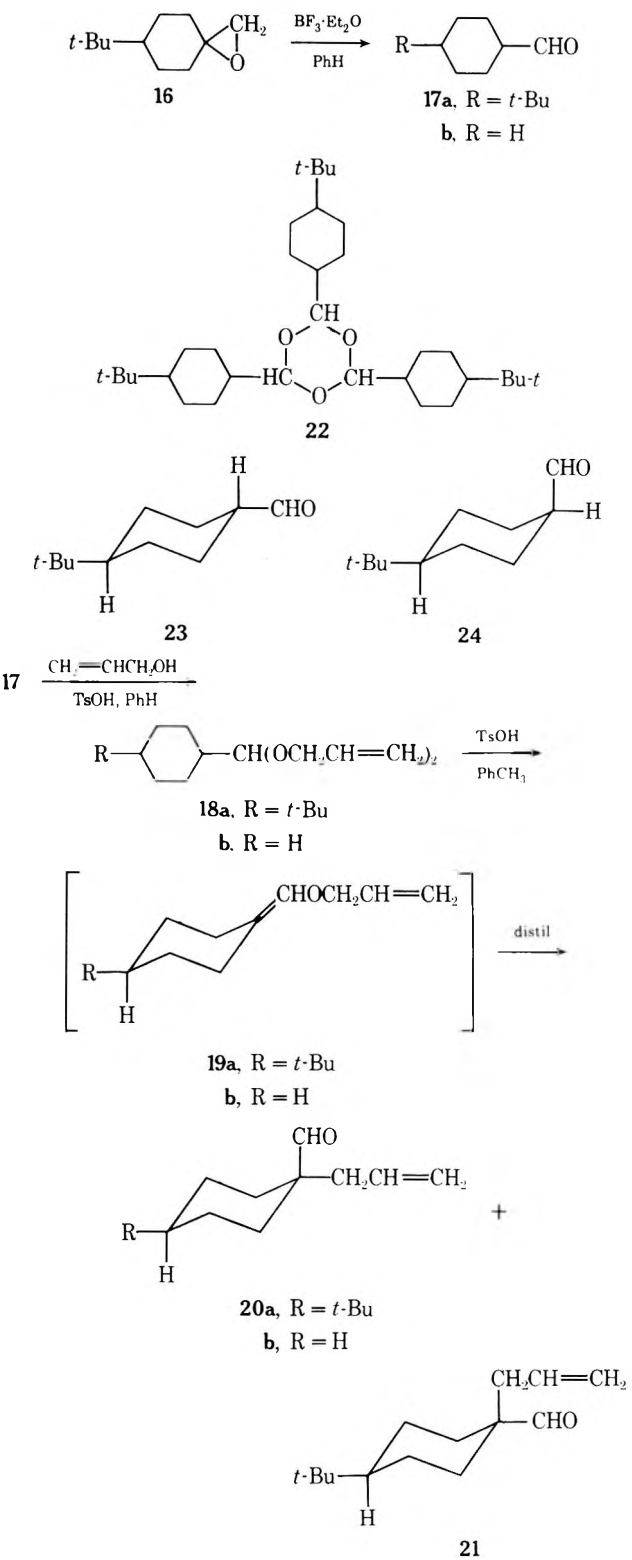
Further evidence supporting these stereochemical assignments was obtained from the proton and ^{13}C nmr spectra of the saturated esters **12** and **13a**. The proton nmr signal (δ 2.23) for the axial CH_2CO_2R group of the more rapidly eluted (glpc) ester **13a** was found at lower field than the signal (δ 2.05) for the equatorial CH_2CO_2R group of the more slowly eluted ester **12** corresponding to the usual generalization for axial and equatorial methyl groups.[6a] The ^{13}C nmr spectrum of ester **13a** has a signal (relative to TMS) at 36.1 ppm for the CH_2 of the axial CH_2CO_2Et group and at 34.5 ppm for the CH_2 of the equatorial ethyl group. In ester **12**, the corresponding values are 45.6 ppm for the CH_2 of the equatorial CH_2CO_2Et group and 25.0 ppm for the CH_2 of the axial ethyl group. Thus, in each case a change from an axial to an equatorial sp^3 carbon results in a downfield shift of about 9 ppm in agreement with previous generalizations.[6b,c]

For the second study, the known[7] epoxide **16** (Scheme II) was isomerized with $BF_3 \cdot Et_2O$ in PhH solution to produce a PhH solution of the aldehyde **17a**. Although we were able to collect small amounts of the aldehyde **17a** from a glpc column as a mixture of diastereoisomers **23** (*ca.* 83%) and **24** (*ca.* 17%),[8] the isolation of substantial quantities of the pure aldehyde **17a** was thwarted by the tendency of this aldehyde **17a** to undergo a variety of condensation reactions including formation of various isomers of the cyclic trimer **22**.

As a model for further study, the aldehyde **17b** was converted to its acetal **18b** which was isolated in pure form. Subsequent reaction of the acetal **18b** with TsOH followed by distillation to effect thermal rearrangement of the intermediate enol ether **19b**[9] afforded the aldehyde **20b** in 50% yield. This same product **20b** was also obtained (Scheme III) by successive conversion of the aldehyde **17b** to the imine **25** and its Li^+ salt **26** followed by alkylation to form the imine **27** and hydrolysis to form the aldehyde **20b**.[10]

Reaction of the benzene solution of aldehyde **17a** with allyl alcohol and TsOH followed by acid-catalyzed cleavage of the crude acetal **18a** and thermal rearrangement of the enol ether **19a** afforded a mixture of aldehydes **20a** and **21** in an overall yield of 31% (based on the epoxide **16**). The aldehyde mixture contained 75–77% of the axial aldehyde **20a** and 23–25% of the equatorial aldehyde **21**. To provide chemical evidence for these stereochemical assignments, the major product **20a** was also synthesized by an alternative route involving alkylation of the lithium salt **29** of the nitrile **28** to form nitriles **30** (88% of the mixture) and **31** (12% of the mixture). Alkylation of this lithium salt **29** had previously been shown[11] to form predominantly the product with an equatorial alkyl group. Subsequent reduction

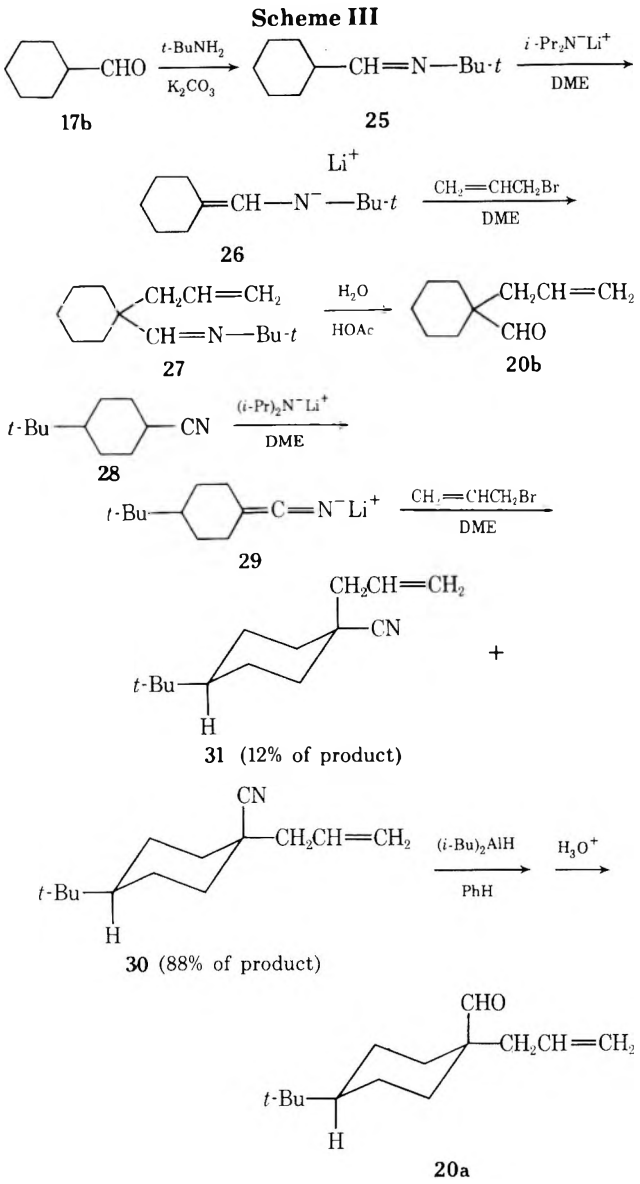
Scheme II



of the nitrile **30** with $(i\text{-Bu})_2AlH$ and hydrolysis yielded the aldehyde **20a**. Our efforts to form this aldehyde **20a** by alkylation of an imine lithium salt analogous to **26** were not successful apparently because of the very limited solubility of the lithium salt in DME.

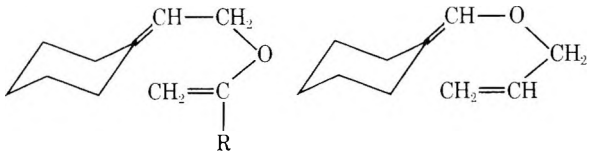
Further evidence for the stereochemical assignments given products **20a** and **21** were obtained from their proton and ^{13}C nmr spectra. Thus, the proton nmr signal for the axial allylic CH_2 group in **21** occurred at lower field (δ 2.36) than the corresponding signal (δ 2.08) for the equatorial allylic CH_2 group in **20a**. The ^{13}C nmr signal for this axial al-

Scheme III



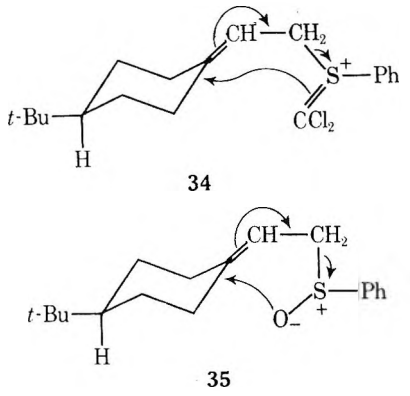
lylic CH_2 group in **21** occurred at about 8 ppm higher field (34.6 ppm) than the corresponding signal (42.7 ppm) for the equatorial allylic CH_2 group in **20a.** Both of these chemical shift differences correspond to the previously mentioned generalizations.[6]

Thus, for the two general systems **32** and **33** we have studied, we have observed only a slight energy preference (0.1–0.9 kcal/mol) favoring attack from an equatorial rath-



32 **33**

er than an axial direction in reactions that almost certainly involve a six-centered cyclic transition state. The closest related examples of which we are aware are the rearrangements (presumably involving five-center cyclic transition states) of compounds **34**[12a] and **35.**[12b] In both cases the indicated rearrangement to form a new equatorial bond is kinetically favored, the ratio being estimated as 82:18 for compounds **35.**[12b] Although slight preference for equatorial attack that we have observed would appear to be adequately explained by the usual assumption that attack from the



"equatorial direction" is subject to less steric hindrance, the possibility that some more profound phenomenon might be involved[13] certainly cannot be excluded. In any case, our data indicate that there is no inherent reason for an addition to a double bond exocyclic to a cyclohexane ring (*e.g.*, **3**) to favor axial attack (*e.g.*, **5a**) simply because a cyclic six-membered transition state (**4a**) is involved.

Experimental Section[14]

Preparation of the Allylic Alcohol 7. Following a previously described procedure,[4] the ester **6** was obtained in 75% yield as a colorless liquid, bp 114–121° (2.1 mm), n^{25}D 1.4783–1.4784 [lit.[4] bp 77–84° (0.1 mm), n^{21}D 1.4773]. This product **6** had ir and nmr absorption corresponding to the spectra previously determined and it lacked nmr absorption at δ 2.93 characteristic[4] of material contaminated with the isomeric β,γ-unsaturated ester. To a solution of 1.44 g (38 mmol) of $LiAlH_4$ in 175 ml of Et_2O was added, dropwise and with stirring during 1 hr, a solution of 10.0 g (46 mmol) of the ester **6** in 60 ml of Et_2O. After the resulting solution had been stirred for 2 hr at 25°, it was treated successively with 0.64 g of EtOH and with 20 ml of Et_2O saturated with H_2O. The precipitated Al salts were filtered and washed with Et_2O and the combined Et_2O solutions were washed with aqueous $NaHCO_3$, dried, and concentrated. The residual yellow liquid (8.17 g, free of C=O groups by ir analysis) was distilled to separate 6.23 g (78%) of the alcohol **7** as a colorless liquid, bp 108–110.5° (1.7 mm), n^{25}D 1.4892: ir (CCl_4) 3620, 3320 (free and associated OH), and 1665 cm^{-1} (C=C); uv (95% EtOH), end absorption with ϵ 1970 at 210 mμ; nmr (CCl_4) δ 5.29 (1 H, t, J = 6.5 Hz, vinyl CH), 4.02 (2 H, d, J = 6.5 Hz, CH_2O), 3.72 (1 H, broad, shifted with pyridine, OH), 0.9–2.9 (9 H, m, aliphatic CH), and 0.84 (9 H, s, *t*-Bu); mass spectrum *m/e* (relative intensity) 182 (M^+, 3), 164 (46), 149 (23), 121 (30), 109 (29), 108 (59), 107 (38), 95 (26), 93 (63), 83 (30), 82 (27), 81 (50), 80 (40), 79 (48), 69 (22), 67 (41), 57 (100), 56 (23), 55 (41), 43 (23), 41 (40), and 39 (23).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.86; H, 12.22.

Preparation and Rearrangement of the Allyl Vinyl Ether 9. A mixture of 16.01 g (88 mmol) of the allylic alcohol **7**, 308 mg (0.4 mmol) of propionic acid, and 81.0 g (520 mmol) of freshly distilled ortho ester **8** (bp 138–143°) was heated under partial reflux with continuous removal of EtOH until no more EtOH distilled (*ca* 1 hr). The solution was cooled and fractionally distilled under reduced pressure to remove the propionic acid and excess ortho ester **8** [bp 42–45° (35 mm)]. The residual yellow liquid was fractionally distilled at 20 mm to effect rearrangement of the enol ether **9.** The first distillation separated 1.089 g of forerun, bp 46–155° (20 mm), n^{25}D 1.4403, and 16.73 g of fractions, bp 155–162° (20 mm), n^{25}D 1.4642–1.4643, that contained (glpc analysis, Apiezon L on Chromosorb P) a small amount of the unchanged alcohol (retention time 6.3 min) and an unresolved mixture of the esters **10** and **11** (17.9 min). Nmr analysis (CCl_4 solution) of the distillate indicated that the distilled product contained both the subsequently described rearranged esters **10** and **11** and a small amount of the unrearranged enol ether **9** with a quartet (J = 7.4 Hz) of resolved nmr peaks at δ 3.49 attributable to the ethoxyl CH_2 group of the unrearranged enol ether **9.** The amount of this unrearranged enol ether **9** was substantially greater in another preparation in which the final distillation was effected at a lower temperature [bp 122–130° (2 mm), n^{25}D 1.4622–1.4633]. When samples of distilled material containing the unrearranged enol ether **9** either were heated

under N_2 to 200° for 10 min or were passed through a glpc column at 250° and recollected, nmr analysis indicated that rearrangement of the enol ether **9** to the esters **10** and **11** was complete. Redistillation of the above fractions containing esters **10** and **11** with a minor amount of the enol ether **9** afforded 13.29 g of fractions, bp 150–159° (20 mm), n^{25}D 1.4645–1.4646, that were free (nmr analysis) of unrearranged ether **9** and contained (glpc analysis) the esters **10** and **11** accompanied by small amounts of the alcohol **7**. We were unsuccessful in attempts to resolve the two stereoisomeric esters **10** and **11** either with a variety of glpc columns or by tlc analysis with either SiO_2 and Al_2O_3 coatings and a variety of eluents. Consequently, a sample of the mixture of esters **10** and **11** was collected (glpc) for characterization as a colorless liquid, n^{25}D 1.4643: ir (CCl_4) 1730 (ester C=O), 1635 (C=C), and 920 cm^{-1} (CH=CH_2); nmr (CCl_4) δ 4.7–6.1 (3 H, m, CH=CH_2), 4.01 (2 H, q, J = 7.3 Hz, ethoxyl CH_2), 0.9–2.1 [12 H, m, aliphatic CH including an ethoxy CH_3 triplet (J = 7.3 Hz) at 1.18], with two singlets at 2.12 (52% of 2 H) and 2.32 (48% of 2 H, CH_2CO_2R signals of each epimer) and two singlets at 0.78 and 0.83 (total 9 H, t-Bu signals of each epimer); mass spectrum m/e (relative intensity) 252 (M^+, 30), 195 (54), 194 (63), 165 (58), 164 (70), 153 (45), 151 (48), 150 (58), 149 (74), 135 (50), 123 (58), 122 (64), 121 (66), 110 (40), 109 (70), 108 (77), 107 (74), 106 (40), 97 (44), 96 (53), 95 (61), 94 (42), 93 (44), 83 (56), 81 (44), 79 (41), 71 (43), 69 (45), 58 (74), 57 (75), 43 (100), 42 (40), and 41 (42).

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.13; H, 11.20.

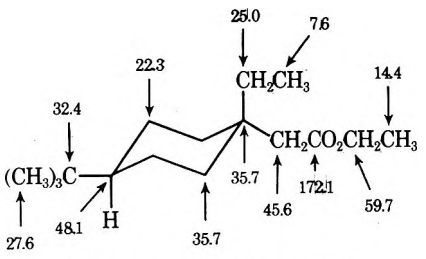
Preparation of the Esters 12 and 13a. A. *Via* Catalytic Hydrogenation. A solution of 2.52 g (10 mmol) of the unsaturated esters **10** and **11** in 60 ml of EtOH was hydrogenated over 50 mg of a 5% Pt-on-carbon catalyst at 25° and 35 psi hydrogen pressure. After a rapid uptake of *ca.* 0.01 mol of H_2, no further hydrogen uptake was observed for 24 hr. The reaction mixture was filtered and concentrated to leave 2.35 g of residual liquid containing (glpc, Apiezon L on Chromosorb P, apparatus calibrated with a known mixture) 48% of the saturated ester **13a** (retention time 18.0 min) and 52% of the ester **12** (19.8 min). A collected (glpc) sample of ester **13a** was obtained as a colorless liquid, n^{25}D 1.4580: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.07 (2 H, q, J = 7.2 Hz, ethoxyl CH_2), 2.23 (2 H, s, CH_2CO), and 0.8–2.0 (26 H, m, aliphatic CH including at t-Bu singlet at 0.87); mass spectrum m/e (relative intensity), 254 (M^+, 3), 209 (30), 195 (52), 169 (57), 167 (95), 166 (83), 111 (98), 110 (69), 109 (98), 108 (85), 97 (84), 95 (72), 89 (84), 88 (95), 81 (80), 70 (50), 69 (77), 67 (85), 61 (64), 57 (100), 55 (79), and 41 (85).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.48; H, 11.88.

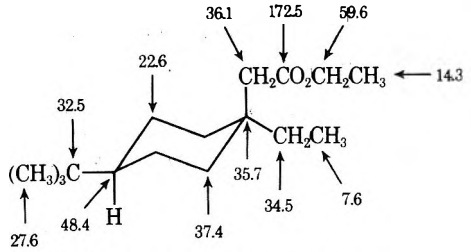
A collected (glpc) sample of ester **12** was obtained as a colorless liquid, n^{25}D 1.4598: ir (CCl_4) 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.05 (2 H, q, J = 7.2 Hz, ethoxyl CH_2), 2.05 (2 H, s, CH_2CO), and 0.7–1.9 (26 H, m, aliphatic CH including a t-Bu singlet at 0.83); mass spectrum m/e (relative intensity), 254 (M^+, 4) 225 (40), 209 (81), 196 (52), 195 (97), 169 (50), 167 (97), 166 (88), 151 (85), 137 (65), 123 (86), 111 (96), 110 (77), 109 (100), 108 (84), 97 (75), 95 (73), 89 (84), 88 (90), 83 (58), 81 (70), 79 (51), 71 (57), 70 (57), 69 (74), 67 (74), 61 (69), 58 (71), 57 (98), 56 (50), 55 (72), 43 (91), and 41 (75).

Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: 75.47; H, 11.93.

The natural-abundance ^{13}C nmr spectrum of each of the esters **12** and **13a** was measured in $CDCl_3$ solution with added TMS as an internal standard. In each case the spectrum was measured both with broad-band proton decoupling and with off-resonance decoupling. The assignments, indicated in ppm in the accompanying structures, are compatible both with the off-resonance decoupling experiments and with chemical shift values previously assigned to related compounds.[6c]



^{13}C nmr δ values for ester **12**



^{13}C nmr δ values for ester **13a**

B. From the Alkylidenecyanoacetate 14. Reaction of 25.5 g (165 mmol) of 4-*tert*-butylcyclohexanone with 17.4 g (150 mmol) of ethyl cyanoacetate in 100 ml of PhH containing 1.8 g of HOAc and 1.35 g of NH_4OAc as previously described[15] followed by crystallization from EtOH afforded 29.8 g (80%) of the crude cyanoacetate **14** as a white solid, mp 34–36°. Recrystallization from pentane at Dry Ice temperatures afforded 22.05 g of the pure cyano ester **14** as white plates, mp 42–43.5° (lit. mp 41–42°,[16] 45–46°[15]): ir (CCl_4) 2230 (conjugated C≡N), 1730 (ester C=O), and 1605 cm^{-1} (C=C); uv maximum (95% EtOH) 230 mμ (ε 27,000); nmr (CCl_4) δ 4.25 (2 H, q, J = 7.0 Hz, ethoxyl CH_2), 1.7–3.4 (9 H, m, aliphatic CH), 1.35 (3 H, t, J = 7.0 Hz, ethoxyl CH_3), and 0.88 (9 H, s, t-Bu); mass spectrum m/e (relative intensity) 249 (M^+, 5), 247 (95), 234 (65), 220 (82), 207 (60), 195 (50), 179 (78), 167 (81), 149 (83), 139 (72), 123 (79), 122 (52), 121 (50), 81 (53), 71 (58), 59 (100), 77 (60), 45 (62), 43 (86), and 41 (58).

A solution of Et_2CuLi was prepared by treating a cold (−50°) slurry of 5.50 g (28.3 mmol) of CuI in 60 ml of Et_2O, dropwise and with stirring, with 43 ml of a PhH solution containing 52.9 mmol of EtLi while the temperature of the mixture was maintained at −40 to −50°. The resulting cold (−30 to −50°), black solution was stirred for 15 min and then a solution of 3.18 g (12.7 mmol) of the cyano ester **14** in 30 ml of Et_2O was added dropwise and with stirring. The reaction mixture was stirred at −20 to −30° for 1 hr and then allowed to warm to room temperature. The reaction mixture was added to excess aqueous NH_4Cl, filtered to remove the precipitated copper, and then extracted with Et_2O. The ethereal extract was washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave 3.10 g (88%) of the crude cyano ester **15** as a viscous yellow liquid. Crystallization of a 550-mg aliquot of the crude product from pentane at Dry Ice temperature separated 350 mg (corresponding to a 56% yield) of the cyano ester **15**, mp 30.5–31.5°. Recrystallization afforded the pure cyano ester **15** as fine white needles, mp 32.5–32.7°: ir (CCl_4) 2255 (C≡N) and 1735 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.25 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.79 [1 H, s, CH(CN)CO_2R], and 0.8–2.2 [26 H, m, aliphatic CH including a triplet (J = 7 Hz) at 1.34 (ethoxyl CH_3) and a singlet at 0.89 (t-Bu)]; mass spectrum m/e (relative intensity), 264 (6), 194 (19), 148 (29), 114 (88), 57 (100), and 41 (26).

Anal. Calcd for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.46; N, 5.01. Found: C, 73.25; H, 10.61; N, 4.92.

A solution of 1.00 g (3.6 mmol) of cyano ester **15**, 3.0 g (46 mmol) of 85% KOH, and 1 ml of H_2O in 15 ml of $HOCH_2CH_2OH$ was refluxed for 65 hr and then cooled and partitioned between H_2O and Et_2O. The aqueous phase was acidified (HCl) and then extracted with Et_2O. This ethereal extract was washed with aqueous NaCl, dried, and concentrated to leave 616 mg (76%) of the acid **13b**, mp 92.6–93.9°. Sublimation (78–80° at 0.04 mm) afforded the pure acid **13b** as fine white needles, mp 94.4–94.9°: ir (CCl_4) 2600–3400 (carboxyl OH) and 1700 cm^{-1} (carboxyl C=O); nmr (CCl_4) δ 11.8 (1 H, broad, OH), 2.32 (2 H, s, CH_2CO_2R), and 0.8–2.0 [23 H, m, aliphatic CH including a singlet at 0.84 (t-Bu)]; mass spectrum m/e (relative intensity), 171 (35), 141 (30), 111 (24), 109 (46), 108 (24), 57 (100), 56 (27), and 41 (30).

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.28; H, 11.58. Found: C, 74.35; H, 11.59.

A solution of 150 mg (0.66 mmol) of the acid **13b** and 1.0 ml (8.8 mmol) of freshly distilled $BF_3 \cdot OEt_2$ in 30 ml of EtOH was refluxed for 65 hr and then cooled and partitioned between H_2O and Et_2O. The ethereal solution was washed successively with aqueous 10% NaOH and with aqueous NaCl and then dried and concentrated. The residual crude ester **13a** (85 mg) was distilled in a short-path still to separate 70 mg (42%) of the pure ester **13b** as a colorless liquid, n^{25}D 1.4580, that was identified with the previously described sample by comparison of ir, nmr, and mass spectra.

Preparation of the Acetal 18b. A solution of 20.0 g (179 mmol) of cyclohexanecarboxaldehyde (**17b**), 62.6 g (1.07 mol) of allyl alco-

hol, and 100 mg of *p*-TsOH in 1 l. of PhH was refluxed with continuous separation of H_2O for 48 hr and then cooled, washed with aqueous $NaHCO_3$, dried, and concentrated. Distillation of the residue afforded 30.39 g (81%) of the crude acetal **18b** as a colorless liquid, bp 79–84° (1 mm), $n^{25}D$ 1.4619–1.4620, that contained (ir analysis) a small amount of the unchanged aldehyde **17b**. Fractional distillation through a 30-cm Holtzmann column afforded the pure acetal **18b**, bp 83–84° (1 mm), $n^{25}D$ 1.4620: ir (CCl_4) 1640 (weak, C=C) and 925 cm^{-1} ($CH=CH_2$); uv (95% EtOH) end absorption with ϵ 725 at 210 mμ; nmr (CCl_4) δ 4.9–6.2 (6 H, m, vinyl CH), 4.17 [1 H, d, J = 6 Hz, $CH(OR)_2$], 3.8–4.1 (4 H, m, allylic CH_2), and 0.9–2.1 (11 H, m, aliphatic CH); mass spectrum *m/e* (relative intensity) 127 (55), 83 (26), 81 (71), 55 (28), and 41 (100).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.38; H, 10.57.

Formation and Rearrangement of the Enol Ether 19b. A solution of 10.0 g (47.5 mmol) of the acetal **18b** and 100 mg of TsOH in 65 ml of toluene was refluxed for 3 hr and then fractionally distilled through a 40-cm Vigreux column[9] over a period of 3 hr. After the temperature of the distillate had risen from 90° (allyl alcohol–toluene azeotrope) to 110°, the residual toluene solution remaining in the stillpot was washed successively with aqueous 5% $FeSO_4$, with aqueous $NaHCO_3$, and with aqueous NaCl and then dried. Fractional distillation separated a forerun followed by 4.25 g (59%) of the aldehyde **20b** as a colorless liquid, bp 85–90° (15 mm), $n^{25}D$ 1.4700 [lit.[17] bp 105–107° (32 mm), $n^{25}D$ 1.4701]. The product contained (glpc, silicone SE-30 on Chromosorb P) the aldehyde **20b** (retention time 4.2 min) accompanied by minor amounts of toluene (1.6 min) and the aldehyde **17b** (2.4 min). Tlc analysis (silica gel coating with 5% Et_2O in pentane as an eluent) gave the following R_f values: aldehyde **17b**, 0.40; aldehyde **20b**, 0.64; acetal **18b**, 0.64. A pure sample of the aldehyde **20b** was collected as a colorless liquid, $n^{25}D$ 1.4699 [lit.[17] bp 105–107° (32 mm), $n^{25}D$ 1.4701]: ir (CCl_4) 2800, 2700, 2680 (aldehyde CH), 1723 (C=O), 1638 (C=C), 1000, and 928 cm^{-1} ($CH=CH_2$); uv (95% EtOH) end absorption with ϵ 140 at 210 mμ; nmr (CCl_4) δ 9.50 (1 H, s, CHO), 4.8–6.2 (3 H, m, vinyl CH), 2.20 (2 H, d, J = 7.0 Hz, allylic CH_2), and 1.0–2.1 (10 H, m, aliphatic CH); mass spectrum *m/e* relative intensity) 152 (M^+, 1), 110 (28), 97 (21), 82 (20), 81 (100), 79 (20), 69 (24), 67 (67), 55 (48), 53 (20), 41 (72), and 39 (39).

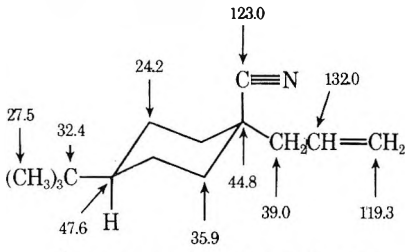
Preparation of the Aldehyde 20b from the Imine Salt 26. A mixture of 5.0 g (45 mmol) of the aldehyde **17b**, 7.0 g (90 mmol) of *t*-$BuNH_2$, 150 ml of PhH, and 10 g of anhydrous K_2CO_2 was stirred at 25° for 65 hr at which time ir analysis indicated conversion to the imine **25** was complete. The mixture was filtered and the filtrate was concentrated under reduced pressure and then distilled to separate 4.12 g (55%) of the crude imine **25** as a colorless liquid, bp 37° (0.55 mm), $n^{25}D$ 1.4511: ir (CCl_4) 1660 cm^{-1} (C=N); nmr (CCl_4) δ 7.45 (1 H, d, J = 4 Hz, CH=N), and 1.1–2.5 (20 H, m, aliphatic CH including a *t*-Bu singlet at 1.10); mass spectrum *m/e* (relative intensity) 167 (M^+, 3), 152 (30), 99 (69), 95 (18), 58 (41), 57 (100), 56 (55), and 41 (39). The imine **25** exhibited a single glpc peak (TCEP on Chromosorb P) with a retention time of 4.8 min; under the same conditions the retention time for the aldehyde **17b** was 6.0 min.

A cold (−38°) solution of (*i*-$Pr)_2NLi$, from 10.2 mmol of CH_3Li, 1.08 g (10.7 mmol) of (*i*-$Pr)_2NH$, and 35 ml of DME, was treated, dropwise and with stirring, with 1.23 g (7.40 mmol) of the imine **25**. The resulting solution of the lithium salt **26** was allowed to warm to 13° over a period of 1 hr and then 1.40 g (11.6 mmol) of freshly distilled allyl bromide was added, dropwise and with stirring. The resulting mixture, which warmed to 24° during the addition, was stirred at 25° for 17 hr during which time some LiBr separated. The mixture was partitioned between Et_2O and saturated aqueous NaCl and the organic layer was dried and concentrated. Distillation of the residual yellow liquid afforded 1.0 g (65%) of the imine **27** as a colorless liquid, bp 51–55° (0.5 mm), $n^{25}D$ 1.4601, that exhibited a single glpc peak (TCEP on Chromosorb P): ir (CCl_4) 1655 (C=N), 1635 (C=C), and 922 cm^{-1} ($CH=CH_2$); nmr (CCl_4), δ 7.40 (1 H, s, CH=N), 4.6–6.8 (3 H, m, vinyl CH), 2.1 [2 H, doublet (J = 7 Hz) with further partially resolved splitting, allylic CH_2], and 1.0–2.0 (19 H, m, aliphatic CH including a *t*-Bu singlet at 1.15); mass spectrum *m/e* (relative intensity) 207 (M^+, 9), 192 (38), 152 (64), 136 (21), 111 (20), 110 (32), 99 (42), 96 (52), 81 (35), 57 (100), 55 (27), 44 (23), and 41 (63).

Anal. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.76. Found: C, 80.99; H, 12.19; N, 6.76.

A mixture of 0.50 g (2.4 mmol) of the imine **27**, 10 ml (9.2 mmol) of aqueous 0.92 *M* HOAc, and 15 ml of hexane was stirred under N_2 at 25° for 16 hr and then partitioned between Et_2O and saturated aqueous NaCl. The organic layer was washed successively with aqeous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. Distillation of the residual liquid in a short-path still (0.15 mm and 55° bath) afforded 138 mg (38%) of the aldehyde **20b** as a colorless liquid, $n^{25}D$ 1.4701, that exhibited a single glpc peak (Apiezon L on Chromosorb P) and was identified with the previously described sample by comparison of ir, nmr, and mass spectra.

Alkylation of the Nitrile 28. Samples of the nitrile **28** were obtained either as previously described[11] or by the low-pressure hydrogenation of an MeOH solution of 4-*tert*-butyl-1-cyclohexenylnitrile[18] over a 5% Pd-on-C catalyst. To a cold (−30°) solution of (*i*-$Pr)_2N^-Li^+$, from 3.8 g (38 mmol) of (*i*-$Pr)_2NH$ and 34 mmol of MeLi in 35 ml of DME, was added a solution of 5.0 g (30 mmol) of the nitrile **28** in 10 ml of DME. The resulting mixture was stirred at 25° for 20 hr, during which time a white solid separated, and then 4.84 g (40.0 mmol) of allyl bromide was added, dropwise with stirring and external cooling to keep the reaction mixture at 25°. After the reaction mixture had been stirred at 25° for 16 hr, it was partitioned between H_2O and Et_2O. The Et_2O solution was dried, concentrated, and distilled to separate 4.63 g (75%) of a mixture of nitriles **30** and **31** as a colorless liquid, bp 88° (0.45 mm), $n^{25}D$ 1.4670. The mixture contained (glpc, TCEP on Chromosorb P, instrument calibrated with a known mixture of the two nitriles) 88% of the nitrile **30** (retention time 51.6 min) and 12% of the nitrile **31** (64.8 min) as well as a small amount of the starting nitrile **28** (33.4 min). A collected (glpc) sample of the major component, nitrile **30**, was obtained as a colorless liquid, $n^{25}D$ 1.4670: ir (CCl_4) 2220 (C≡N), 1640 (C=C), 990, and 920 cm^{-1} ($CH=CH_2$); nmr (CCl_4) δ 4.9–6.4 (3 H, m, $CH=CH_2$), and 0.9–2.4 [20 H, m, aliphatic CH including a doublet (J = 7 Hz) at 2.26 attributable to an allylic CH_2 and a *t*-Bu singlet at 0.90]; mass spectrum *m/e* (relative intensity) 190 (20), 149 (35), 148 (44), 121 (100), 120 (44), 57 (63), and 41 (56). The natural abundance ^{13}C nmr spectrum of the nitrile **30**, measured in $CDCl_3$ solution with added TMS, is summarized in the accompanying structure.



^{13}C nmr δ values for nitrile **30**

Anal. Calcd for $C_{14}H_{23}N$: C, 81.99; H, 11.29; N, 6.82. Found: C, 81.80; H, 11.31; N, 6.87.

The stereoisomeric nitrile **31** was collected (glpc) as a colorless liquid, $n^{25}D$ 1.4700: ir (CCl_4) 2225 (C≡N), 1640 (C=C), 993, and 920 cm^{-1} ($CH=CH_2$); nmr (CCl_4) δ 4.8–6.5 (3 H, m, $CH=CH_2$), 2.35 (2 H, d, J = 7 Hz, allylic CH_2), and 0.8–2.2 (18 H, m, aliphatic CH including a *t*-Bu singlet at 0.87); mass spectrum *m/e* (relative intensity) 205 (M^+, 26), 190 (34), 150 (73), 149 (25), 148 (50), 123 (20), 121 (100), 120 (40), 81 (30), 79 (30), 67 (22), 58 (31), 57 (100), 56 (60), 55 (31), 53 (20), 43 (51), 41 (94), and 39 (34).

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.85; H, 11.27; N, 6.88.

Conversion of the Nitrile 30 to the Aldehyde 20a. To a cold (9°) solution of 210 mg (1.03 mmol) of the nitrile **30** in 10 ml of PhH was added a solution of 2.51 mmol of (*i*-$Bu)_2AlH$ in 10 ml of PhH. The resulting solution was stirred at 25° for 3 hr and then cooled to 10° and treated with 10 ml of aqueous NH_4Cl. After the mixture had been stirred for 20 min, 10 ml of aqueous 1 *M* H_2SO_4 was added and the mixture was extracted with Et_2O. The organic phase was dried, concentrated, and distilled under reduced pressure in a short-path still to separate 160 mg (75%) of the aldehyde **20a** as a colorless liquid, $n^{25}D$ 1.4700, that was identified with a subsequently described sample by comparison of glpc retention times and of mass spectra, ir spectra, and proton and ^{13}C nmr spectra.

Preparation of the Aldehyde 17a. Trimethylsulfoxonium iodide (57.8 g or 260 mmol, mp 171–173°, lit.[19] mp 172–174°) was converted to the ylide by reaction with 5.70 g (260 mmol) of NaH (the oil dispersion was washed with petroleum ether, bp 30–60°) in 250 ml of DMSO.[7] Following a previously described procedure,[7] this ylide solution was treated with 28.4 g (184 mmol) of 4-*tert*-butylcyclohexanone and allowed to react for 15 min at 25° and 30

min at 55–60°. The reaction mixture was cooled and partitioned between Et_2O and H_2O. The Et_2O solution was washed with aqueous NaCl, dried, concentrated, and distilled (with extra care because of foaming) to separate 19.24 g (64%) of the epoxide **16**, bp 95–98° (10 mm), $n^{25}D$ 1.4583–1.4584 [lit.[7] bp 110° (13 mm)]: ir (CCl_4) 3040 cm^{-1} (epoxide CH) with no OH or C=O absorption in 3- or 6-μ regions; nmr (CCl_4) δ 2.45 (2 H, s, epoxide CH_2), 1.0–2.1 (9 H, m, aliphatic CH), and 0.90 (9 H, s, *t*-Bu); mass spectrum *m/e* (relative intensity) 168 (M^+, 2), 153 (27), 111 (25), 84 (71), 81 (25), 79 (27), 57 (100), 55 (18), 43 (30), and 41 (44).

Although earlier workers had reported[7] the successful BF_3-catalyzed rearrangement of the epoxide **16** to the aldehyde **17a** when the aldehyde was isolated as its 2,4-dinitrophenylhydrazone, we encountered considerable difficulty in isolating the pure aldehyde **17a** from this reaction because of the predominant formation of high molecular weight by-products when distillation of the crude aldehyde **17a** was attempted. The nmr spectrum (CCl_4) of these by-products had absorption at δ 4.5–4.6 [$CH(OR_2$] suggesting that they were mixtures of stereoisomers of the trimer **22** of aldehyde **17a**. A cold (5–10°) solution of 5.00 g (30 mmol) of the epoxide **16** in 25 ml of PhH was treated with 2.0 ml (15 mmol) of freshly distilled $BF_3 \cdot Et_2O$. After the mixture had been allowed to stand for 1 min at 10°, it was washed with aqueous $NaHCO_3$ and dried. The resulting PhH solution had nmr absorption at δ 9.32 (d, J = 4.5 Hz, CHO) corresponding to about 80% aldehyde **17a** as well as absorption at δ 4.8 corresponding to about 20% of the trimer **22**. Even concentration of this solution under reduced pressure increased the amount of trimer present in the crude product. When various fractions of this crude product were allowed to stand, the crude trimer **22** (a mixture of stereoisomers) separated as a white solid, mp 168–172°. Recrystallization from pentane at Dry Ice temperatures separated one diastereoisomer of the trimer **22** as white plates, mp 210–212°: ir (CCl_4) no absorption in the 3- or 6-μ regions attributable to OH or C=O groups; nmr (CCl_4) δ 4.45 [3 H, broad, $CH(OR)_2$] and 0.7–2.0 (*ca.* 57 H, m, aliphatic CH including a *t*-Bu singlet at 0.78).

Anal. Calcd for $C_{33}H_{60}O_3$: C, 78.51; H, 11.98. Found: C, 78.40; H, 11.97.

A PhH solution of the aldehyde **17a**, formed from the epoxide **16**, exhibited two major glpc peaks (TCEP on Chromosorb P) corresponding to the axial isomer **24** (retention time 24.8 min, *ca.* 23% of the mixture) and the equatorial isomer **23** (30.0 min, *ca.* 77% of the mixture) as well as several minor more rapidly eluted components. A collected (glpc) sample of the mixture of aldehyde epimers **23** (*ca.* 83%) and **24** (*ca.* 17%) was obtained as a colorless liquid, $n^{25}D$ 1.4611 (lit.,[8] aldehyde **24**, $n^{25}D$ 1.4635; aldehyde **23**, $n^{25}D$ 1.4630): ir (CCl_4) 2870, 2805, 2715 (aldehyde CH), and 1724 cm^{-1} (C=O); nmr (CCl_4) δ 9.71 (*ca.* 0.2 H, s, CHO), 9.60 (*ca.* 0.8 H, s, CHO), and 0.8–2.4 [19 H, m, aliphatic CH including *t*-Bu singlets at 0.88 (major) and 0.85 (minor)]; mass spectrum *m/e* (relative intensity), 168 (M^+, 1), 111 (11), 94 (15), 83 (13), 57 (100), 56 (26), and 41 (27). The ^{13}C nmr spectrum ($CDCl_3$) of this mixture of epimers exhibits two low-field peaks at δ 205.6 (*ca.* 25%, axial CHO) and 204.6 (*ca.* 75%, equatorial CHO).

Preparation of the Aldehydes 20a and 21 by a Claisen Rearrangement. Following the previously described procedure, 1.60 g (9.35 mmol) of the epoxide **16** in 35 ml of cold (7°) PhH was rearranged by reaction with 1.27 g (9.0 mmol) of $BF_3 \cdot Et_2O$ for 2 min, and the resulting mixture was washed successively with aqueous NaHCO and aqueous NaCl and then dried. The resulting PhH solution of the crude aldehyde **17a** (*ca.* 9 mmol) was treated with 0.90 g (15 mmol) of allyl alcohol, 100 mg (0.55 mmol) of *p*-TsOH, and 50 ml of PhH and then refluxed for 24 hr with continuous separation of H_2O. The PhH was distilled from the mixture at atmospheric pressure and the residual liquid was heated to 200° until all the allyl alcohol had distilled from the mixture. Distillation of the resulting liquid in a short-path still separated 0.605 g (31%) of a mixture of aldehyde **20a** (77%) and aldehyde **21** (23%). From a comparable reaction using 5.0 g (30 mmol) of the epoxide **16**, 2.5 g (18 mmol) of $BF_3 \cdot Et_2O$, 1.8 g (31 mmol) of allyl alcohol, and 200 mg (1.1 mmol) of *p*-TsOH, the yield of aldehydes was 1.30 g (21%) of a colorless liquid, bp 118–123° (3.5 mm), containing 75% of aldehyde **20a** and 25% of aldehyde **21**. The compositions of the mixtures were determined on glpc equipment (TCEP on Chromosorb P) that have been calibrated with known mixtures prepared from the axial aldehyde **20a** (retention time 43.6 min), the equatorial aldehyde **21** (50.4 min), and an internal standard, 2-methylnaphthalene (61.2 min).

In another experiment the PhH solution of the crude aldehyde **17a** (*ca.* 18 mmol), from 3.0 g (18 mmol) of the epoxide **16** and 1.3 g (9.0 mmol) of $BF_3 \cdot Et_2O$ in 150 ml of PhH, was mixed with 250 ml of PhH, 5.0 g (86 mmol) of allyl alcohol, 100 mg (0.5 mmol) of *p*-TsOH, and 5 mg of 2,5-di-*tert*-butylhydroquinone (a free-radical inhibitor). The resulting solution was refluxed with continuous removal of H_2O for 63 hr and then cooled, washed with aqueous $NaHCO_3$, dried, and concentrated under reduced pressure to leave 3.8 g of pale yellow liquid. Distillation of a 2.0-g portion of this liquid separated 692 mg of fractions of colorless liquid, bp 65–95° (0.55 mm), that contained (glpc, TCEP Chromosorb P) the starting aldehyde **17a** (retention times 13.0 min for axial isomer **24** and 15.8 min for equatorial isomer **23**) and the product aldehydes **20a** (25.3 min, 79% of the product) and **21** (29.4 min, 21% of the product).

A collected (glpc) sample of the more rapidly eluted axial aldehyde **20a** was obtained as a colorless liquid, $n^{25}D$ 1.4700: ir (CCl_4) 2680, 2710, 2810 (aldehyde CH), 1723 (C=O), 1640 (C=C), 1000, and 930 cm^{-1} ($CH=CH_2$); mass spectrum *m/e* (relative intensity), 208 (M^+, 2), 166 (40), 151 (37), 137 (23), 133 (25), 111 (22), 110 (38), 109 (54), 97 (50), 95 (38), 93 (34), 91 (28), 83 (27), 81 (73), 79 (38), 69 (47), 67 (62), 57 (100), 55 (45), 53 (24), 43 (32), 41 (62), and 39 (26); nmr (CCl_4) δ 9.42 (1 H, s, CHO), 4.7–6.0 (3 H, m, vinyl CH), 2.08 (2 H, d, J = 7 Hz, allylic CH_2), 0.82 (9 H, s, *t*-Bu), and 0.7–2.4 (9 H, m, aliphatic CH).

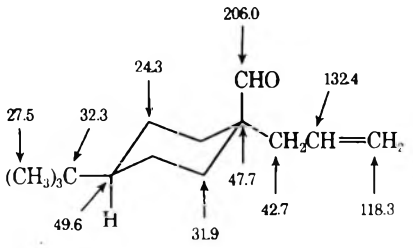
Our efforts to obtain a satisfactory elemental analysis for the aldehyde **20a** were thwarted by the rapidity with which this product reacted with oxygen from the air to form the corresponding acid as a contaminant (ir and mass spectral analyses). Consequently, 12.5 g (0.060 mmol) of the collected (glpc) aldehyde **20a** was added to 1.5 ml of a solution prepared from 218 mg (1.1 mmol) of 2,4-dinitrophenylhydrazine, 0.5 ml of concentrated HCl, and 25 ml of EtOH.[20] The resulting solution was refluxed for 20 min and then cooled to precipitate 15.6 mg (67%) of the crude 2,4-dinitrophenylhydrazone. Recrystallization from EtOH afforded 12.3 mg (53%) of the pure 2,4-dinitrophenylhydrazone of aldehyde **20a** as orange plates, mp 171.5–172.5°: ir (CCl_4) 3288 (NH), 1617 (C=N), 1510, and 1333 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 11.22 (1 H, broad, NH), 7.1–9.3 (4 H, m, aryl CHand CH=N), 4.8–5.8 (3 H, m, vinyl CH), 0.9–2.4 (11 H, m, aliphatic CH), and 0.83 (9 H, s, *t*-Bu).

Anal. Calcd for $C_{20}H_{28}N_4O_4$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.61; H, 7.31; N, 14.36.

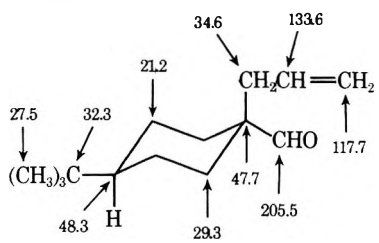
A collected (glpc) sample of the equatorial aldehyde **21** was obtained as a colorless liquid, $n^{25}D$ 1.4740: ir (CCl_4) 2680, 2710, 2820 (aldehyde CH), 1720 (C=O), 1638 (C=C), 1000, and 926 cm^{-1} ($CH=CH_2$); mass spectrum *m/e* (relative intensity), 208 (M^+, 3), 166 (36), 151 (49), 137 (30), 133 (34), 123 (58), 110 (35), 109 (62), 97 (43), 95 (46), 91 (29), 83 (32), 79 (37), 69 (51), 67 (64), 57 (100), 55 (47), 53 (26), 43 (36), 41 (62), and 39 (26); nmr (CCl_4) δ 9.36 (1 H, s, CHO), 4.7–6.0 (3 H, m, vinyl CH), 2.36 (2 H, d, J = 7 Hz, allylic CH_2), 0.88 (9 H, s, *t*-Bu), and 0.8–2.0 (9 H, m, aliphatic CH).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.83; H, 11.83.

The natural-abundance ^{13}C nmr spectra of the isomeric aldehydes **20a** and **21**, measured in $CDCl_3$ solution with added TMS, are summarized in the structures as shown.



^{13}C nmr δ values for aldehyde **20a**



^{13}C nmr δ values for aldehyde **21**

Registry No.—**6**, 13733-50-1; **7**, 41498-18-4; **8**, 78-39-7; **9**, 53260-29-0; **10**, 53188-54-8; **11**, 53188-55-9; **12**, 53188-56-0; **13a**,

53188-57-1; **13b**, 53188-58-2; **14**, 22700-58-9; **15**, 53188-59-3; **16**, 2815-45-4; **17b**, 2043-61-0; **18b**, 53188-60-6; **19b**, 53188-61-7; **20a**, 53188-62-8; **20a** 2,4-DNP, 53188-63-9; **20b**, 29517-58-6; **21**, 53188-64-0; **22**, 53188-65-1; **23**, 15763-62-9; **24**, 15763-61-8; **25**, 53188-66-2; **26**, 53188-67-3; **27**, 53188-68-4; **28**, 31865-37-9; **30**, 53188-69-5; **31**, 53188-70-8; 4-*tert*-butylcyclohexanone, 98-53-3; ethyl cyanoacetate, 105-56-6; allyl alcohol, 107-18-6; 4-*tert*-butyl-1-cyclohexenylnitrile, 7370-14-1.

References and Notes

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Electron Impact Induced Fragmentation of Macrocyclic Polyethers (Crown Ethers)[1]

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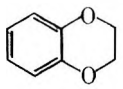
The mass spectra of catechol ethylene diether (1) and a series of macrocyclic polyethers (crown ethers) of the general class benzo-3*n*-crown-*n* (n = 3, 4, 5, 6) were correlated. The molecular ion (M) of benzo-18-crown-6 (5) loses C_2H_4O to give a peak at *m/e* 268. Other important peaks were found at *m/e* 224, 180, and 136, which formally correspond to the loss of two, three, and four C_2H_4O units, respectively, from M. Mass spectra of **2, 3,** and **4** also displayed a series of peaks corresponding to the formal loss of C_2H_4O units from M; a peak at *m/e* 136 was the terminus in this series for each crown ether. Mass spectra of open-chain analogs **6** and **7** were compared with those of **3** and **4**, respectively. Mass spectra of deuterated analogs **4a** and **4b** allowed formulation of plausible fragmentation pathways for **4**.

Macrocyclic polyethers (crown ethers)[2] have unique chemical properties associated with their ability to form complexes with cations[2,3] and with other species.[4] Crown ethers have been employed in mechanistic,[5] physical,[6] and synthetic[7] studies and in chromatographic processes.[8] The chemical importance of crown ethers warranted study of their electron impact induced fragmentation pathways for qualitative identification purposes. Also, it was hoped that the novel chemical properties of crown ethers might be paralleled by unusual mass spectral fragmentation characteristics.

Aliphatic, aryl alkyl, and aromatic ethers have been subjects of numerous mass spectrometry investigations.[9] Several studies have included cyclic ethers,[10] notably catechol polymethylene diether derivatives[10a] and methylene dioxybenzenes.[10c,d] In the present investigation mass spectra of a homologous series of crown ethers were correlated and compared with those of open-chain analogs.

The mass spectra of catechol ethylene diether (1),[11,12] benzo-9-crown-3 (2),[2a,13] benzo-12-crown-4 (3),[2a] and benzo-18-crown-6 (5)[2a] are compiled in Table I, and that of benzo-15-crown-5 (4)[2a] is given in Figure 1. The mass spectrum of 5 displayed a base peak at *m/e* 136 and other important peaks at *m/e* 268, 224, 180, 121, 110, 109, 108, 80, and 52. The elemental compositions of most of the important fragment ions for 5 were determined by high-resolution mass spectrometry and are listed in Table II. The results indicate that the molecular ion (M) of 5 loses C_2H_4O to give the mass 268 ion and that ions of *m/e* 224, 180, and 136 formally correspond, respectively, to the loss of two, three, and four C_2H_4O units from M. The mass spectra of



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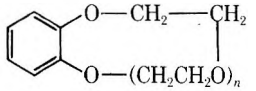


2, $n = 1$
3, $n = 2$
4, $n = 3$
5, $n = 4$

Table I
Mass Spectra of Compounds 1, 2, 3, and 5[a]

Ion m/e	Relative Abundance			
	1	2	3	5
41		6	7	7
43	2	17	20	21
44		2	3	3
45		16	38	37
50	37	11	4	1
51	33	18	8	1
52	100	48	27	7
53	9	8	5	1
63	12	21	7	2
64	6	18	10	3
65	5	17	11	6
71		1	6	9
73	1	1	7	9
77	6	11	8	3
79	4	6	4	2
80	83	100	71	28
81	11	18	12	4
91		6	8	2
92		6	4	2
108	12	31	23	16
109	5	6	7	5
110	3	18	11	7
121	11	92	75	35
135	1	5	5	3
136	48[b]	94	100	100
149			1	1
154			1	1
180		80[b]	2	6
224			54[b]	3
268				3
312				18[b]

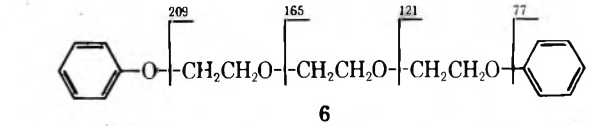
[a] Peaks with relative abundance ≥5 in the spectrum of at least one compound are included for *m/e* 41–140, and all peaks with *m/e* >140 are listed. Peaks due solely to isotope contributions in the spectra of all compounds are not listed, however. [b] Molecular ion.

Table II
Elemental Compositions of Fragment Ions in the Mass Spectrum of 5

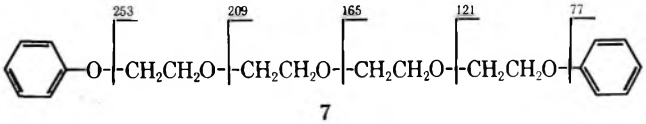
Mass	Composition	Mass	Composition
268	$C_{14}H_{22}O_5$	110	$C_6H_6O_2$
224	$C_{12}H_{18}O_4$	109	$C_6H_5O_2$
180	$C_{10}H_{14}O_3$	108	$C_6H_4O_2$
136	$C_8H_{10}O_2$	80	C_5H_4O
121	$C_7H_5O_2$		

2, 3, and **4** also displayed series of peaks corresponding to the formal loss of C_2H_4O units from M to yield a peak at *m/e* 136 as the terminus in the sequence in each case. This sequence of peaks starting with M and ending with *m/e* 136 with members separated by 44 mass units is unusual and diagnostic for benzo-3*n*-crown-*n* ethers.

Open-chain analogs of **3** and **4** are represented by 1,8-diphenoxy-3,6-dioxaoctane (**6**) and 1,11-diphenoxy-3,6,9-trioxaundecane (**7**), respectively, and their mass spectra are compiled in Table III (Experimental Section). Peaks were not observed at M − 44 (*m/e* 258) and M − 88 (*m/e* 214) with **6** nor at M − 44 (*m/e* 302), M − 88 (*m/e* 258), and M − 132 (*m/e* 214) with **7** as they were with **3** and **4**, respectively. However, starting with the peak at *m/e* 253 in the spectrum of **7**, a series was observed at *m/e* 209, 165, 121, and 77, which corresponds to the loss of one, two, three, and four C_2H_4O units, respectively. Likewise, starting with *m/e* 209 in the spectrum of **6**, an analogous series was observed at *m/e* 165, 121, and 77. Possible fragmentations leading to the above series with **6** and **7** are indicated.



6



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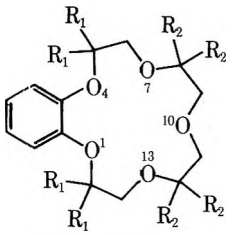
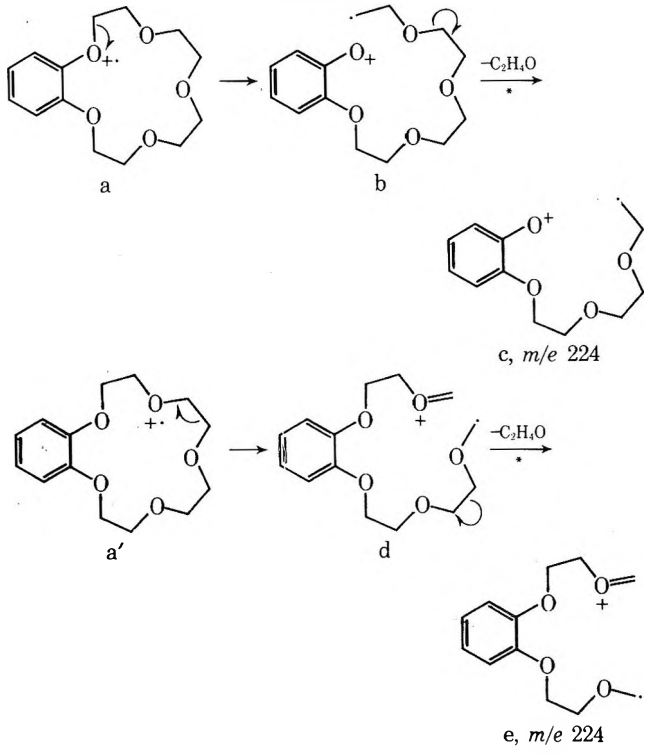
The mass spectra of deuterated crown ethers **4a** and **4b** are given in Figures 2 and 3, respectively. With the use of these spectra and high-resolution data of Table II[14] it is possible to formulate plausible fragmentation pathways for **4**. The formal loss of C_2H_4O units from M of **4** to give peaks at *m/e* 224, 180, and 136 can occur by several routes.



4, $R_1 = R_2 = H$
4a, $R_1 = D$; $R_2 = H$
4b, $R_1 = H$; $R_2 = D$

The mass spectrum of **4a** displayed peaks at *m/e* 226 and 228 and that of **4b** a peak at *m/e* 228. These results indicate that with **4**, C-8 and C-12 are not involved in the process M − C_2H_4O to give a peak at *m/e* 224 and C-5, C-9, C-11, and C-15 are. A metastable transition was observed for this process, and a combination of the two mechanisms outlined in Scheme I is consistent with the deuterium la-

Scheme I



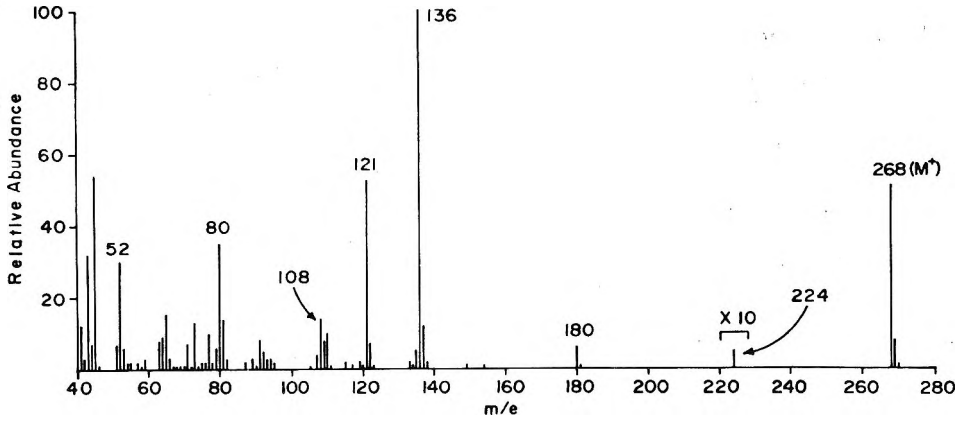


Figure 1. Mass spectrum of **4**.

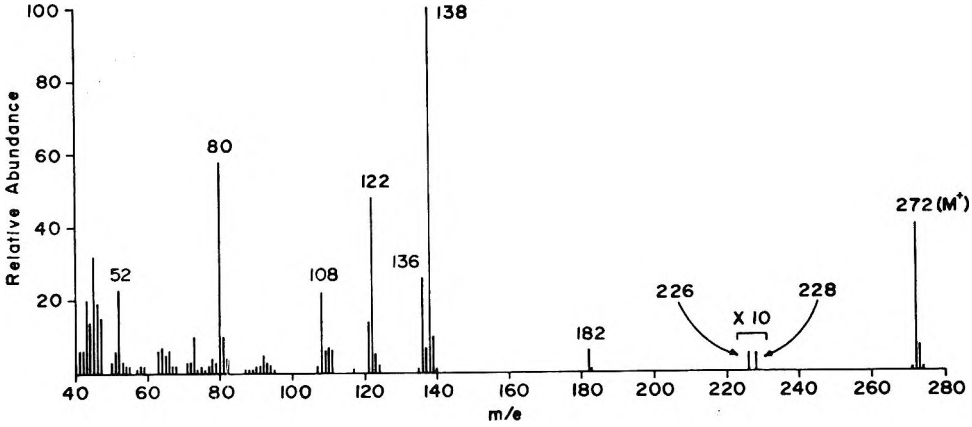


Figure 2. Mass spectrum of **4a**.

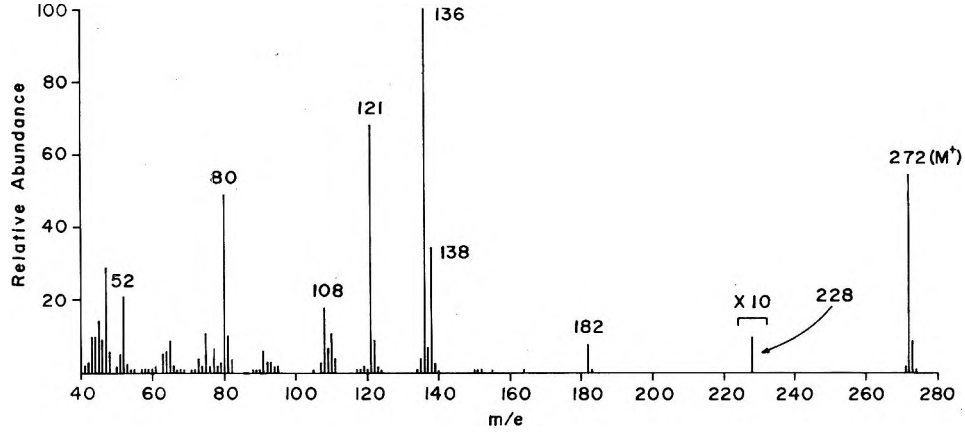


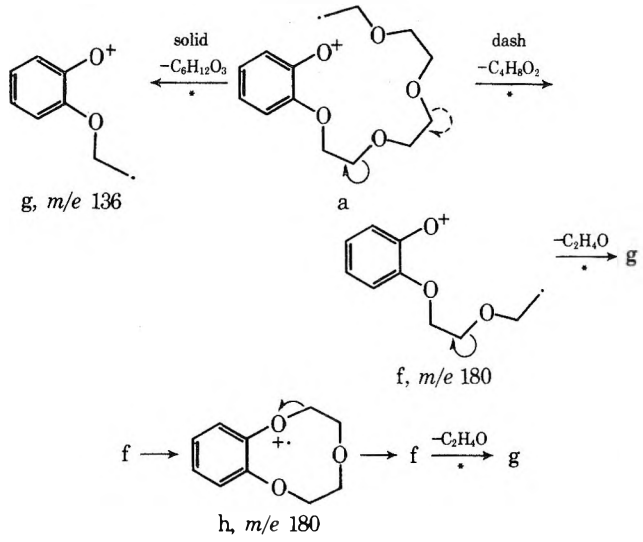
Figure 3. Mass spectrum of **4b**.

beling results.[15] The pathway to ion c involves initial cleavage of the bond between O-4(1) and C-5(15) in a[16] and that to ion e involves initial α cleavage of the bond between C-8(12) and C-9(11) in a'.

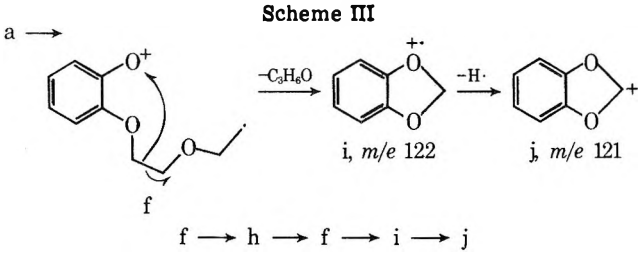
A metastable transition was observed for the process M $-$ $C_4H_8O_2$ to give the *m/e* 180 peak with **4**. In the spectra of **4a** and **4b** a peak was observed at *m/e* 182. Additionally, with 4 metastable transitions were observed for the processes *m/e* 268 and *m/e* 180 $\rightarrow$ *m/e* 136. In the spectra of both **4a** and **4b** peaks were displayed at *m/e* 136 and 138. Mechanisms for generation of mass 136 and 180 ions are given in Scheme II. Formation of the mass 180 ion f can be rationalized in a straightforward manner as indicated. The pathway for formation of the mass 136 ion is more complicated since spectra of both **4a** and **4b** contained peaks at *m/e* 136 and 138. Therefore, ion a and ion f formed *directly* from a cannot be the only precursors of the mass 136 ion since **4a** would yield *only* an ion of *m/e* 138 and **4b** *only* an ion of *m/e* 136. It is proposed that ion f closes to give h, the molecular ion of **2**. Then h opens to regenerate ion f and subsequently g. However, this pathway through h cannot be the *sole* route to the mass 136 ion because the *m/e* 136 and 138 peaks in spectra of **4a** and **4b** would be expected to be approximately equal in intensity, which they clearly are not. In the spectrum of **4a** the ratio of intensity of the *m/e* 138 peak to that of the *m/e* 136 peak was 1:0.26 whereas in the spectrum of **4b** the ratio was 0.34:1. A combination of the above three pathways to g is consistent with the deuterium labeling results. It is proposed that all or a portion of ion f produced directly from a closes to give h and subsequently g; any remainder can lead *directly* to g.

The peaks at *m/e* 121, 110, 109, 108, 80, and 52 in the spectrum of **4** are also characteristic of benzo-3*n*-crown-*n* ethers. In the spectrum of **4a** peaks were observed at *m/e* 121 and 122 and in that of **4b** a peak was observed at *m/e* 121. Pathways for formation of the mass 121 ion are given

Scheme II



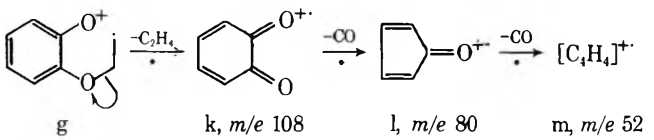
Scheme III



in Scheme III. Although neither a discrete peak at *m/e* 122 nor a metastable peak at *m/e* 120.0 for the process *m/e* 122 → 121 was observed, ion i is a reasonable intermediate in the formation of ion j.[17] Formation of j *directly* from a through f and i cannot be the *only* route because the spectrum of **4a** displayed peaks at *m/e* 121 *and* 122. However, a combination of this route and the second of Scheme III which involves closure of f to h and regeneration of f is consistent with the deuterium labeling results. Such a combination is also compatible with the blend of mechanistic pathways proposed for formation of the mass 136 ion in Scheme II.

Metastable transitions were observed for the *m/e* 136 → 108, *m/e* 108 → 80, and *m/e* 80 → 52 processes in the spectrum of **4**. In Scheme IV plausible mechanistic pathways

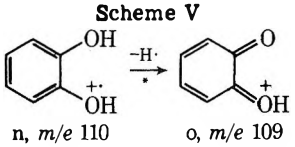
Scheme IV



are given for the formation of ions of mass 108, 80, and 52. It is certainly possible that ion g closes to form the molecular ion of **1** before ethylene is lost to give k. Ions k, l, and m were also implicated in the mass spectral fragmentation of *o*-phenylene sulfite.[18]

A metastable transition was observed for the *m/e* 110 → 109 process in the spectrum of **4**. In Scheme V plausible

Scheme V



structures are given for the mass 110 and 109 ions. In the spectra of both **4a** and **4b** a peak was observed at *m/e* 111 which is not found in that of **4**. The mechanistic pathway(s) leading to ion n cannot be formulated with certainty although in at least one precursor hydrogen transfer from what was initially C-5(15) or C-8(12) must take place. Ions i, j, k, l, m, n, and o were also indicated as fragment ions in the electron impact induced fragmentation of a series of homologous catechol polymethylene diethers.[10a] Ring opening and subsequent closure to yield i and j were proposed.

In formation of all of the preceding ions no deuterium scrambling was detected either between methylene positions or between aromatic and methylene positions. The mechanistic pathways given are in part supported by metastable data. Other routes consistent with the deuterium labeling data for which metastable transitions were not observed certainly could be operative also. In the mass spectra of **1–3** and **5** many metastable transitions were detected identical with those of **4**, and all important metastable transitions for **1–5** are given in the Experimental Section. It can be reasonably assumed that electron impact induced fragmentation pathways for **1–3** and **5** are analogous and in some cases identical with those of **4**.

Experimental Section

General. Low-resolution mass spectra were recorded with a Varian MAT CH-5 spectrometer. The ionizing voltage was 70 eV, the filament current, 300 μA, and the ion-source temperature, 150°. Compound **1** was introduced by heated inlet with inlet temperature 200°, and all other compounds by direct insertion with probe temperature 12–85°. High-resolution mass spectra were recorded with a Du Pont 21-110B spectrometer and processed with a Grant microdensitometer. The pmr spectra were obtained with a Varian HA-100 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Three columns were employed for analyses and preparative separations by vpc: column A, 5 ft × 0.25 in. stainless steel column packed with 3% SE-30 on 100–120 mesh Varaport 30; column B, 5 ft × 0.25 in. stainless steel column packed with 1% OV-101 on 100–120 mesh Chromosorb G; column C, 6 ft × 0.25 in. aluminum column packed with 1% SE-30 on 60–80 mesh AW-DMCS Chromosorb W. All melting and boiling points are uncorrected. Microanalyses were performed by Huffman Laboratories, Wheat Ridge, Colo.

Catechol Ethylene Diether, 2,3-Benzo-1,4-dioxacyclohexa-2-ene (1). Compound **1**, bp 94–95° (12 mm), lit.[11] 125° (25 mm), was prepared as previously described,[11] and preparative vpc (column A, 100°) yielded a sample for mass spectrometry.

2,3-Benzo-1,4,7-trioxacyclonona-2-ene, Benzo-9-crown-3 (2). Crown ether **2**, mp 66–67° (hexane), lit.[2a] 67–69°, was prepared as previously described,[2a] and preparative vpc (column A, 125°) yielded a sample for mass spectrometry.

2,3-Benzo-1,4,7,10-tetraoxacyclododeca-2-ene, Benzo-12-crown-4 (3). Crown ether **3**, mp 46–46.5°, lit.[2a] 44–45.5°, was prepared as previously described[2a] and employed for mass spectrometry. By vpc (column B, 240°) **3** was homogeneous.

2,3-Benzo-1,4,7,10,13-pentaoxacyclopentadeca-2-ene, Benzo-15-crown-5 (4). Crown ether **4**, mp 79.5–80° (hexane), lit.[2a] 79–79.5°, was prepared as previously described[2a] and employed for mass spectrometry. By vpc (column B, 240°) **4** was homogeneous.

2,3-Benzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2-ene, Benzo-18-crown-6 (5). Crown ether **5**, mp 43.5–44° (hexane), lit.[2a] 43–44°, was prepared as previously described[2a] and employed for mass spectrometry. By vpc (column B, 240°) **5** was homogeneous.

2,3-Benzo-1,4,7,10,13-pentaoxacyclopentadeca-2-ene-*5,5,15,15-d*$_4$ (4a). To a stirred slurry of 0.60 g (25 mmol) of NaH in 100 ml of dimethoxyethane under nitrogen was added 2.66 g (25.0 mmol) of diethylene glycol followed by 4.18 g (25.0 mmol) of ethyl bromoacetate after gas evolution ceased. The mixture was refluxed for 4 hr, 0.60 g of NaH and then 4.18 g of ethyl bromoacetate were added, and reflux was continued for 12 hr. The mixture was filtered and concentrated by rotary evaporation, and the residue was fractionally distilled to yield 1.5 g (21%) of diethyl 3,6,9-trioxaundecanedicarboxylate, bp 126–128° (0.05 mm). The pmr spectrum of the diester displayed a triplet at δ 1.22 (J = 7 Hz, 6 H, CH_3); a singlet at δ 3.63 (8 H, CH_2CH_2); and a singlet at δ 4.05 (OCH_2CO_2)

overlapping with a quartet at δ 4.13 (J = 7 Hz, CH_2OCO, 8 H total). For elemental analysis a sample was purified by preparative vpc (col C, 175°).

Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.97. Found: C, 51.85; H, 8.08.

Reduction of 2.50 g (9.00 mmol) of the above diester with 0.53 g (13 mmol) of $LiAlD_4$ (99% D) in ether gave 1.30 g (73%) of 3,6,9-trioxaundecane-1,11-diol-*1,1,11,11-d*$_4$ which was converted (62%) to 3,6,9-trioxaundecane-1,11-diol-*1,1,11,11-d*$_4$ di-*p*-toluenesulfonate using the procedure[19] for perprotio material.

Under nitrogen with stirring, a mixture of 148 mg (3.70 mmol) of NaOH, 193 mg (1.75 mmol) of catechol, and 0.77 g (1.5 mmol) of the above di-*p*-toluenesulfonate in 0.18 ml of water and 2.8 ml of 1-butanol was refluxed for 26 hr. After addition of 0.04 ml of concentrated hydrochloric acid, the reaction mixture was filtered and rotary evaporated. The residue was extracted with hexane to yield 300 mg of crude **4a** as an oil which was purified by column chromatography on silica gel packed in hexane. Elution with 75% ether–hexane yielded **4a** which was recrystallized from hexane to give **4a**, mp 79–80°, lit.[2a] for **4**, 79–79.5°. The pmr spectrum of **4a** displayed a singlet at δ 3.68 (8 H, CH_2CH_2); a singlet at δ 3.82 (4 H, CD_2CH_2); and a singlet at δ 6.81 (4 H, aromatic). The pmr spectrum of **4** was identical except that the singlet at δ 3.82 was replaced by an A_2B_2 pattern with multiplets at δ 3.78–3.93 (4 H) and δ 4.01–4.18 (4 H).

2,3-Benzo-1,4,7,10,13-pentaoxacyclopentadeca-2-ene-*8,8,12,12-d*$_4$ (4b). Esterification of 2,2′-oxydiacetic acid (MCB) in absolute methanol with concentrated sulfuric acid as catalyst yielded (58%) dimethyl 2,2′-oxydiacetate, mp 36–38°, lit.[20] 36°.

Reduction of 9.00 g (55.6 mmol) of dimethyl 2,2′-oxydiacetate with 2.5 g (60 mmol) of $LiAlD_4$ (99% D) in ether gave 2.94 g (48%) of 3-oxapentane-1,5-diol-*1,1,5,5-d*$_4$. The pmr spectrum of this material displayed a singlet at δ 3.49 (4 H) and a broad peak at δ 4.25 (2.5 H) whereas that of perprotio material displayed an A_2B_2 pattern centered at δ 3.58 (8 H) and a sharp singlet at δ 4.60 (2 H).

The crude 3-oxapentane-1,5-diol-*1,1,5,5-d*$_4$ was converted (71%) to bis-2-chloroethyl-*2,2-d*$_2$ ether with the general procedure of Perry and Hibbert.[21] The pmr spectrum of this material displayed a singlet at δ 3.69 whereas that of perprotio material displayed an A_2B_2 pattern centered at δ 3.61.

The bis-2-chloroethyl-*2,2-d*$_2$ ether was converted (~74%) to 3,6,9-trioxaundecane-1,11-diol-*4,4,8,8-d*$_4$ using a modified procedure of Perry and Hibbert.[21] In dry glassware under nitrogen 1.06 g (46.2 mmol) of clean Na was dissolved in 18.0 ml (0.32 mol) of ethylene glycol. To the stirred solution at 75° was added dropwise during 10 min 2.76 g (19.4 mmol) of bis-2-chloroethyl-*2,2-d*$_2$ ether. The mixture was then stirred at 75° for 23 hr, diluted with absolute ethanol and ether, and filtered to remove precipitated NaCl. The filtrate was concentrated by rotary evaporation, and the residue, pH 10, was neutralized to pH 7 with 10% hydrochloric acid. From the resulting mixture water and excess ethylene glycol were removed by fractional distillation to leave a residue containing NaCl. This material was diluted with absolute ethanol, filtered, and concentrated by rotary evaporation to leave 2.77 g of crude 3,6,9-trioxaundecane-1,11-diol-*4,4,8,8-d*$_4$ containing a small amount of NaCl.

Without further purification 1.5 g (7.6 mmol) of the above diol was converted[20] to 2.8 g (73%) of 3,6,9-trioxaundecane-1,11-diol-*4,4,8,8-d*$_4$ di-*p*-toluenesulfonate. With the procedure for **4a**, 2.80 g (5.54 mmol) of di-*p*-toluenesulfonate yielded 0.45 g (30%) of crystalline **4b** which was recrystallized three times from hexane to give **4b**, mp 78.5–79.5°, lit.[2a] for **4**, 79–79.5°. The pmr spectrum of **4b** displayed a singlet at δ 3.67 (4 H, CD_2CH_2); an A_2B_2 (CH_2CH_2) pattern with multiplets at δ 3.78–3.90 (4 H) and δ 3.99–4.15 (4 H); and a singlet at δ 6.80 (4 H, aromatic).

1,8-Diphenoxy-3,6-dioxaoctane (6). A solution of 8.00 g (0.200 mol) of NaOH, 18.8 g (0.200 mol) of phenol, and 9.35 g (0.050 mol) of 1,8-dichloro-3,6-dioxaoctane (Baker) in 40 ml of 50% aqueous ethanol was refluxed for 16 hr. The solution was filtered, and an ether solution of the filtrate was washed twice with 5% aqueous NaOH, twice with water, and once with saturated aqueous NaCl, and dried ($MgSO_4$). Rotary evaporation of ether left 9.72 g (64%) of crystalline material which was recrystallized twice from aqueous ethanol to give **6**, mp 43.5–45°. The pmr spectrum of **6** displayed a singlet at δ 3.64 (4 H, $CH_2OCH_2CH_2OCH_2$); an A_2B_2 pattern with multiplets at δ 3.68–3.84 and 3.94–4.12 (8 H total, C_6H_5O-CH_2CH_2O); a multiplet at δ 6.73–6.98 (6 H, ortho and para); and a multiplet at δ 7.07–7.30 (4 H, meta). For mass spectrometry and elemental analysis samples were purified by preparative vpc (column C, 200°).

Table III
Mass Spectra of Open Chain Analogs 6 and 7[a]

Ion	Relative Abundance		Ion	Relative Abundance	
m/e	6	7	*m/e*	6	7
41	8	12	103	8	9
43	22	25	105	6	5
44	11	11	106	6	1
45	31	58	107	6	9
47	13		118	5	
49	6		119	6	8
50	37	8	120	19	42
51	53	20	121	61	73
52	22	3	127	1	
54		5	128	1	
55	9		133	2	8
59	5	7	135	2	3
62	5	2	136	1	1
63	15	5	137	1	1
65	37	40	138	2	3
66	22	24	147	2	3
71	2	6	149	1	2
73	10	17	151	1	2
74	5	2	159		2
76	5	2	164	3	5
77	100	100	165	4	11
78	53	10	166	1	2
79	10	8	182	8	2
87	1	7	208	2	1
89	5	8	209	6	1
91	33	31	253		2
92	7	3	302	10[b]	
93	48	59	346		8[b]
94	30	36			

[a] Peaks with relative abundance ≥5 in the spectrum of either ether are included for *m/e* 41–121, and all peaks with *m/e* >121 are listed. Peaks due solely to isotope contributions in the spectra of both ethers are not listed, however. [b] Molecular ion.

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.26; H, 7.40.

1,11-Diphenoxy-3,6,9-trioxaundecane (7). With the procedure for **6**, 1,11-dichloro-3,6,9-trioxaundecane[2a] was converted (39%) to **7**, isolated as an oil. The pmr spectrum of **7** displayed a singlet at δ 3.58 (8 H, $CH_2O(CH_2CH_2O)_2CH_2$); an A_2B_2 pattern with multiplets at δ 3.66–3.86 and 3.94–4.12 (8 H total, C_6H_5O-CH_2CH_2O); a multiplet at δ 6.75–6.96 (6 H, ortho and para); and a multiplet at δ 7.08–7.32 (4 H, meta). For mass spectrometry and elemental analysis samples were purified by preparative vpc (column C, 250°).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.16; H, 7.58.

Important Metastable Transitions in the Mass Spectra of 1–5. For **1**, **2**, **3**, and **4** a metastable transition was observed for the process *m/e* 80 → 52. For all compounds metastables were observed for *m/e* 110 → 109, *m/e* 108 → 80, and *m/e* 136 → 108. For **2**, **3**, **4**, and **5** a metastable was observed for *m/e* 180 → 136. For **3** metastables were observed for *m/e* 224 → 136 and 180; for **4** metastables for *m/e* 268 → 180 and 224; and for **5** a metastable for *m/e* 312 → 268.

Acknowledgments. We wish to thank Mr. R. J. Mendoza for recording the low-resolution mass spectra and Dr. J. H. Weber, Laramie Petroleum Research Center, U. S. Bureau of Mines, for the high-resolution mass spectrum.

Registry No.—**1**, 493-09-4; **2**, 17454-39-6; **3**, 14174-08-4; **4**, 14098-44-3; **4a**, 53129-26-3; **4b**, 53129-27-4; **5**, 14098-24-9; **6**, 53129-28-5; **7**, 20768-77-8; diethylene glycol, 111-46-6; ethyl bromoacetate, 105-36-2; diethyl 3,6,9-trioxaundecanedicarboxylate, 53129-29-6; 3,6,9-trioxaundecane-1,11-diol-*1,1,11,11-d*$_4$, 53129-30-9; 3,6,9-trioxaundecane-1,11-diol-*1,1,11,11-d*$_4$ di-*p*-toluenesulfonate, 53129-31-0; 2,2′-oxydiacetic acid, 110-99-6; 3-oxapentane-

1,5-diol-*1,1,5,5-d*$_4$, 53129-32-1; dimethyl 2,2'-oxydiacetate, 7040-23-5; 3,6,9-trioxaundecane-1,11-diol-*4,4,8,8-d*$_4$ di-*p*-toluenesulfonate, 53129-33-2; bis-2-chloroethyl-*2,2-d*$_2$ ether, 53129-34-3; 3,6,9-trioxaundecane-1,11-diol-*4,4,8,8-d*$_4$, 53129-35-4; phenol, 108-95-2; 1,8-dichloro-3,6-dioxaoctane, 112-26-5; 1,11-dichloro-3,6,9-trioxaundecane, 638-56-2.

References and Notes

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Marathon Oil Company for support of this research.
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(12) The mass spectrum of **1** has been reported previously.[10a]
(13) Trivial names as suggested by Pedersen[2a] are employed for this and other cyclic polyethers. Systematic names are given in Experimental Section.
(14) The reasonable assumption is made that elemental compositions of fragment ions of **4** are identical with those of isobaric fragment ions of **5**.
(15) Structural identities of the C_2H_4O species lost are uncertain. They could be open chain species as indicated, or ring closure concomitant with bond cleavage would yield ethylene oxide.
(16) A mechanism initiated by cleavage of the bond between O-4(1) and C-5(15) of a with charge retention by carbon cannot be distinguished from that given. It is also possible but unlikely that initial cleavage in a involves the bond between O-4(1) and C-3(2).
(17) However, the mass spectrum (70 eV) of catechol methylene diether displays a molecular ion (*m/e* 122) with relative intensity ~75; the base peak is at *m/e* 121.[10a]
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Electrochemical and Electron Spin Resonance Studies of the Dibenzonorcaradiene Anion Radical

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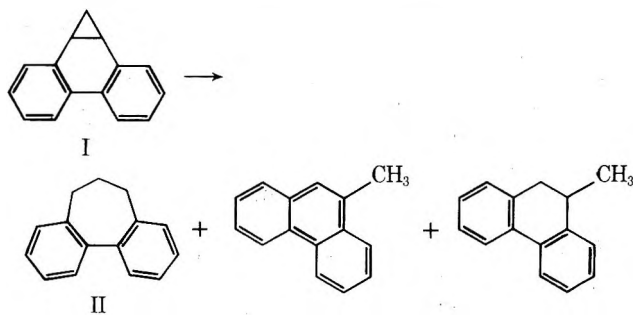
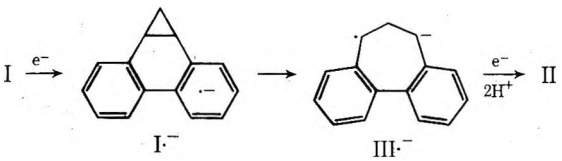
Electrochemical and esr studies of dibenzonorcaradiene have been carried out. Cyclic voltammetry data and esr hyperfine coupling constants are consistent with the reversible formation of a stable radical anion which does not undergo rapid isomerization to the anion radical of dibenzo[*a,c*]cycloheptatriene. Possible mechanisms for the cyclopropane ring opening in the parent radical anion are discussed in terms of correlation diagrams.

Isomerization reactions of ion radicals have received limited attention but are of some theoretical interest. In particular, a model to handle the influence of orbital symmetry on reactions of these open-shell species has not been well defined. With this in mind, the electron-transfer reduction of dibenzonorcaradiene (DBNC) had been investigated previously.[1] The reduction products from I and sodium in glyme include dibenzo[*a,c*]cycloheptadiene, II.



This product might arise from the concerted reaction



As described earlier[1] the bond cleavage is sterically constrained to occur in a disrotatory fashion and thus the presence or absence of this mechanism provides a test of the influence orbital symmetry considerations on the paths of ion radical isomerizations.

A correlation diagram for the I·$^-$ → III·$^-$ reaction (*vide infra*) predicts the product of the allowed thermally initiated reaction will be electronically excited III·$^-$ while the forbidden photochemical product will be ground-state III·$^-$. Using a combination of cyclic voltammetry and electron spin resonance spectroscopy, we will show below that neither of these processes actually occurs.

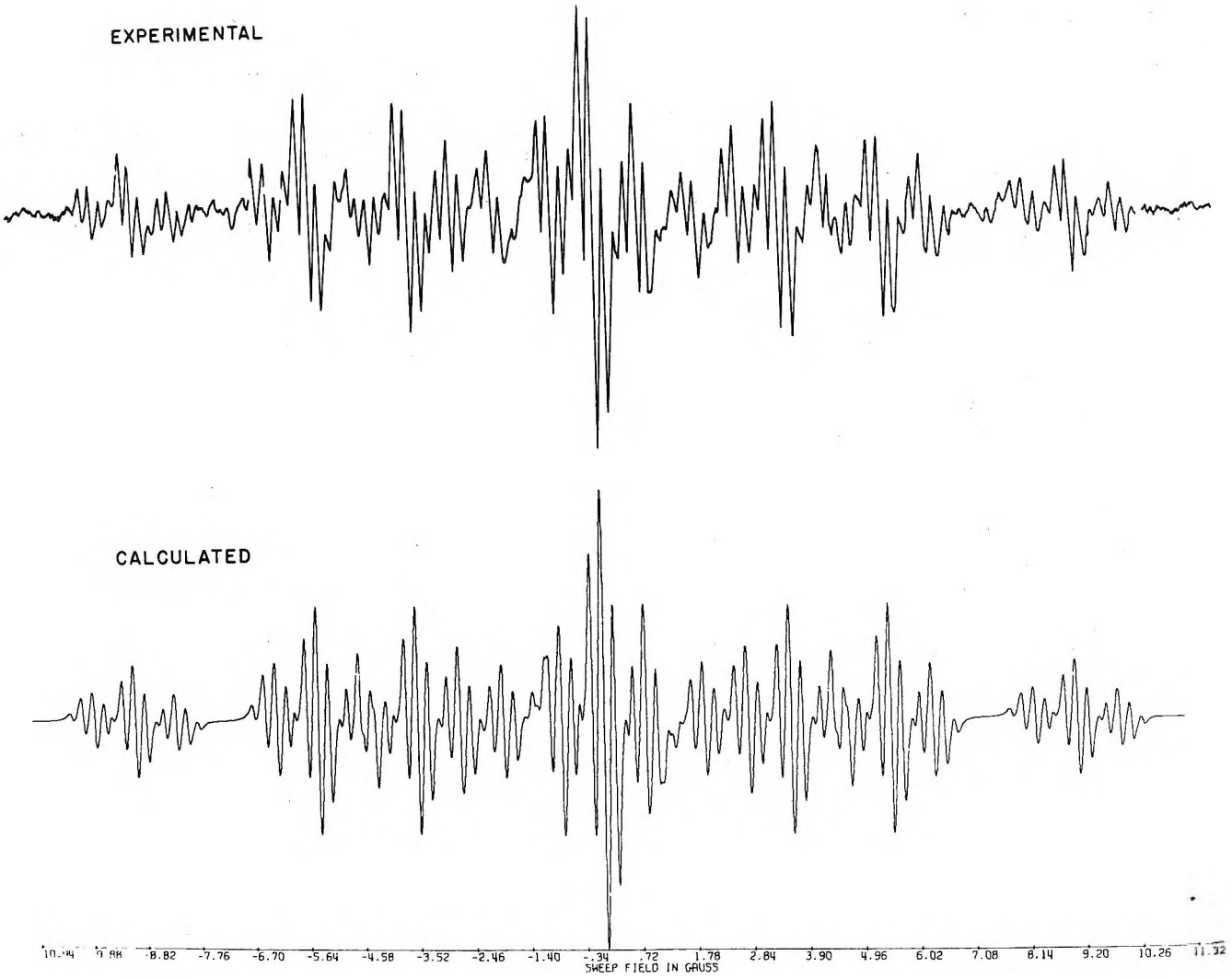


Figure 1. Top: esr spectrum of the anion radical generated by the reduction of dibenzonorcaradiene with potassium in THF at −85°. Bottom: computer-simulated spectrum using the hyperfine splitting constants given in text. The fit is not perfect because of the presence of a small amount of the impurity radical.

Results

Electrochemical studies on the reduction of DBNC were performed in DMF–tetrabutylammonium perchlorate (TBAP) at a mercury electrode. Polarograms run on 10^{-3} M DBNC in dry DMF gave $E_{1/2} = -2.55$ V *vs.* sce. A plot of $E_{1/2}$ *vs.* $I/(I_d - I)$ was linear with a slope of 72 mV.

Cyclic voltammetry was employed in search for intermediates in the reduction. Data are compiled in Table I. In DMF–TBAP a 10^{-3} M solution of DBNC gave a reduction peak $E_p^c = 2.56$ V and on the return (anodic) sweep an anodic peak $E_p^a = 2.49$ V. The peak separation of 70 mV was independent of sweep rate and the current was diffusion controlled at all sweep rates as judged by the constancy of $I_p^c v^{1/2}$. The ratio I_{pa}/I_{pc} was poorly reproducible, but always near unity.

The data are consistent with the reversible formation of a radical anion with a lifetime of several seconds in DMF. It is required that the radical anion have a structure closely related to that of the neutral molecule so that electron transfer is not slowed by a large free energy of activation for a structural change. I·⁻ is clearly acceptable and III·⁻ could only be if the isomerization were remarkably fast.

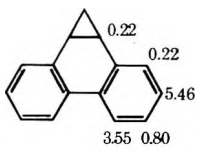
Next, we studied the radical formed by the electron spin resonance (esr) technique. Figure 1 shows the esr spectrum of the anion radical formed by the reduction of DBNC with potassium in tetrahydrofuran (THF) at −85°.[2] A similar spectrum was obtained when 1,2-dimethoxyethane was the solvent or when the reduction was carried out electrolytically using TBAP as supporting electrolyte in THF. Analysis of the spectrum yielded the hyperfine splitting constants 0.22 G (4), 0.80 G (2), 3.55 G (2), and 5.46 G (2) where the number in parentheses denotes the number of equivalent protons. The hyperfine splitting constants for two of the protons are too small to be observed. Assignment of these hyperfine splitting constants by simple molecular orbital calculations is difficult since neither I·⁻ nor III·⁻ is fully aromatic.

If the radical formed has structure I·⁻, the spin density distribution should resemble that of 9,10-dihydrophenanthrene, IV·⁻.[3] The agreement for the couplings observed is very good, the only discrepancy being that one might have expected a substantial coupling from the methylene pro-

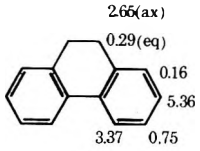
Table I
Cyclic Voltammetry Data for Dibenzonorcaradiene[a]

v, mV /sec	E_p^c, V	E_p^a, V	$I_p^c / v^{1/2}$
10	2.56	2.49	7.72
50	2.56	2.49	6.36
100	2.56	2.49	6.40
200	2.56	2.49	6.51
500	2.56	2.49	6.57

[a] 1×10^{-3} M DBNC in 0.1 M TBAP–DMF. Hanging Hg drop weight 3.9 mg; sce reference electrode.



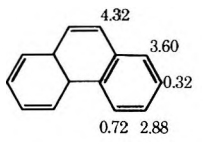
I·⁻



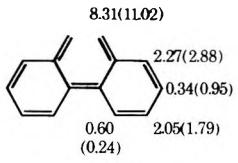
IV·⁻

tons in I·⁻ since the half-filled molecular orbital is symmetric with respect to reflection through the plane containing the methylene group and dividing the rings. Systems with similar symmetry[4,5] normally give large couplings to the methylene protons; however, the methylene group in I·⁻ is at least one bond length further removed from the π system than in the systems previously studied. Assuming one treats I·⁻ as a 1,1′-disubstituted biphenyl radical, the coupling should be substantially smaller.

If the radical formed has structure III·⁻ the predicted coupling constants depend critically on the atom 9–atom 10 distance assumed. If the distance is short (*i.e.*, ~1.4 Å), the radical will resemble the homo[*a*,*c*]dibenzocycloheptatriene anion radical and the spin density distribution will be similar to that of the phenanthrene anion radical (V·⁻). On the other hand, if there is no overlap between the 9 and 10 positions, the radical will resemble the 2,2′-dimethylenebiphenyl anion radical (VI·⁻). We assume the actual radical



V·⁻



VI·⁻

lies somewhere between these two extremes. The experimental couplings for V·⁻ [6] are compared below with those for VI·⁻ calculated using simple Hückel theory ($Q = -31$) and, in parentheses, including McLachlan's polarizability correction[7] ($Q = -27$, $\lambda = 1.2$). Independent of which extreme is the best approximation for III·⁻ it is clear that too many big couplings are predicted, six instead of the four observed, and too few small couplings, four instead of six, for this radical to be considered as a model for the observed stable anion radical.

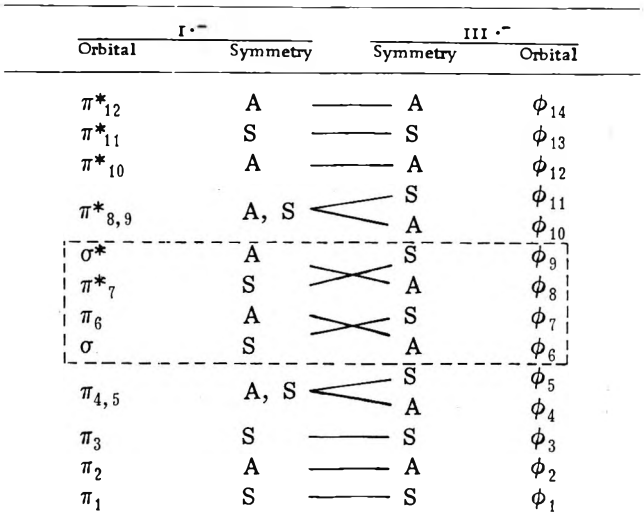
Finally, the following observations are also of interest. Except for the poorer resolution at higher temperatures (probably due to ion pairing), the spectrum is basically the same over a large temperature range (+25 to −100°). The same spectrum is obtained when the reduction was carried out in THF-d_8. Furthermore, on prolonged contact with the alkali metal, the solution yielded another radical whose esr spectrum is similar to that of the 9-methylphenanthrene anion radical. The reduction of 9-methyldihydrophenanthrene with potassium in THF gave no esr signals.

Discussion

Following the discussion in ref 1, we choose the π orbitals of biphenyl plus a σ orbital as a model for discussing the orbital symmetry of the dibenzonorcaradiene anion and 2,2′-dimethylenebiphenyl for the dibenzocycloheptatriene anion. A correlation diagram for their molecular orbitals is given in Chart I where S and A refer to symmetric and antisymmetric with respect to the mirror plane.

The positioning of the σ and σ^* orbitals within the biphenyl π system is arbitrary. The position chosen here allows correlation of the π orbitals of biphenyl (symmetry D_{2h}) with those of the same symmetry in III if the methylene carbons are ignored and thus presumably allows the most facile isomerization. If the σ orbital is buried deeper in the π system, the ground-state symmetry of the anion

Chart I



will be the same but the isomerization barrier higher. Chart II gives a correlation diagram for the ground state and photochemically accessible excited states for the orbitals in the box in Chart I.

Chart II

Chart II shows that if I·⁻ were to isomerize rapidly to III·⁻ by a concerted electrocyclic ring opening, III·⁻ would be created in an electronic excited state which would be expected, in solution, to decay rapidly to the ground state. This mechanism is clearly ruled out by our cyclic voltammetric results since the reoxidation of III·⁻ (ground state) to I would clearly have an activation barrier at least as great as $E\phi_9 - E\phi_8$ which we estimated[1] to be greater than 2 eV.

The $\pi \rightarrow \pi^*$ transition in the biphenyl anion occurs at 24,700 cm^{-1} [8] (blue-violet), so this first electronic excited state is populated under normal experimental conditions. Chart II shows that the photochemical reaction has an orbital symmetry barrier, so the reaction would proceed slowly by this path if at all. A slow (several hours) isomerization of this type is ruled out as a reaction mechanism if the anion radical III·⁻ is stable since only one esr spectrum is observed and we attribute it to I·⁻.

In conclusion, both the electrochemical and esr results are consistent with a stable I·⁻ radical which does not isomerize rapidly to III·⁻. Thus the primary mechanism for the observed formation of II is most probably according to the general scheme

$$\mathrm{I} \xrightarrow{e^-} \mathrm{I}^{\cdot-} \xrightarrow[\text{solvent}]{H^+} \mathrm{IH}^{\cdot} \xrightarrow{e^-} \mathrm{IH}^- \xrightarrow[\text{solvent}]{H^+} \mathrm{IH_2} \equiv \mathrm{II}$$

This work, however, gives no new information about the possible structures of IH· and IH·⁻, several of which were proposed in ref 1. We have not observed any effects of visible light on the reaction rate or products, but the photochemical mechanism in which I·⁻ slowly isomerizes to an unstable III·⁻ is not ruled out by the present work though it is deemed unlikely through orbital symmetry considerations. A referee has suggested the ring-opening step may involve dianions, *i.e.*, $\mathrm{I}^{2-} \rightarrow \mathrm{III}^{2-}$, which would be allowed

photochemically. The dianion I^{2-} is not accessible electrochemically so we have no way of estimating the disproportionation equilibrium constant in order to calculate the I^{2-} concentration, nor do we have any information on the frequency of the $\pi^* \rightarrow \sigma^*$ transition involved so this mechanism cannot be ruled out. The difficulty in producing dianions of the biphenyl-like systems, however, makes it unlikely that appreciable concentrations of I^{2-} are present.

Experimental Section

Materials. Dibenzonorcaradiene was prepared as previously indicated. DMF was dried by distillation from calcium hydride. Tetrahydrofuran and 1,2-dimethoxyethane were purified by first refluxing and then distilling from calcium hydride. These solvents were then stored over Na–K alloy before use.

Equipment. Esr spectra were recorded on a Varian E-3 spectrometer equipped for variable-temperature experiments.

Cyclic voltammograms were run on a Princeton Applied Research Model 170 instrument. The cell was purged of air with argon.

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Registry No.—I, 949-41-7; $I^{\cdot-}$, 34468-58-1; $III^{\cdot-}$, 53166-03-3.

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A New Synthesis of Cyclohexadienes

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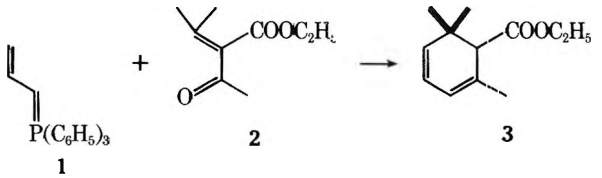
The two bicyclic cyclohexadienes 13 and 17–18 were synthesized by condensation of the two ketones 12 and 16 with 1-butadienyltriphenylphosphonium bromide prepared *in situ* from 2-butenylenetriphenylphosphonium bromide (9) or 4-bromo-2-butenyltriphenylphosphonium bromide (10) and potassium *tert*-butoxide in ether. Efforts to combine ketone 16 with the butadienylphosphonate 25 failed. Phosphonate 25 was prepared by a new method. Alkylation of diethyl ethylphosphonate (23) with propargyl bromide afforded the acetylene 24 which was isomerized to the more stable diene 25 with potassium *tert*-butoxide.

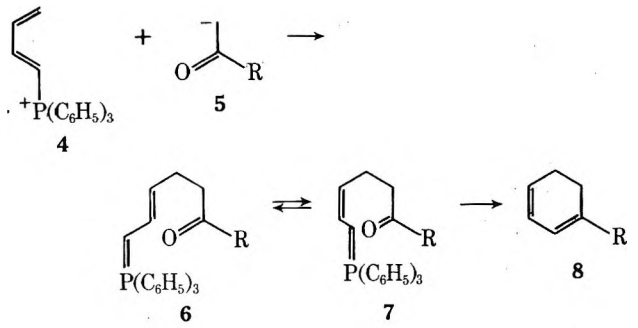
In conjunction with work on the synthesis of damascenones it was found that allyltriphenylphosphorane (1) combines with the highly electron deficient α,β-unsaturated ketone 2 to produce the cyclohexadiene 3.[1] Subsequent work



1 2 3

demonstrated the method to be useful with simple α,β-unsaturated ketones[2,3] lacking an electron-withdrawing substituent and with more highly substituted phosphoranes.[4] It served also in strikingly simple preparations of cyclohexadienes containing bridgehead double bonds.[5] In this synthesis the cyclohexadiene is constructed from two structural units each containing three carbon atoms.

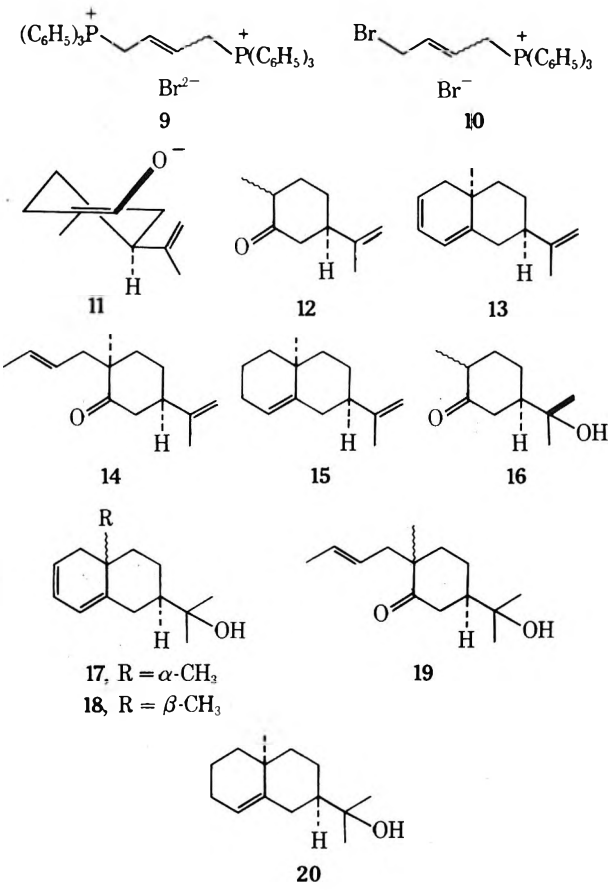
Cyclohexadienes in principle should also be available from starting materials supplying two and four carbon atoms, respectively. More specifically, an enolate 5 should add to the terminal double bond of a butadienylphosphonium salt 4 to produce stereoisomeric ylides 6 and 7. If these are in equilibrium the *Z* isomer 7 should undergo an intramolecular olefin synthesis to afford cyclohexadiene 8. A search of the literature produced little on the chemistry of butadienylphosphonium salts but nucleophilic additions to vinylphosphonium salts, their lower vinylogs, have been explored thoroughly.[6,7]



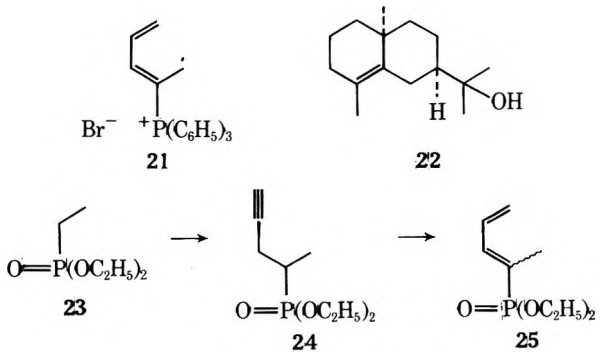
4 5 6 7 8

Slurries of the diphosphonium salt 9[8] or the bromophosphonium salt 10,[9] both of undefined stereochemistry, in ether on treatment with potassium *tert*-butoxide yielded brown solutions presumably containing 1-butadienyltriphenylphosphonium bromide. Addition of dihydrocarvone (12) or hydroxytetrahydrocarvone (16) in *tert*-butyl alcohol solutions produced the anticipated cyclohexadienes 13 and 17–18. The former appeared to be a single diastereomer and in analogy to the products formed in Robinson annelations[10] structure 13 was assigned. Addition of the most stable enolate 11 to the phosphonium salt 4 should give a ketone in the chair conformation containing the new substituent in axial orientation. Annelation to hydroxytetrahydrocarvone (16) led to a 4:1 mixture of products assumed to be epimers 17 and 18, respectively. Hydrolysis of the reaction mixtures shortly after the addition of the ketones 12 and 16 led to substitution products 14 and 19 with

(*E*)-crotyl side chains undoubtedly derived from the (*E*)-phosphoranes **6** by hydrolysis to olefins and triphenylphosphine oxide. The three cyclohexadienes **13**, **17**, and **18** proved to be air sensitive but the products **15** and **20** resulting from selective catalytic hydrogenation of the cis-disubstituted double bonds were stable.



In an attempted synthesis of 10-*epi*-γ-eudesmol (**22**)[11,12] we tried to replace the unknown and seemingly inaccessible phosphonium salt **21** with the corresponding phosphonate **25**. However, efforts to condense **25** with the hydroxy ketone **16** failed, displaying again the inability of nonstabilized phosphonate anions to undergo the Horner–Emmons olefin synthesis.



Since 1,3-butadiene-1-phosphonates are difficult to synthesize,[13] but have found uses,[14] we describe a new and facile method for their preparation. Alkylation of the lithium salt prepared *in situ* from diethyl ethylphosphonate **23** and *n*-butyllithium in tetrahydrofuran with propargyl bromide afforded the alkynyl phosphonate **24**. Isomerization to diethyl 1,3-pentadiene-4-phosphonate (**25**) was accomplished in 82% yield with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol.

Experimental Section

Microanalyses were performed in the laboratory of Dr. F. Gautschi, Firmenich et Cie., Geneva. Boiling points and melting points are uncorrected. Gas–liquid chromatography was performed on a F&M 720 instrument, using silicone rubber gum SE-30 and Carbowax 20M columns. Silicic acid "Mallinckrodt" 100 mesh and silica gel "Merck" 0.05–0.2 mm was used for column chromatography. The following spectrometers were used: nmr, Varian T-60; ir, Perkin-Elmer Model 247; uv, Cary Model 14′; mass spectra, Hitachi RMU 6D. All experiments were carried out under nitrogen.

Annelation of Dihydrocarvone (12). To a slurry of 7.4 g (10 mmol) of phosphonium salt **9**[8] in 100 ml of dry ether was added, at −20°, 4.5 g (40 mmol) of potassium *tert*-butoxide. The resulting brown mixture was stirred for 10 min, followed by dropwise addition of a solution of 1.5 g (10 mmol) of dihydrocarvone (**12**) in 6 ml of dry *tert*-butyl alcohol and 60 ml of dry ether. The mixture was kept for 1 hr at −20° and was then allowed to warm up to room temperature. After stirring for 3 hr at room temperature, the mixture was heated under reflux for 4 hr. The reaction mixture was poured into cold water, extracted with hexane, washed with water, dried (Na_2SO_4), and evaporated. The remaining oil (6.2 g) was chromatographed on 70 g of silicic acid. Elution with hexane gave 1.3 g of triphenylphosphine; with hexane + 20% benzene, 1.6 g (85%) of olefin **13** was eluted: bp 84° (0.1 mm); ir ($CHCl_3$) 1640, 1580, 890 cm^{-1}; uv (EtOH) 269 nm (ε 4760); nmr (CCl_4) δ 1.0 (3 H, s), 1.7 (3 H, s), 2.4 (2 H, s broad), 4.6–5.0 (2 H, m), 5.4–6.0 (3 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 188 (61), 145 (68), 91 (100).

Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71. Found: C, 88.95; H, 10.95.

In a similar experiment the reaction mixture was worked up shortly after the addition of dihydrocarvone (**12**). Purification by column chromatography (silicic acid, benzene + 10% AcOEt) gave pure ketone **14**: ir ($CHCl_3$) 1700, 1640, 960, 890 cm^{-1}; nmr (CCl_4) δ 1.0 (3 H, s), 2.0 (6 H, m), 2.3 (2 H, m), 4.7 (2 H, s broad), 5.2–5.5 (2 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 206 (26), 123 (26), 109 (100).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.36; H, 10.67.

Hydrogenation of Triene 13. A mixture of 0.4 g (2.2 mmol) of triene **13** in 60 ml of ethyl acetate was hydrogenated over 100 mg of Lindlar catalyst. After absorption of 1 equiv of hydrogen the reaction was interrupted and the mixture was filtered and evaporated. The remaining oil was distilled to give 0.4 g of diene **15**: bp 76° (0.1 mm); ir ($CHCl_3$) 1640, 1380, 890 cm^{-1}; nmr (CCl_4) δ 1.1 (3 H, s), 1.7 (3 H, s with fine splitting), 4.7 (2 H, s broad), 5.2–5.5 (1 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 190 (57), 175 (45), 147 (100).

Anal. Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.12; H, 11.10.

Annelation of Hydroxytetrahydrocarvone (16). To a suspension of 7.4 g (10 mmol) of phosphonium salt **9** in 100 ml of dry ether was added, at −20°, 4.5 g (40 mmol) of potassium *tert*-butoxide. To the resulting brown mixture was added dropwise a solution of 1.7 g (10 mmol) of hydroxy ketone **16** in 6 ml of dry *tert*-butyl alcohol and 60 ml of dry ether. The mixture was kept for 1 hr at −20° and was then stirred for 10 hr at room temperature, poured into cold water, extracted with hexane, washed with water, dried (Na_2SO_4), and evaporated. The residue (4.6 g) was chromatographed on 50 g of silica gel. Elution with benzene gave 2.0 g of triphenylphosphine. Benzene + 10% AcOEt eluted 1.45 g (73%) of an epimeric mixture **17** and **18** in a ratio of 4:1. Pure samples were obtained by preparative glc.

Epimer 17: ir ($CHCl_3$) 3610, 1590, 1390, 1370 cm^{-1}; nmr (CCl_4) δ 0.9 (3 H, s), 1.1 (3 H, s), 1.2 (3 H, s), 2.2 (1 H, s, disappears on exchange with D_2O), 5.4–6.0 (3 H, m); uv (EtOH) 269 nm (ε 5360); mass spectrum (70 eV) *m/e* (rel intensity) 206 (15), 188 (100), 173 (45), 145 (82), 117 (94).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.72; H, 10.97.

Epimer 18: mass spectrum (70 eV) *m/e* (rel intensity) 206 (23), 188 (100), 173 (58), 145 (84), 117 (77).

In a similar experiment the reaction mixture was worked up shortly after the addition of hydroxytetrahydrocarvone (**16**). Purification by column chromatography (silica gel, benzene + 20% AcOEt) gave pure hydroxy ketone **19**: ir ($CHCl_3$) 3640, 1700, 970 cm^{-1}; nmr (CCl_4) δ 0.9 (3 H, s), 1.2 (6 H, s), 1.7 (3 H, d, J = 6 Hz), 2.0 (1 H, s, disappears on exchange with D_2O), 5.3–5.5 (2 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 224 (6), 206 (30), 49 (100).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.33; H, 10.67.

Hydrogenation of Diene 17. A mixture of 2.1 g (10 mmol) of diene **17**, 120 ml of ethyl acetate, and 0.5 g of Lindlar catalyst was hydrogenated. Hydrogen uptake ceased after 1 equiv had been absorbed. The mixture was filtered and evaporated and the remaining oil was distilled to afford 2.0 g of alcohol **20**: bp 92° (0.1 mm); ir ($CHCl_3$) 3550, 1650, 940 cm^{-1}; nmr (CCl_4) δ 1.1 (6 H, s), 1.2 (3 H, s), 1.4 (1 H, s, disappears on exchange with D_2O), 2.1–2.4 (2 H, m), 5.2–5.5 (1 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 208 (4), 190 (69), 175 (60), 147 (100).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.55; H, 11.43.

Preparation of Triene 13 Using Bromophosphonium Salt 10.[9] To a solution of 1.5 g (10 mmol) of dihydrocarvone (**12**), 6.7 g (60 mmol) of potassium *tert*-butoxide, and 80 ml of *tert*-butyl alcohol was added, at 5–15°, a slurry of 4.8 g (10 mmol) of bromophosphonium salt **10**[9] and 60 ml of *tert*-butyl alcohol. After the addition was complete, the mixture was stirred for 10 hr at room temperature. The dark brown mixture was heated under reflux for 5 hr, poured into cold water, extracted with hexane, washed with water, dried (Na_2SO_4), and evaporated. The remaining oil was distilled to afford 1.2 g (64%) of triene **13**. According to glc this product was contaminated with 15% of ketone **14** and 10% of dihydrocarvone **12**.

Preparation of Alcohol 17–18 Using Bromophosphonium Salt 10. A solution of 1.7 g (10 mmol) of hydroxy ketone **16**, 4.5 g (40 mmol) of potassium *tert*-butoxide, and 50 ml of dry *tert*-butyl alcohol was placed into a flask. A suspension of 4.8 g (10 mmol) of bromophosphonium salt **10** in 60 ml of dry *tert*-butyl alcohol was added dropwise at 5–15°. The mixture was stirred for 10 hr at room temperature and then heated under reflux for 3 hr. The reaction mixture was poured into cold water, extracted with hexane, washed with water, dried (Na_2SO_4), and evaporated. The remaining oil was distilled to afford 1.8 g (86%) of alcohol **17**, bp 90–95° (0.1 mm). According to glc this product was contaminated with 10% of **16** and 5% of ketone **19**.

Diethyl 1-Pentynyl-4-phosphonate (24). To a stirred solution of 34.0 g (0.20 mol) of diethyl ethylphosphonate (**23**) in 400 ml of dry tetrahydrofuran at −40°, 140 ml (0.2 mol) of butyllithium in hexane (15%) was added. Stirring was continued for 15 min at the same temperature, then a solution of 24.0 g (0.20 mol) of freshly distilled propargyl bromide in 200 ml of tetrahydrofuran was added dropwise. After 1 hr at room temperature, the mixture was poured into 1 l. of water, extracted with hexane, washed with water, dried (Na_2SO_4), and evaporated. Distillation of the residue afforded 24.3 g (58%) of alkynyl phosphonate **24**: bp 87° (0.5 mm); ir ($CHCl_3$) 3350, 1260, 1030 cm^{-1}; nmr (CCl_4) δ 1.3 (6 H, t, J = 7 Hz), 1.2 (3 H, d of d, J_1 = 7 Hz, J_2 = 18 Hz), 2.1 (1 H, t, J = 2.5 Hz), 4.0 (4 H, d of q, J_1 = 7 Hz, J_2 = 7 Hz).

Anal. Calcd for $C_9H_{17}O_3P$: C, 52.96; H, 8.39. Found: C, 52.19; H, 8.34.

Diethyl 1,3-Pentadiene-4-phosphonate (25). A solution of 5.6 g (0.05 mol) of potassium *tert*-butoxide and 10.2 g (0.05 mol) of alkynyl phosphonate **24** in 100 ml of dry *tert*-butyl alcohol was heated at reflux for 2 hr. After removal of most of the solvent *in vacuo* water was added and the mixture extracted with hexane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated. Distillation gave 8.5 g (82%) of **25**: bp 85° (0.5 mm); ir ($CHCl_3$) 1630, 1585, 1250, 965 cm^{-1}; nmr (CCl_4) δ 1.3 (6 H, t, J = 7 Hz), 1.9 (3 H, d, J = 15 Hz), 4.1 (4 H, d of q, J_1 = 7 Hz, J_2 = 7 Hz), 5.3–5.7 (2 H, m), 6.4–7.2 (2 H, m); uv (EtOH) 237 nm (ϵ 25,870); mass spectrum (70 eV) *m/e* (rel intensity) 204 (42), 148 (100), 147 (85), 66 (54).

Anal. Calcd for $C_9H_{17}O_3P$: C, 52.96; H, 8.39. Found: C, 52.31; H, 8.54.

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Registry No.—**9**, 18189-24-7; **10**, 53142-03-3; **12**, 7764-50-3; **13**, 53142-04-4; **14**, 53142-05-5; **15**, 53142-06-6; **16**, 7712-37-0; **17**, 53142-07-7; **18**, 53142-08-8; **19**, 53142-09-9; **20**, 53177-30-3; **23**, 78-38-6; **24**, 53142-10-2; **25**, 53142-11-3.

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Electron Spin Resonance and Nuclear Magnetic Resonance Studies of Cation Radicals Derived from 9,9-Dialkylthioxanthenes

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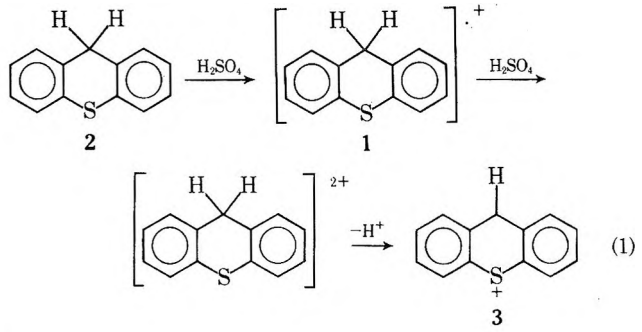
The cation radical of 9,9-dimethylthioxanthene has been prepared in acidic solution and characterized by esr and pmr spectroscopy. Broadening of the aryl region of the pmr is discussed in terms of exchange phenomena. A MO calculation of spin densities in the cation radical is presented. An acidic solution of 9-methyl-9-isopropylthioxanthene is weakly paramagnetic and is presumed to contain the corresponding radical cation.

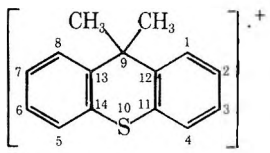
While the so-called "magic acids" appear to protonate sulfides and sulfoxides with little immediate decomposition,[1,2] sulfuric acid or other one-electron oxidants convert diaryl sulfides into the cation radical of the diaryl sulfides.[3] The treatment of diaryl sulfoxides with sulfuric acid also affords the cation radical of the corresponding diaryl sulfide.[3d] One limitation on this route to cation radicals is that the diaryl compound must be substituted with at least one electron-donating group. Thus Shine and coworkers[3b] were unable to form diphenyl sulfide cation radical while Oae and Kunieda[3d] formed a poorly characterized radical from phenyl *p*-tolyl sulfoxide.

Previous attempts[4] to prepare and detect the cation radical of thioxanthene (1) have been fruitless, although it has been postulated[4] as an intermediate in the conversion of thioxanthene (2) to the thioxanthylium cation (3) (eq 1). It occurred to us that replacement of the methylene hydrogens of 2 with alkyl groups would prevent the formation of 3 by proton loss and that a stable cation radical of the thioxanthene system might, therefore, result. This expectation has been realized and we describe below our electron spin resonance and nuclear magnetic resonance studies of the 9,9-dialkylthioxanthene system in oxidizing acidic media. Because of their significance in other nmr studies,[5] we have employed 9,9-dimethylthioxanthene (4) and 9-methyl-9-isopropylthioxanthene (5) in this investigation.



Results

Electron Spin Resonance. When 5 μl of 9,9-dimethylthioxanthene (4) is treated with 0.5 ml of 97% sulfuric acid, an immediate green color is observed. The resulting solution gives an electron spin resonance (esr) spectrum consisting of 21 lines. Analysis indicates that the spectrum is a quintet of quintets with four lines lost by overlap. The hyperfine splittings are a^H(4 H) = 3.10 ± 0.05 G and a^H(4 H) = 0.68 ± 0.05 G, with a *g* value of 2.00668 ± 0.00003. Shine and coworkers[3b] found for *p*-tolyl sulfide cation radical $a_{CH_3}{}^H$ = 4.9 G, $a_{o\text{-}H}{}^H$ = 2.7 G, and $a_{m\text{-}H}{}^H$ = 0.6 G, with a *g* value of 2.00737. The initial color of their solution also was green. This similarity of splitting constants and color supports our assignment of this spectrum to the cation radical of 9,9-dimethylthioxanthene (6), with the a^H = 3.10 G



splitting coming from the ortho- and para-like positions 4 and 2 and a^H = 0.68 G splitting arising from the meta-like positions 3 and 1. We would anticipate that $a_4{}^H$ and $a_2{}^H$ are really different and likewise $a_3{}^H$ and $a_1{}^H$, but that these differences are obscured by the line widths (*ca.* 0.3 G). The radical could also be formed in 75% CH_3NO_2–25% H_2SO_4, but there was no improvement in the resolution.

Reaction of 5 μl of 4 with 0.5 ml of trifluoroacetic acid gave a spectrum consisting of a single broad line which defied further attempts to resolve it. The total width of the line coincided exactly with the total width at the resolved spectrum in H_2SO_4. A broad unresolved line was also obtained using 50% CH_3NO_2–50% CF_3COOH as a medium. We believe this result can best be interpreted in connection with the nmr results (*vide infra*).

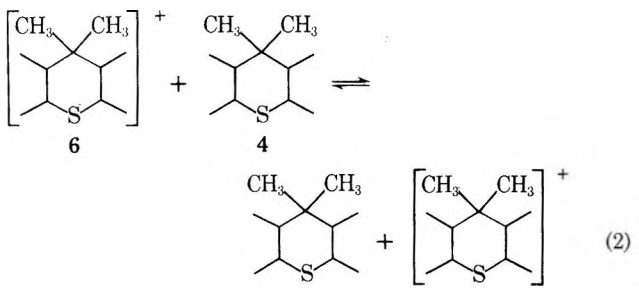
Nuclear Magnetic Resonance. A 10% (w/v) solution of 4 in trifluoroacetic acid produces a light green solution whose nmr spectrum consists of a sharp singlet (CH_3) at δ 1.69 and two broad, *unstructured* resonances centered at δ 7.2 and 7.6. This is to be contrasted to the spectrum of 4 in carbon disulfide which possesses a sharp singlet (CH_3) at δ 1.63 and a highly structured aromatic absorption extending from 6.9 to 7.7.[6] The presence of broadened aryl absorptions in trifluoroacetic acid indicates that a paramagnetic species is produced; however, its presence does not broaden the resonance of the methyl groups at C-9. This is interpreted in terms of eq 2, with rapid exchange between a low concentration of radical cation 6 and the parent sulfide, 4.

This result is consistent with what is known of electron exchange between radical anions[7] and cations[8] and their neutral precursors. In the nmr spectra the lines are broad-

Table I
Theoretical and Experimental Spin Densities in the 9,9-Dialkylthioxanthene System[a]

	Exptl ρ	ρ, K_{CS} = 0.65	ρ, K_{CS} = 0.8	ρ, K_{CS} = 1.0
ρ_1[b]	−0.024	−0.040	−0.042	−0.045
ρ_2	+0.111	+0.098	+0.105	+0.122
ρ_3	−0.024	−0.022	−0.021	−0.026
ρ_4	+0.111	+0.067	+0.087	+0.112
ρ_{11}		+0.040	+0.019	+0.002
ρ_{12}		+0.087	+0.108	+0.129
$\rho_{10}(\rho_S)$		+0.540	+0.490	+0.411

[a] Experimental spin densities calculated from McConnell's equation with Q_{CH}^{H} = −28.0 G. Signs of experimental spin densities are assigned from the theoretical calculations. For the McLachlan calculations λ = 1.2. [b] See structure 6 for numbering.



6 4 (2)

ened and shifted with the amount of the broadening proportional to the square of the hyperfine splitting. Since the methyls of **6** have no measurable hyperfine splitting, they remain unbroadened.

Attempts to obtain resolved nmr spectra of **4** in 96% sulfuric acid have been foiled, thus far, by the insolubility of **4** in this medium at 25–30°. Even at elevated temperatures (~60°) the solubility did not improve sufficiently to provide acceptable data while prolonged contact with 96% acid at elevated temperatures appeared to lead to decomposition.[9]

The behavior of 9-methyl-9-isopropylthioxanthene (**5**) in 96% sulfuric acid was similar to that of **4** in 96% sulfuric acid and useful nmr data could not be obtained.[10]

Molecular Orbital Calculations. A very thorough molecular orbital study of *p,p'*-dihydroxydiphenyl sulfide and diphenyl ether cation radicals has been carried out by Sullivan and Shine.[3c] These authors calculated spin densities from McConnell's equation $a_{CH}^{H} = \rho Q_{CH}^{H}$[11] using a Q_{CH}^{H} value of 28 G. Theoretical spin densities were obtained *via* McLachlan's modification of simple HMO theory,[12] using a fixed set of parameters for the OH group and adjusting the sulfur parameters. A set of sulfur parameters which they found satisfactory was h_S = 1.11 and K_{CS} = 0.65.[13] We carried out a similar set of calculations using those parameters. The inductive effect of the dimethyl-substituted carbon was accounted for by assigning C-12 and -13 (see **6** for numbering) a parameter $h_{C\text{-}sub}$ = −0.5.

The benzene rings of *p,p'*-dihydroxyldiphenyl sulfide are presumed to be twisted, a condition which undoubtedly exists in di-*p*-tolyl sulfide and its cation radicals. Crystallographic studies show that the thioxanthene system is folded rather than planar.[14] The cation radical, however, may be more planar than its parent. When one compares the *g* values of 9,9-dimethylthioxanthene and di-*p*-tolyl sulfide cation radicals, the smaller *g* value of the former (about 0.0007 less) indicates less spin density on the sulfur in the thioxanthene radical. This is consistent with a closer approach to planarity in **6**, as opposed to the tolyl sulfide radical, with increased spin delocalization on the rings. One expects that as radical cation **6** approaches planarity the value of the carbon–sulfur resonance integral should increase. To model this behavior, we also carried out calculations for K_{CS} = 0.8 and 1.0. The results of these calculations and the experimental spin densities are shown in Table I.

Those calculations carried out with K_{CS} = 1.0 seem to fit the experimental data reasonably well. An increase in K_{CS} results in a decrease in sulfur spin density and a concomitant increase in ring spin density. The spin densities at C-2 and -4, with K_{CS} = 1.0, are sufficiently similar that one might expect the splitting constant differences to be lost in the line width. One might have expected to see differences between C-1 and -3 but, of course, the theoretical spin densities need not exactly equal the experimental spin densities.

It is also possible to use the *g* value to see which of our sulfur spin densities are in agreement with the results of Sullivan and Shine. As pointed out by these authors, Stone's theory of *g* values[15] gives the following expression for the *g* value of a π organic radical

$$g_{rad} = 2.0023 + \Sigma_{Het}\rho_{Het}\gamma_{Het} + \Sigma_{C}\rho_{C}\gamma_{C}$$

In this equation, the first term expresses the *g* value for a free electron. The second term accounts for the effects of heteroatoms with the γ parameter dependent on the spin–orbit coupling of the particular heteroatom and the energy of the molecular orbital containing the unpaired electron. The third term is an identical expression for carbon atoms. If one ignores the sulfur lone pair, diphenyl sulfide cation radicals are isoelectronic with diphenylmethyl radical. Stone's theory predicts that the *g* values of neutral odd alternant radicals should be 2.0027. Therefore, we take $\Sigma_C\rho_C\gamma_C$ as ≃0.0004. The *g* value of *p,p*-dihydroxydiphenyl sulfide cation radical is 2.00687. Using parameters K_{CS} = 0.65 and h_S = 1.11, Sullivan and Shine calculated for this radical that ρ_S = 0.434 and ρ_O = 0.026. Defining Δg as the difference between the experimental *g* value and 2.0027, we derive the following expression

$$\frac{\Delta g(\text{dihydroxydiphenyl sulfide radical})}{\Delta g(\text{dimethylthioxanthene radical})} = \frac{\rho_S\zeta_S + 2\rho_O\zeta_O}{\rho_S\zeta_S}$$

In this expression we have assumed that the orbital energies are about the same so that we can replace γ with ζ, the spin–orbit coupling parameter. We can put in the requisite numbers and solve for ρ_S in the thioxanthene derivative. The answer obtained is

$$\frac{0.00417}{0.00397} = \frac{0.434(382) + 2(0.026)(151)}{\rho_S(382)}$$

ρ_S = 0.433. This, too, is fairly close to the value obtained for K_{CS} = 1.0.

Our results above can be used to estimate ρ_S for di-*p*-tolyl sulfide cation radical. It should be simply 0.00397/0.00467 = 0.433/ρ_S, which gives ρ_S = 0.509.

The experimental results of Sullivan and Shine were obtained in the $AlCl_3$–CH_3NO_2 system. Considering the differences in solvent systems, our lack of experimental resolution, and the deficiencies in the theory, it is gratifying that our results are reasonably consistent with those of Sullivan and Shine.

Experimental Section

Nmr spectra were recorded on a Varian Model HA-100D spectrometer operating at 100 MHz with a probe temperature of 34.5°. Chemical shifts are reported with respect to internal tetramethylsilane. Esr spectra were obtained with a Varian V-4500 epr spec-

trometer equipped with a Varian Fluxmeter and a Hewlett Packard 5245L electronic counter. The solutions were not deoxygenated prior to obtaining the esr spectra. The g values were determined with reference to a 2.2×10^{-3} M solution of 4-acetamido-2,2,6,6-tetramethylpiperidinyl-1-oxyl in benzene, sealed in a capillary tube and taped to the aqueous sample cell. The g value of the standard was first determined with reference to that of p-benzosemiquinone in n-butyl alcohol. The semiquinone value given by Segal *et al.* is 2.004679.[16] Allendoerfer has pointed out[17] that the values of Segal *et al.* should be lowered by 14×10^{-6}. The value we used was 2.004665. The measured g value for the nitroxyl is 2.00603 ± 0.00003 with $a^N = 15.29 \pm 0.10$ G. The latter splittings were directly determined with the fluxmeter. By comparison, the g value of di-*tert*-butyl nitroxide in toluene is 2.00606 ± 0.00001 with $a^N = 15.26 \pm 0.07$ G.[18] To test our procedure in a similar solvent system, we measured a g value of 2.00808 for thianthrene cation radical in sulfuric acid. The literature value is 2.0081.[19]

9,9-Dimethylthioxanthene (4) was prepared as described earlier.[20]

9-Methyl-9-isopropylthioxanthene (5). A suspension of 9-methylthioxanthene[21] (3.50 g, 16.5 mmol) in 100 ml of ether was cooled to 0–5° (ice bath) and treated with 6.75 ml of a 22.3% solution of n-butyllithium in hexane. After stirring for 10 min at 25°, a solution of isopropyl bromide (2.01 g, 16.4 mmol) in 25 ml of ether was added to the suspension containing the carbanion of 9-methylthioxanthene. The resulting suspension was stirred at room temperature for 10 hr and then diluted with water (100 ml). The ethereal layer was separated, washed with water (2 × 100 ml), dried ($MgSO_4$), and concentrated (stream of nitrogen gas) to afford a viscous, orange oil. Molecular distillation (60° (0.1 Torr)) of this oil yielded 4.10 g (16.2 mmol, 99%) of **5** as a clear, light-yellow oil. This material was essentially homogeneous on tlc; mp 39°.

Anal. Calcd for $C_{17}H_{18}S$: C, 80.26; H, 7.13; S, 12.60. Found: C, 80.30; H, 7.19; S, 12.42.

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Registry No.—**4,** 19019-10-4; **5,** 51966-11-1; 9-methylthioxanthene, 16860-11-0.

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(2) Thioxanthene forms an S-protonated cation while 9-methylthioxanthene forms a mixture of cis and trans S-protonated isomers in $HF-SbF_5-SO_2$. In this mixture thioxanthene slowly is converted into the thioxanthylium ion; manuscript in preparation.
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(9) Solutions of **4** in 96% sulfuric acid which were quenched (water) immediately after preparation did not produce any readily discernible secondary reaction products (tic, silica gel, chloroform eluent, uv and iodine visualization).
(10) A solution of **5** in a 1:1 mixture of trifluoroacetic acid–trifluoroacetic anhydride, prepared on a vacuum line, exhibited normal methyl and isopropyl resonances and a highly structured aryl multiplet (δ 7.05–7.60). The spectrum of this sealed sample was essentially unchanged after 28 days at 25°. Admission of pure oxygen produced an immediate blue-green hue and an nmr spectrum which possessed normal, but slightly broadened, alkyl resonances and an aryl region exhibiting only two broad, unstructured humps centered near δ 7.5 and 8.1.[6] Although relatively insoluble, a mixture of 10.2 mg of **5** in 0.5 ml of 97% sulfuric is *faintly* green and exhibits an esr spectrum (an order of magnitude less intense than **4**). Some hyperfine structure was discernible but spectral analysis was impossible. These data suggest the formation of a radical cation similar to **6**.
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Syntheses and Properties of Some Pyrimidine 2,4′-Cyclo Nucleosides

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Four pyrimidine 2,4′-cyclo nucleosides, 2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (**6a**), 2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-*endo*-anisylidene-α-L-lyxosyl)uracil (**6b**), its exo stereomer (**6c**), and N^4-benzoyl-2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-*exo*-anisylidene-α-L-lyxosyl)cytosine (**14**), were synthesized from the corresponding 4′,5′-didehydro nucleosides (**2a–c** and **5b**) and *tert*-butyl hypochlorite in dry media. Their characteristic chemical and optical properties are presented.

Since Todd and coworkers reported 2′,3′-*O*-isopropylidene-2,5′-anhydrocytidine tosylate in 1951 as the first base–sugar cyclized nucleoside,[1] 2,2′-,[2] 2,3′-,[3] 2,5′-,[1,4] 6,5′-,[5] 6,2′-[6] anhydro pyrimidine nucleosides and analogous purine 8-cyclo nucleosides[7] have been described and proved to be useful intermediates for chemical modifications of base and sugar moieties in natural nucleosides. The cyclo nucleosides have themselves served as prominent models for physicochemical studies on the base–sugar conformations in nucleosides and nucleotides.[8–10] Some anhydro nucleosides with nitrogen and sulfur bridges have also been obtained.[7,11] Probably, the last target in cyclo nucleoside chemistry is the one involving cyclization at the 4′ position in nucleosides. In this field, 5′-bromo-5′-deoxy-2′,3′-*O*-isopropylidene-N^3→4′-cycloadenosine bromide was recorded in 1968 in a synthetic study related to the total synthesis of angustmycin A.[12] Recently, we have reported the synthesis of 2,4′-didehydro-1-(5′-bromo-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil as the first pyrimidine 2,4′-cyclo nucleoside.[13] However, the fragility and low yield of this compound have hampered further study of its chemistry. This paper describes a more efficient synthesis of pyrimidine 2,4′-cyclo nucleosides and some of their chemical and optical properties.

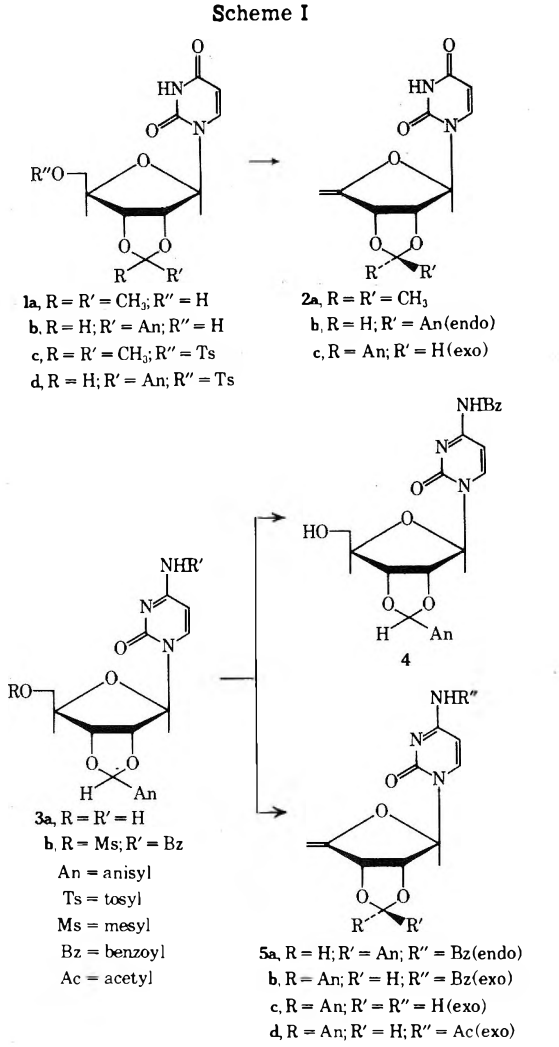
Syntheses of 4′,5′-Didehydro Pyrimidine Nucleosides (Scheme I). 1-(5-Deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**2a**) was prepared according to the described procedure.[14] Its 2,3-*O*-anisylidene analogs (**2b** and **c**) were also synthesized in the hope that the large aryl protecting group would facilitate the isolations of products in succeeding reactions and would be removed under relatively mild conditions, perhaps even by hydrogenolysis.[15]

2′,3′-*O*-Anisylideneneuridine (**1b**)[16] was tosylated to 5′-*O*-tosyl-2′,3′-*O*-anisylideneuridine (**1d**), which was directly treated with excess potassium *tert*-butoxide to give a diastereoisomeric mixture of 1-(5-deoxy-2,3-*O*-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**2b** and **c**). The endo and exo isomers were successfully separated by column chromatography, the major isomer being assigned the endo structure.[17] The corresponding 4′,5′-didehydro nucleosides in the cytosine series were obtained similarly. 2′,3′-*O*-Anisylidenecytidine (**3a**)[18] was successively treated with mesyl chloride and benzoyl chloride to give 2′,3′-*O*-anisylidene-5′-*O*-mesyl-N^4-benzoylcytidine (**3b**) which was directly treated with potassium *tert*-butoxide. Partial crystallization and column chromatography separated two isomers of N^4-benzoyl-1-(5-deoxy-2,3,-*O*-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (**5a** and **5b**). The major product (42%) was assigned the exo structure **5b**, the minor product (5%) the endo structure **5a**.

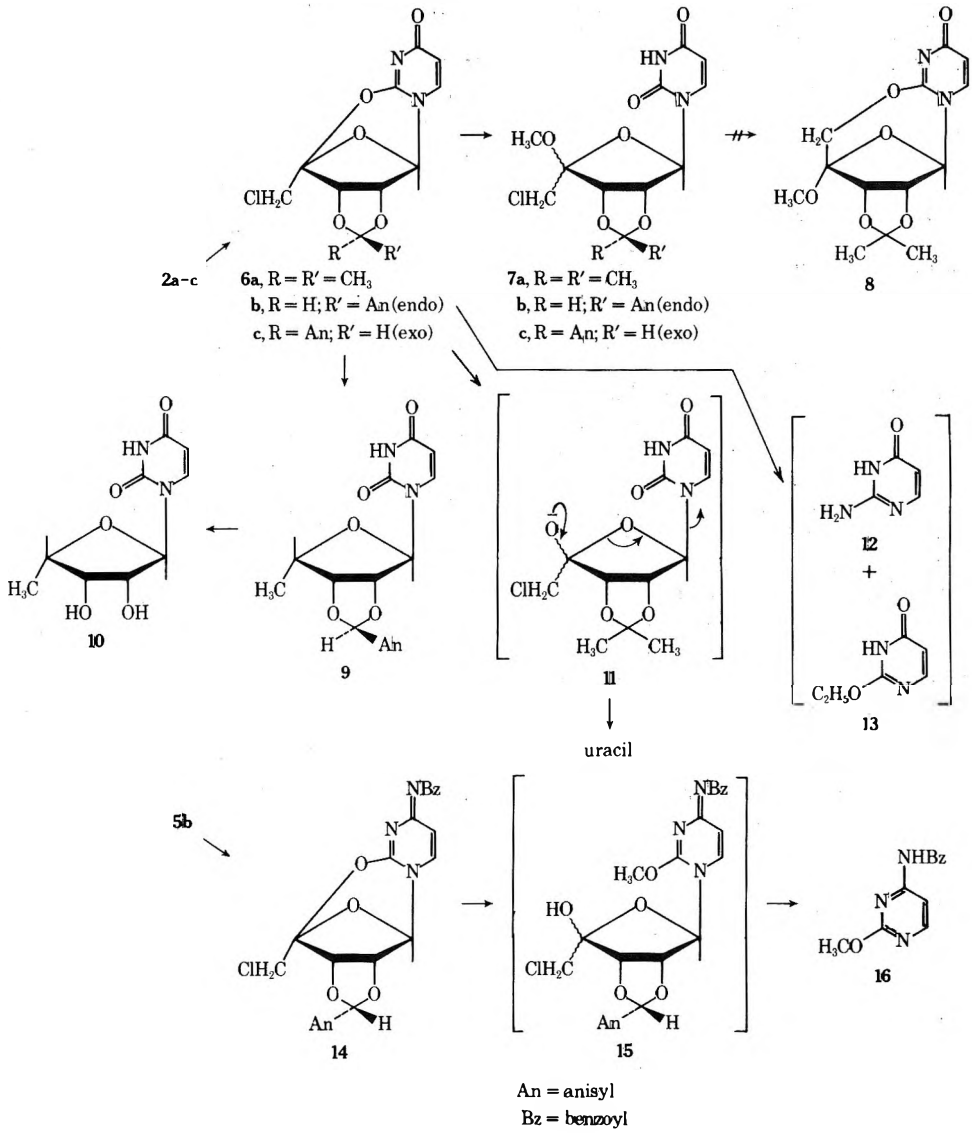
The configurations of the anisylidene groups in these 4′,5′-didehydro nucleosides were deduced from the corresponding configurational assignments for compounds **6** and **7** as follows. Bagget, Lipkin, and coworkers[19,20] discussed the chemical shifts of the benzyl protons (benzyl methine protons) of 2′,3′-*O*-benzylidene nucleosides and assigned the exo configuration to the stereomer with the higher benzyl proton signals. It is seen from Table I that the chemical shifts of the anisylidene methine protons of **6b** and **7b** (or of **6c** and **7c**) coincide and that there is a difference of 0.17 to 0.19 ppm between the members of each pair. These coincidences regardless of the skeletal difference between **6** and **7** series seem to justify an analogous interpretation for the differences of the chemical shifts, while the rule of Lipkin and coworkers seems to be reversed when there is an exocyclic double bond at the 4′ position of the furanose ring.[21]

In the preparation of **5a** and **5b**, a third highly polar product, 2′,3′-*O*-anisylidene-N^4-benzoylcytidine (**4**), was

Scheme I



Scheme II



invariably obtained as a side product. The structural assignment was essentially based on analysis and uv absorptions at 224, 259, and 302 nm, but the configuration of the anisylidene remains unknown.

The major 4′,5′-didehydro isomer (**5b**) was quantitatively debenzoylated to 1-(5-deoxy-2,3-*O*-*exo*-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (**5c**) using a mixture of acetone and aqueous ammonium hydroxide. Acetylation on **5c** gave N^4-acetyl-1-(5-deoxy-2,3-*O*-*exo*-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (**5d**) in high yield. All the above stated 4′,5′-didehydro nucleosides exhibited in the nmr spectra characteristic 5′-olefin proton signals at around 4.3 and 4.5 ppm as a set of doublets with coupling constants of 2.3–3.0 Hz.

Pyrimidine 2,4′-Cyclo Nucleosides (Scheme II). 2,4′-Cyclization can be achieved in principle by generating a carbonium ion at $C_{4'}$ using an appropriate dipolar addition reagent. It was expected that such an intermediate ion would be particularly stabilized by neighboring ether oxygen participation in our case, and the use of *tert*-butyl hypochlorite instead of hypobromous acid[13] would be more profitable since the former is used in dry media, thus precluding ionic side reactions.

Treatment of **2a** with *tert*-butyl hypochlorite in dry acetonitrile gave crystalline 2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (**6a**) in fair yield (60%). Similar treatment of **2b** and **2c** in dry acetone gave the corresponding stereomers (**6b** and **6c**) of 2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-anisylidene-α-L-lyxosyl)uracil. Compounds **6a–c** showed uv absorptions at around 230 and 245 nm, the latter being always inflections, and similar well-resolved nmr spectra (see Experimental Section). It is interesting to compare the resonance pattern of **6a** with the characteristic resonance spectra of 2′,3′-*O*-isopropylidene-2,5′-cyclouridine and 2′,3′-*O*-isopropylidene-2,5′-cyclo-6-azauridine,[22] in which the signals of $H_{2'}$ and $H_{3'}$ appeared as overlapping singlets and those of the 5′-methylene as unusually wide-spread quartets. This nmr-spectroscopic comparison suggests that compounds **6a–c** do not have a 2,5′-bridged structure. An intramolecular nuclear Overhauser effect was observed only between $H_{1'}$ and H_6, as in the case of a purine 3,5′-cyclo nucleoside (between $H_{1'}$ and H_8).[23] Thus, irradiation on the H_6 signal caused 15% enhancement of the $H_{1'}$ resonance, while $H_{1'}$ irradiation caused 13% enhancement of the H_6 resonance in dimethyl sulfoxide-d_6.[24]

A notable property of **6a–c** is their unusually high acid lability as expected on the basis of their unique polycyclic structures in which a bridged 1,3-dioxane component exists. Thus, treatment with strong acids like mineral acids,

Table I
Chemical Shifts of Anisylidene Methine Protons in 4′,5′-Didehydro Nucleosides (2b and 2c, 5a and 5b), 2,4′-Cyclo Nucleosides (6b and 6c), and 4′-Methoxy-4′-chloromethyleneuracil Nucleosides (7b and 7c)

Compd	Chemical shifts, δ	Compd	Chemical shifts, δ
2b	5.78	**6b**	6.03
2c	5.91	**6c**	5.86
5a	5.83	**7b**	6.03
5b	5.93	**7c**	5.84

dichloroacetic acid, or trifluoroacetic acid in any form resulted in complete destruction and only afforded uracil as a tangible product, while our earlier experiments with the 5′-bromo analog of compound **6a** revealed that short contact with dry, neat acetic acid gave quantitatively a stereoisomeric mixture of 1-(2′,3′-*O*-isopropylidene-4′-acetoxy-4′-bromomethylene-β-D-*erythro*-furanosyl)uracil (**7a**, acetoxyl instead of methoxyl, Br instead of Cl).[25,26] It was finally found that nitromethane, a weak acid, was an excellent catalyst for methanolysis of compounds **6a–c** to give 1-(2′,3′-*O*-isopropylidene-4′-chloromethylene-4′-methoxy-β-D-*erythro*-furanosyl)uracil (**7a**), 1-(2′,3′-*endo*-anisylidene-4′-chloromethylene-4′-methoxy-β-D-erythrofuranosyl)uracil (**7b**), and its *exo*-anisylidene analog (**7c**) as described in the Experimental Section. While in each methanolysis reaction one 4′ stereomer was isolated as crystals, isolation of the counterpart was abandoned.

Compound **7a** and the corresponding stereoisomeric mixture was treated with basic systems, 10–15% triethylamine–methanol, sodium methoxide–methanol, potassium *tert*-butoxide–tetrahydrofurane, silver acetate–methanol, to obtain a 2,5′-anhydro nucleoside (**8**). All efforts resulted in the recovery of the starting material or in intractable mixtures depending upon the reaction conditions.

Substitution of the 5′-chlorine atom with usual nucleophiles also proved to be difficult, presumably due to steric reasons. Atmospheric pressure hydrogenation (Pd–C) of **6b** gave unexpectedly 1-(5′-deoxy-2′,3′-*O*-*endo*-anisylidene-α-L-lyxofuranosyl)uracil (**9**), the anisylidene group being unaffected. The structure of compound **9** became evident from the uv absorption at 260 nm and nmr spectrum, in which the signal of 5′-methyl appeared at 1.27 ppm as a doublet with $J_{4',5'}$ = 6.0 Hz. Compound **9** was also obtained from **2b** by similar hydrogenation and could be converted to the known 1-(5′-deoxy-α-L-pentofuranosyl)uracil (**10**)[14] by acid hydrolysis. Neutral hydrolysis of **6a** in a mixture of acetone and water gave only uracil, most probably through the intermediacy of a 4′-hydroxy-4′-chloromethylene compound (**11**). Reaction of **6a** with ethanolic ammonia at ambient temperature formed isocytosine (**12**)[27] as the major product with 3,4-dihydro-4-keto-2-ethoxypyrimidine (**13**).[27] The behavior of a 2,4′-cyclo uracil nucleoside toward amines seems to be analogous to those of 2,5′-anhydro uracil nucleosides,[4,28] 4′-hydroxy anion having accelerated the deglycosidation as in **11**.

In the cytidine series, treatment of **5b** with *tert*-butyl hypochlorite gave crystalline N^4-benzoyl-2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-*exo*-anisylidene-α-L-lyxosyl)-cytosine (**14**) in fair yield. Although we could not find an appropriate compound in the literature for a uv spectral comparison, the dramatic blue shifts of the longer wave length absorptions of **14** as compared with those of **5b** (see Experimental Section), as usually observed with uracil 2-cyclo nucleosides,[2–4] substantiated a 2-bridged structure. The nmr spectrum of **14** also coincides with that of uracil analog (**6a**) (see Experimental Section). The exact coincidence of the resonance pattern of the furanose protons seems to be rather fortuitous but is strong evidence for the 2,4′-cyclic structure. Formations of analogous cyclo nucleosides from **5a** and **5d** with *tert*-butyl hypochlorite were suggested by thin-layer chromatography,[29] but their isolations were unsuccessful. Compound **14** seems to be the second cytidine 2-cyclo nucleoside with a 4-imino (not immonium) structure after 2,3′-anhydro-1-(2′,5′-di-*O*-trityl-β-D-xylofuranosyl)cytosine synthesized by Mizuno and coworkers.[3c]

Methanolysis of **14** in the presence of nitromethane also proceeded smoothly to give a mixture of two products, but surprisingly, these were not 4′-methoxy compounds as indicated by the uv spectrum of the crude reaction mixture, which was quite similar to that of **14**. This is understandable if the methoxy anion attacked the 2 position of the base to give a diastereoisomeric mixture (**15**), which would be highly unstable due to the presence of a hemiacetal partial structure at $C_{4'}$ as observed in the neutral hydrolysis of **6a**. In effect, the separated major product (**15**) easily formed 2-methoxy-4-benzamidopyrimidine (**16**) on heating at 50–55° under vacuum. This methanolysis reaction was 100% specific and in sharp contrast to the behavior of uracil analogs.

The cyclo nucleosides **6a–c** and **14** showed distinct negative ORD and/or CD Cotton effects at the 260–280 nm region indicating their syn conformations (see Experimental Section),[8,30] although the CD spectrum of **14** is complicated by the presence of a benzoyl group. A typical example (**6a**) is represented in Figure 1 together with the uv absorption.

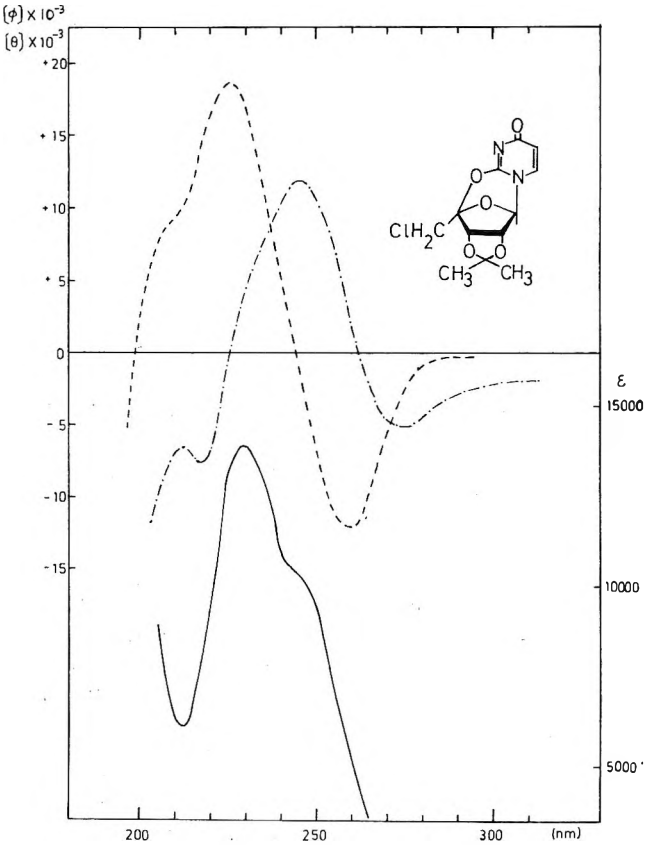


Figure 1. Uv (—), ORD (·--), and CD spectra (---) of 2,4′-anhydro-1-(5′-deoxy-5′-chloro-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (**6a**) in methanol.

It is interesting to note that the ORD curve of **6a** is an approximate mirror image, despite the difference in the measurement conditions, to that of 6,5′-cyclo-6-hydroxyuri-

dine;[8a] hence it could better serve as an optical model of syn conformations than that of 2,5′-anhydrouridine.[8a]

Experimental Section

All the melting points are uncorrected. The electronic spectra were measured on a JASCO Model ORD/UV-5 spectrophotometer. The nuclear magnetic resonance spectra were determined using a JNM C-60 HL spectrometer and tetramethylsilane as an internal standard, while a few of the 100-MHz spectra were recorded with a Varian HA-100 spectrometer in the laboratory of the Takeda Chemical Industries Co., Ltd., for which we are grateful. The circular dichroism spectra were recorded with a JASCO Model J-20 recording spectropolarimeter in the laboratory of the Japan Spectroscopic Co., Ltd., and of Kitazato University, Tokyo, to which we owe a great deal. Wakogel B-5 silica gel was used for thin-layer chromatography, while column chromatography was carried out using Mallinkrodt silicic acid (100 mesh) after washing with ethyl acetate.

1-(5-Deoxy-2,3-*O*-*endo*- (and *exo*-) anisylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (2b and 2c). A mixture of **1b**[16] (3.36 g, 9.28 mmol) and tosyl chloride (2.30 g, 12.0 mmol) in dry pyridine (20 ml) was stirred at room temperature overnight, treated with methanol (1 ml) for 20 min, and evaporated *in vacuo* to a gum, which was dissolved in acetone (10 ml) and dropped into stirred ice–water (100 ml). The precipitate was collected by suction, dissolved in ethyl acetate, dried over sodium sulfate, and filtered with Norit. Evaporation of the solvent gave 4.35 g (91%) of 5′-*O*-tosyl-2′-3′-*O*-anisylideneuridine (**1d**) as a homogeneous foam. The total product (8.33 mmol) was dissolved in dry tetrahydrofuran (THF) (34 ml) and treated with potassium *tert*-butoxide (*t*-BuOK) (2.24 g, 20 mmol) under ice cooling for 1 hr and then at room temperature for 9 hr. The mixture was neutralized with acetic acid and evaporated to a dark residue, which was partitioned between ethyl acetate (200 ml) and water (50 ml). The separated organic layer was dried over sodium sulfate and evaporated to a gum, which was applied on a silica gel column (2 × 50 cm). Elution with chloroform–ethyl acetate (5:1, v/v) gave from the first fraction 1.31 g (45.8%) of 1-(5-deoxy-2,3-*O*-*endo*-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**2b**) as a homogeneous foam: λ_{max} (MeOH) (ε) 225 nm (13,800) and 256 (9800); nmr (DMSO-d_6) δ 3.75 (3 H, s, methoxyl), 4.33 (1 H, br d, J_{gem} = 2.25 Hz, $H_{5'a}$), 4.50 (1 H, br d, J_{gem} = 2.25 Hz, $H_{5'b}$), 5.20 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{2'}$ or $H_{3'}$), 5.47 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$ or $H_{2'}$), 5.65 (1 H, d, $J_{5,6}$ = 7.5 Hz, H_5), 5.78 (1 H, s, anisylidene methine), 6.03 (1 H, s, $H_{1'}$), 6.97 (2 H, d, J = 8.5 Hz, aryl protons), 7.42 (2 H, d, J = 8.5 Hz, aryl protons), 7.74 (1 H, d, $J_{5,6}$ = 7.5 Hz, H_6), and 11.45 (1 H, s, NH).

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.13. Found: C, 59.55; H, 4.80; N, 8.25.

The second fraction gave 520 mg (18.2%) of an isomeric product (**2c**) as colorless crystals of mp 195–196° (from ethanol–acetone): λ_{max} (MeOH) (ε) 224 nm (14,100) and 257 (9700); nmr (DMSO-d_6) δ 3.75 (3 H, s, methoxyl), 4.23 (1 H, d, J_{gem} = 2.25 Hz, $H_{5'a}$), 4.43 (1 H, d, J_{gem} = 2.25 Hz, $H_{5'b}$), 5.22 (1 H, d, $J_{2',3'}$ = 7.5 Hz, $H_{2'}$ or $H_{3'}$), 5.34 (1 H, d, $J_{2',3'}$ = 7.5 Hz, $H_{3'}$ or $H_{2'}$), 5.63 (1 H, d, $J_{5,6}$ = 7.5 Hz, H_5), 5.91 (1 H, s, anisylidene methine), 6.03 (1 H, s, $H_{1'}$), 6.95 (2 H, d, J = 8.5 Hz, aryl protons), 7.40 (2 H, d, J = 8.5 Hz, aryl protons), 7.77 (1 H, d, $J_{5,6}$ = 7.5 Hz, H_6), and 11.46 (1 H, s, NH).

Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.13. Found: C, 59.60; H, 4.75; N, 8.19.

2′,3′-*O*-Anisylidene-5′-*O*-mesyl-N^4-benzoylcytidine (3b). To a solution of **3a** (5.0 g, 13.9 mmol) in pyridine at −20° was added dropwise methanesulfonyl chloride (1.2 ml, 15.3 mmol) under stirring. After standing at −20° for 15 hr, benzoyl chloride (1.95 ml, 16.7 mmol) was added and the total was left at 0° for 24 hr. The mixture was treated with methanol (2 ml) and evaporated *in vacuo* to a paste, which was dissolved in methanol (20 ml) and poured into ice–water (300 ml). The precipitate was filtered, washed with water, and air dried. The semi-dry solid was dissolved in chloroform, thoroughly dried over sodium sulfate, and evaporated to give 7.2 g (95%) of an essentially homogeneous foam (**3b**), which was directly used for the next step: ir (KBr) $\nu_{C=O}$ 1690 cm^{-1}.

N^4-Benzoyl-1-(5-deoxy-2,3-*O*-*endo*- (and *exo*-) anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (5a and 5b) and 2′,3′-*O*-Anisylidene-N^4-benzoylcytidine (4). A solution of **3b** (3.26 g, 6.0 mmol) in THF (34 ml) was treated with *t*-BuOK (1.62 g, 14.4 mmol) at room temperature overnight, and the mixture was worked up as in the case of **2b** and **2c**. The ethyl acetate solution finally obtained (*ca.* 100 ml) was concentrated *in vacuo* to the one-third volume, when a crystalline solid (**5b**) precipitated. It was collected and shown to be practically homogeneous by tlc using solvent systems chloroform–ethyl acetate (1:1 and 3:1) and ethanol–benzene (1:4). The filtrate was concentrated and applied on a silica gel column (2 × 25 cm) and eluted with chloroform–ethyl acetate (5:1). The first band corresponding to the minor product gave crystals (**5b**) and the second major band gave another crop of **5b**. **5a** was recrystallized from ethyl acetate to give 135 mg (5%) of colorless needles, mp 222–223.5°: λ_{max} (MeOH) (ε) 222 nm (27,000), 258 (27,000) and 302 (8700); nmr (DMSO-d_6) δ 3.80 (3 H, s, methoxyl), 4.36 (1 H, d, J_{gem} = 3.0 Hz, $H_{5'a}$), 4.51 (1 H, d, J_{gem} = 3.0 Hz, $H_{5'b}$), 5.23 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$), 5.58 (1 H, dd, $J_{2',3'}$ = 6.0 Hz, $J_{1',2'}$ = 1.5 Hz, $H_{2'}$), 5.83 (1 H, s, anisylidene methine), 6.13 (1 H, d, $J_{1',2'}$ = 1.5 Hz, $H_{1'}$), 6.88–7.03 (2 H, m, J = 8.0 Hz, aryl protons), 7.38–7.56 (6 H, m, aryl protons of the anisyl and benzoyl groups and H_5), 8.00 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_6), and 8.15–8.29 (2 H, m, aryl protons). The NH signal did not appear clearly.

Anal. Calcd for $C_{24}H_{21}N_3O_6$: C, 64.43; H, 4.70; N, 9.40. Found: C, 64.16; H, 4.79; N, 9.16.

The combined crop of exo isomer **5b** was also crystallized from ethyl acetate to give 1.12 g (42%) of colorless needles, mp 237–238.5°: λ_{max} (MeOH) (ε) 223 nm (18,500), 259 (20,500), and 302 (6550); nmr (DMSO-d_6) δ 3.77 (3 H, s, methoxyl), 4.29 (1 H, d, J_{gem} = 3.0 Hz, $H_{5'a}$), 4.48 (1 H, d, J_{gem} = 3.0 Hz, $H_{5'b}$), 5.25 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$), 5.40 (1 H, dd, $J_{2',3'}$ = 6.0 Hz, $J_{1',2'}$ = 1.50 Hz, $H_{2'}$), 5.93 (1 H, s, anisylidene methine), 6.10 (1 H, d, $J_{1',2'}$ = 1.50 Hz, $H_{1'}$), 6.87–7.02 (2 H, m, J = 8.0 Hz, aryl protons of the anisyl), 7.33–7.54 (6 H, m, aryl protons of the anisyl and benzoyl groups and H_5), 8.00 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_6), 8.13–8.26 (2 H, m, J = 8.0 Hz, aryl protons).

Anal. Calcd for $C_{24}H_{21}N_3O_6$: C, 64.43; H, 4.70; N, 9.40. Found: C, 64.65; H, 4.83; N, 9.29.

The column was then thoroughly eluted with ethyl acetate to give a third crystalline product which was almost homogeneous in terms of tlc. Crystallization from aqueous ethanol gave 600 mg (22%) of 2′,3′-*O*-anisylidene-N^4-benzoylcytidine (**4**) as hydrate of mp 236–238.5°: ir (KBr) $\nu_{C=O}$ 1690, 1660, and 1645 cm^{-1}. Uv absorption maxima at 224, 259, and 302 nm were revealed by qualitative measurements.

Anal. Calcd for $C_{24}H_{23}N_3O_7 \cdot H_2O$: C, 59.62; H, 5.21; N, 8.69. Found: C, 59.90; H, 5.25; N, 8.62.

Mesylation of this compound gave 3b as indicated by tlc.

1-(5-Deoxy-2,3-*O*-*exo*-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (5c). A suspension of **5b** (1.5 g, 3.36 mmol) in a mixture of acetone (75 ml) and concentrated aqueous ammonia (75 ml) was stirred at room temperature overnight. The resulting solution was evaporated *in vacuo* to a paste, which was repeatedly coevaporated with a small amount of ethanol. The obtained solid mass was triturated with a small volume of ethanol, filtered, and washed with ether. Crystallization from methanol gave 1.06 g (92%) of fine needles, mp 206–208°: ir (KBr) ν_{N-H} 3440 and 3400 cm^{-1}; λ_{max} (MeOH) (ε) 226 nm (19,800), 268 (8300), and 278 (7200).

Anal. Calcd for $C_{17}H_{17}N_3O_5$; C, 59.47; H, 4.99; N, 12.24. Found: C, 59.44; H, 5.09; N, 11.96.

N^4-Acetyl-1-(5-deoxy-2,3-*O*-*exo*-anisylidene-β-D-*erythro*-pent-4-enofuranosyl)cytosine (5d). To a stirred ice-cold suspension of **5c** (820 mg, 2.39 mmol) in pyridine (20 ml) was added acetyl chloride (0.19 ml, 2.63 mmol). The resulted solution was left at room temperature overnight, treated with a small amount of methanol, and evaporated *in vacuo* at below 40° to a thick gum, which afforded crystals on triturating with a small amount of methanol (3–4 ml). The crystals were separated and the filtrate was poured into ice–water (50 ml). The precipitate was collected, combined with the above obtained crystals, and recrystallized from acetone. A yield of 810 mg (88%) of fine needles (**5d**) was obtained, mp 233–235°: λ_{max} (MeOH) (ε) 213 nm (27,000), 226 (20,800, inflection), 246 (18,100) and 296 (6050); nmr ($CDCl_3$ + DMSO-d_6) δ 2.16 (3 H, s, acetyl), 3.78 (3 H, s, methoxyl), 4.30 (1 H, d, J_{gem} = 3.0 Hz, $H_{5'a}$), 4.52 (1 H, d, J_{gem} = 3.0 Hz, $H_{5'b}$), 5.16 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$), 5.40 (1 H, dd, $J_{2',3'}$ = 6.0 Hz, $J_{1',2'}$ = 1.5 Hz, $H_{2'}$), 5.89 (1 H, s, anisylidene methine), 5.95 (1 H, d, $J_{1',2'}$ = 1.5 Hz, $H_{1'}$), 6.85 (2 H, d, J = 8.0 Hz, aryl protons), 7.30 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_5), 7.39 (2 H, d, J = 8.0 Hz, aryl protons), 7.87 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_6), and 10.75 (1 H, br, s, NH).

Anal. Calcd for $C_{19}H_{19}N_3O_6$: C, 59.21; H, 4.97; N, 10.90. Found: C, 59.41; H, 4.96; N, 10.66.

2,4′-Didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (6a). To an ice-cold stirred suspension

of 2a (266 mg, 1 mmol) in acetonitrile (2 ml) was added *tert*-butyl hypochlorite (130 mg, 1.2 mmol). After 30 min, the precipitate was rapidly filtered by suction, washed with a small amount of ethyl acetate and ether, and dried in a desiccator under high vacuum. The filtrate was evaporated *in vacuo* at room temperature and the residue was left at −20° with a small amount of ethyl acetate to give another crop of crystals. The combined products were recrystallized from methanol at room temperature to give 180 mg (60%) of colorless needles, mp 190–192°: λ_{max} (MeOH) (ϵ) 229 nm (13,800) and 245 (10,400, inflection); CD (MeOH) (θ) (nm) −12,300 (259), +18,700 (225), and +9400 (210, shoulder); nmr (DMSO-d_6) δ 1.30 (3 H, s, methyl), 1.44 (3 H, s, methyl), 4.04 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'a}$), 4.19 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'b}$), 4.98 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{2'}$, or $H_{3'}$), 5.11 (1 H, d, $J_{2',3'}$ = 6.0 Hz, H_3, or $H_{2'}$), 5.89 (1 H, d, $J_{5,6}$ = 7.5 Hz, H_5), 6.24 (1 H, s, $H_{1'}$), and 7.68 (1 H, d, $J_{5,6}$ = 7.5 Hz, H_6).

Anal. Calcd for $C_{12}H_{13}N_2O_5Cl$: C, 47.93; H, 4.36; N, 9.32. Found: C, 47.65; H, 4.44; N, 9.18.

2,4′-Didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-*endo*-anisylidene-α-L-lyxosyl)uracil (6b). **2b** (650 mg, 1.89 mmol) in dry acetone (5.2 ml) was treated with *tert*-butyl hypochlorite (0.34 ml, 2.83 mmol) at 0° for 2 hr, and the total was evaporated *in vacuo* to a semi-solid residue, which was triturated with a small amount of ethyl acetate. The crystals were collected by suction, dried under high vacuum, and recrystallized from a mixture of ethyl acetate and acetone to give 300 mg (42%) of **6b**, mp 166–167°: λ_{max} (MeOH) (ϵ) 227 nm (28,500) and 245 (9700, inflection); CD (MeOH) [θ] (nm) −22,000 (257) and +45,200 (226); (DMSO-d_6) δ 3.73 (3 H, s, methoxyl), 4.24 (1 H, d, J_{gem} = 13.50 Hz, $H_{5'a}$), 4.46 (1 H, d, J_{gem} = 13.50 Hz, $H_{5'b}$), 5.21 (1 H, d, $J_{2',3'}$ = 5.0 Hz, $H_{2'}$ or $H_{3'}$), 5.30 (1 H, d, $J_{2',3'}$ = 5.0 Hz, $H_{3'}$ or $H_{2'}$), 5.93 (1 H, d, $J_{5,6}$ = 7.5 Hz, H_5), 6.03 (1 H, s, anisylidene methine), 6.42 (1 H, s, $H_{1'}$), 6.94 (2 H, d, J = 9.0 Hz, aryl protons), 7.40 (2 H, d, J = 9.0 Hz, aryl protons), and 7.72 (1 H, d, $J_{5,6}$ = 7.50 Hz, H_6).

Anal. Calcd for $C_{17}H_{15}N_2O_6Cl$: C, 53.91; H, 3.99; N, 7.39. Found: C, 54.12; H, 4.00; N, 7.25.

2,4′-Didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-*exo*-anisylidene-α-L-lyxosyl)uracil (6c). **2c** (220 mg, 0.64 mmol) in dry acetone (3.4 ml) was treated with *tert*-butyl hypochlorite (0.11 ml, 1.04 mmol) at room temperature for 3 hr, and the mixture was worked up as in the case of **6b** to give 140 mg (57.6%) of **6c** as colorless needles, mp 151–152° (ethyl acetate + acetone): λ_{max} (MeOH) (ϵ) 227 nm (25,000) and 245 (8800, inflection); CD (MeOH) [θ] (nm) −12,200 (260) and +28,800 (235); nmr (DMSO-d_6) δ 3.75 (3 H, s, methoxyl), 4.04 (1 H, d, J_{gem} = 13.5 Hz, $H_{5'}$), 4.32 (1 H, d, J_{gem} = 13.5 Hz, $H_{5'b}$), 5.07 (1 H, d, $J_{2',3'}$ = 5.0 Hz, $H_{2'}$ or $H_{3'}$), 5.22 (1 H, d, $J_{2',3'}$ = 5.0 Hz, $H_{3'}$ or $H_{2'}$), 5.86 (1 H, s, anisylidene methine), 5.93 (1 H, d, $J_{5,6}$ = 7.50 Hz, H_5), 6.42 (1 H, s, $H_{1'}$), 6.98 (2 H, d, J = 9.0 Hz, aryl protons), 7.41 (2 H, d, J = 9.0 Hz, aryl protons) and 7.71 (1 H, d, $J_{5,6}$ = 7.50 Hz, H_6).

Anal. Calcd for $C_{17}H_{15}N_2O_6Cl$: C, 53.91; H, 3.99; N, 7.39. Found: C, 53.68; H, 4.19; N, 7.14.

1-(2′,3′-*O*-isopropylidene-4′-chloromethylene-4′-methoxy-β-D-*erythro*-furanosyl)uracil (7a). To a stirred suspension of **6a** (200 mg) in methanol (20 ml) was added nitromethane (3 drops), when the mixture rapidly went into solution. Tlc after 1 hr showed only one faster moving spot and no starting material with several solvent systems such as ethanol–benzene (1:4) and chloroform–ethyl acetate (1:1, 2:1, 3:1, as well as 4:1). The mixture was concentrated *in vacuo* to give a solid which was filtered (70 mg). The filtrate was evaporated and the residue was chromatographed on a silica gel column (1.5 × 25 cm) using chloroform–ethyl acetate (5:1). No distinct separation was effected. However, some earlier collected eluants gave an additional solid (10 mg). The combined solid was recrystallized from ethyl acetate to give 70 mg of colorless needles (**7a**), mp 229–231°: λ_{max} (MeOH) 261 nm (ϵ 7000); nmr ($CDCl_3$ + DMSO-d_6) δ 1.38 (3 H, s, methyl), 1.58 (3 H, s, methyl), 3.20 (3 H, s, methoxyl), 3.0–3.60 (2 H, m, 5′-methylene), 4.68 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$), 5.02 (1 H, dd, $J_{2',3'}$ = 6.0 Hz, $J_{1',2'}$ = 1.7 Hz, $H_{2'}$), 5.66 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.28 (1 H, d, $J_{1',2'}$ = 1.7 Hz, $H_{1'}$), and 7.30 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_6).

Anal. Calcd for $C_{13}H_{17}N_2O_6Cl$: C, 46.89; H, 5.15; N, 8.42. Found: C, 46.77; H, 5.19; N, 8.23.

The noncrystalline part seemed to be an 4′-epimer contaminated with **7a** as indicated by its nmr spectrum, in which appeared two sets of the methyl signals and multiple splittings for the sugar protons, and so was not chased further. This was also the case with the methanolysis products of compound **6b** and **6c.**

1-(2′,3′-*O*-*endo*-Anisylidene-4′-chloromethylene-4′-methoxy-β-D-*erythro*-furanosyl)uracil (7b). 2,4′-Cyclo nucleoside **6b** (200 mg, 0.53 mmol) in methanol (5 ml) was treated with nitromethane (0.05 ml) at room temperature for 1 hr, during which the mixture went into solution. On standing at room temperature overnight, the mixture gave crystals which were filtered and dried. Column chromatography on the filtrate using chloroform–ethyl acetate (4:1) gave a second crop of crystals. The combined product was recrystallized from methanol to give 55 mg (25%) of needles (**7b**), mp 205–207°: λ_{max} (MeOH) (ϵ) 225 nm (17,600) and 256 (12,000); nmr (DMSO-d_6) δ 3.07 (3 H, s, 4′-methoxyl), 3.75 (3 H, s, methoxyl of the anisyl), 3.76 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'a}$), 4.10 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'b}$), 4.78 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{2'}$ or $H_{3'}$), 5.56 (1 H, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$ or $H_{2'}$), 5.69 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.03 (1 H, s, anisylidene methine), 6.30 (1 H, s, $H_{1'}$), 6.95 (2 H, d, J = 8.50 Hz, aryl protons), 7.43 (2 H, d, J = 8.50 Hz, aryl protons), 7.57 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_6), and 11.38 (1 H, s, NH).

Anal. Calcd for $C_{18}H_{19}N_2O_7Cl \cdot \frac{1}{2}CH_3OH$: C, 52.06; H, 4.96; N, 6.56. Found: C, 51.92; H, 4.78; N, 6.47.

1-(2′,3′-*O*-*exo*-Anisylidene-4′-chloromethylene-4′-methoxy-β-D-*erythro*-furanosyl)uracil (7c). **6c** (200 mg, 0.53 mmol) in methanol (5 ml) was treated with nitromethane (0.07 ml) at room temperature overnight. The separated crystals were collected, dried, and recrystallized from methanol to give 80 mg (37%) of needles (**7c**), mp 243–246°: λ_{max} (MeOH) (ϵ) 225 nm (16,000) and 256 (12,300); nmr (DMSO-d_6) δ 3.08 (3 H, s, 4′-methoxyl), 3.66 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'a}$), 3.75 (3 H, s, methoxyl of the anisyl), 4.28 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'b}$), 4.81 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{2'}$ or $H_{3'}$), 5.33 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$ or $H_{2'}$), 5.65 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 5.84 (1 H, s, anisylidene methine), 6.23 (1 H, s, $H_{1'}$), 6.96 (2 H, d, J = 8.5 Hz, aryl protons), 7.42 (2 H, d, J = 8.5 Hz, aryl protons), 7.53 (1 H, d, $J_{5,6}$ = 8.5 Hz, H_6), and 11.43 (1 H, br s, NH).

Anal. Calcd for $C_{18}H_{19}N_2O_7Cl$: C, 52.06; H, 4.96; N, 6.56. Found: C, 52.12; H, 5.01; N, 6.39.

1-(5′-Deoxy-2′,3′-*O*-*endo*-anisylidene-α-L-lyxopentofuranosyl)uracil (9). (A) Compound **6b** (400 mg, 1.06 mmol) in acetone (40 ml) was stirred under hydrogen (1 atm) in the presence of triethylamine (1.47 ml, 10.6 mmol) and 10% palladium on charcoal (200 mg) for 2 days. The catalyst was removed by filtration and the filtrate was evaporated to a semisolid residue, which was triturated with ethyl acetate and filtered. On washing the filter cake with a small amount of water, 150 mg of the starting material was recovered. The ethyl acetate layer was then applied on a silica gel column (1 × 20 cm) and eluted with chloroform–ethyl acetate (5:1) to give a crystalline product, which was repeatedly crystallized from ethanol to colorless needles (**9**) of mp 134–135° (50 mg, 22.5%): λ_{max} (MeOH) (ϵ) 224 nm (13,800) and 260 (8400); nmr (DMSO-d_6) δ 1.27 (3 H, d, $J_{4',5'}$ = 6.0 Hz, 5′-methyl), 3.74 (3 H, s, methoxyl), 4.24–4.60 (1 H, br m, $H_{3'}$), 4.68–4.95 (1 H, br m, $H_{2'}$), 5.30 (1 H, dd, $J_{4',5'}$ = 6.0 Hz, $J_{3',4'}$ = 12.0 Hz, $H_{4'}$), 5.55 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 5.69 (1 H, s, anisylidene methine), 5.81 (1 H, s, $H_{1'}$), 6.90 (2 H, d, J = 8.5 Hz, aryl protons), 7.36 (2 H, d, J = 8.50 Hz, aryl protons), and 7.65 ($J_{5,6}$ = 8.0 Hz, H_6).

Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.95; H, 5.33; N, 7.86.

(B) Compound **2b** (110 mg, 0.32 mmol) in acetone (15 ml) was submitted to atmospheric pressure hydrogenation using 10% palladium on charcoal (100 mg) for 18 hr. The catalyst was filtered off and the filtrate was evaporated to a paste, which crystallized on scratching in the presence of a small amount of ethyl acetate. Recrystallization from a mixture of ethanol and ethyl acetate gave 95 mg (86%) of needles of mp 132–134°, identified with the product (**9**) in procedure A by infrared spectroscopy and mixture melting point determination.

Acidic Hydrolysis of 1-(5′-Deoxy-2′,3′-*O*-*endo*-anisylidene-α-L-lyxopentofuranosyl)uracil (9). Compound **9** (150 mg, 0.43 mmol) in 80% acetic acid (3 ml) was held at 50° for 5.5 hr and evaporated *in vacuo*. The obtained gum was repeatedly coevaporated with ethanol to remove the residual acetic acid to give a solid mass, which was digested with ether and filtered. Crystallization from methanol gave 75 mg (76%) of colorless needles of mp 226–228°, which were identified with an authentic specimen of 1-(5′-deoxy-α-L-lyxopentofuranosyl)uracil (**10**) (lit.[14] mp 228–230°) in all respects.

Hydrolysis of 2,4′-Didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (6a). Compound **6a** (60 mg, 0.2 mmol) in a mixture of acetone (8 ml) and water (2 ml) was heated to reflux for 1 hr and the mixture was evaporated. The residue was dried by coevaporation with ethanol and triturated with

ether to give a solid, which was filtered (17 mg, 78%) and infrared spectroscopically identified with an authentic specimen of uracil.

Ammonolysis of 2,4′-Didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)uracil (6a). A suspension of **6a** (0.21 g, 0.7 mmol) in saturated ethanolic ammonia (25 ml) was stirred at room temperature overnight. The yellow solution was evaporated *in vacuo* and the residue was triturated with a small amount of acetone to give a tlc-pure solid, which was filtered (60 mg) and recrystallized from a mixture of methanol and ethanol. There was obtained 50 mg (64%) of colorless crystals (**12**) of mp 273–276° dec, identified with an authentic sample[27] of isocytosine by infrared spectroscopy and mixture melting point determination: λ_{max} (MeOH) (ϵ) 216 nm (6700, inflection) and 278 (5600).

Anal. Calcd for $C_4H_5N_3O$: C, 43.24; H, 4.54; N, 37.83. Found: C, 43.50; H, 4.66; N, 37.55.

The acetone solution separated from **12** was concentrated and applied on a silica gel column (1 × 15 cm). Elution with chloroform–ethyl acetate (3:1) gave a small amount of a less polar crystalline substance, which melted at 130–132° after recrystallization from ethyl acetate and identified as 3,4-dihydro-4-keto-2-ethoxypyrimidine (**13**) (lit.[27] mp 127.5–129° from water): yield 12 mg (12%); nmr ($CDCl_3$) δ 1.40 (3 H, t, J = 7.45 Hz, methyl), 4.47 (2 H, q, J = 7.45 Hz, methylene), 6.13 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_5), and 7.77 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_6).

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.68; H, 5.80; N, 19.80.

N^4-Benzoyl-2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-*exo*-anisylidene-α-L-lyxosyl)cytosine (14). To a stirred ice-cold suspension of **5b** (153 mg, 0.34 mmol) in acetone (4 ml) was added *tert*-butyl hypochlorite (0.04 ml, 0.35 mmol). The suspension became clear rapidly and, after 15 min, a crystalline solid began to separate. After 1 hr of being stirred at 0°, the solid was filtered, washed with a small volume of ether, dried *in vacuo*, and recrystallized from a mixture of acetone and ethyl acetate to give 80 mg (48.8%) of needles, mp 235–237° dec: λ_{max} (MeOH) (ϵ) 226 nm (23,600), 242 (14,100, inflection), and 279 (18,700); CD (MeOH) [θ] (nm) −490 (280), −260 (273), −640 (268), and +380 (243); nmr (DMSO-d_6) δ 3.76 (3 H, s, methoxyl), 4.08 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'a}$), 4.18 (1 H, d, J_{gem} = 12.0 Hz, $H_{5'b}$), 5.05 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{2'}$ or $H_{3'}$), 5.21 (1 H, d, $J_{2',3'}$ = 6.0 Hz, $H_{3'}$ or $H_{2'}$), 5.84 (1 H, s, anisylidene methine), 6.41 (1 H, s, $H_{1'}$), 6.42 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_5), 6.95 (2 H, d, J = 8.0 Hz, aryl protons of the anisyl), 7.39 (2 H, d, J = 8.0 Hz, aryl protons of the anisyl), 7.40–7.47 (3 H, m, benzoyl), 7.65 (1 H, d, $J_{5,6}$ = 7.0 Hz, H_6), and 7.93 (2 H, dd, benzoyl).

Anal. Calcd for $C_{24}H_{20}N_3O_6Cl$: C, 59.81; H, 4.15; N, 8.72. Found: C, 59.53; H, 4.09; N, 8.45.

Methanolysis of N^4-Benzoyl-2,4′-didehydro-1-(5′-chloro-5′-deoxy-2′,3′-*O*-*exo*-anisylidene-α-L-lyxosyl)cytosine (14). **14** (0.5 g, 1.04 mmol) in methanol (25 ml) was treated with nitromethane (0.5 ml) at room temperature for 1.5 hr. Tlc with an aliquot of the resulted solution revealed a major product with a slightly faster moving minor product in solvent systems chloroform–ethyl acetate (3:1 and 2:1). The mixture was evaporated to a paste and chromatographed on a silica gel column using chloroform–ethyl acetate (4:1) to give two pasty products, both of which showed quite similar uv absorption with that of **14** on qualitative measurements in methanol and did not become foamy on evaporating at room temperature under vacuum of 7–10 mm. The minor product was neglected and the major product was submitted to nmr measurement ($CDCl_3$) which revealed an additional methoxyl signal at 3.98 ppm and some ill-resolved signal envelope due to the sugar protons. The total major product was then dried at 50–55° under high vacuum for 20 hr, when crystallization occurred with a certain degree of decomposition. The total was then submitted to preparative tlc using silica gel and chloroform–ethyl acetate (1:1) to give *ca.* 100 mg of powder, which was recrystallized from a mixture of ethyl acetate and ether to give 90 mg (38%) of 2-methoxy-4-benzamidopyrimidine (**16**) as needles of mp 107–108°: λ_{max} (MeOH) (ϵ) 238 nm (12,700) and 281 (16,600); nmr ($CDCl_3$) δ 3.93 (3 H, s, methoxyl), 7.40–7.66 (3 H, m, aryl protons), 7.80–8.0 (3 H, m, aryl protons and H_5), 8.45 (1 H, d, $J_{5,6}$ = 6.0 Hz, H_6), and 8.60 (1 H, br s, NH, D_2O exchangeable).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.53; H, 5.00; N, 18.44.

Registry No.—, **1b,** 53166-52-2; **2a,** 17331-67-8; **2b,** 53166-53-3; **2c,** 53166-54-4; **3a,** 53166-55-5; **3b,** 53166-56-6; **4,** 53166-57-7; **5a,** 53166-58-8; **5b,** 53166-59-9; **5c,** 53166-60-2; **5d,** 53166-61-3; **6a,** 53198-11-1; **6b,** 53198-12-2; **6c,** 53228-48-1; **7a,** 53166-62-4; **7b,** 53166-63-5; **7c,** 53187-87-4; **9,** 53166-65-7; **12,** 108-53-2; **13,** 25957-58-8; **14,** 53166-64-6; **16,** 53166-66-8.

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(17) Here, endo and exo terms refer to the diastereomeric hydrogen, *i.e.*, anisylidene is exo when the anisylidene methine proton is projected outward from, and endo when it is underneath the sugar ring.
(18) S. Chládek, *Syn. Proced. Nucleic Acid Chem.*, **1,** 292 (1968).
(19) N. Bagget, A. B. Foster, J. M. Webber, D. Lipkin, and B. E. Phillips, *Chem. Ind. (London)*, 136 (1965).
(20) N. Bagget, K. W. Buck, A. B. Foster, M. H. Randall, and J. M. Webber, *Proc. Chem. Soc., London*, 118 (1964).
(21) NOE measurements were carried out[24] on compounds **2b** and **2c** for eventual interactions between the anomeric proton and the methine and/or aryl protons of the anisylidene group. None was observed except a slight interaction between $H_{1'}$ and H_6.
(22) J. Žemlicka and F. Šorm, *Collect. Czech. Chem. Commun.*, **32,** 579 (1966).
(23) P. A. Hart and J. P. Davis, *J. Amer. Chem. Soc.*, **91,** 512 (1969).
(24) The measurements were carried out by Takeda Chemical Industries Co., Ltd., for which we are grateful.
(25) Unpublished data.
(26) It is difficult to find a correct nomenclature for compounds **7** and **15** as long as the configuration at $C_{4'}$ remains unknown. These compounds might be named as derivatives of a 4′-substituted 5′-chloro-5′-deoxy-β-D-ribofuranoside when the chloromethylene group stands upward and as the corresponding 4′-substituted derivatives of a α-L-lyxofuranosyl nucleoside when it is oriented downward as once suggested for the epimeric 5′-deoxy-4′-fluoro-5′-iodoadenine nucleosides: I. D. Jenkins, J. P. H. Verheyden, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **93,** 4323 (1971). For the time being, however, we simply name this class of compounds as the derivatives of a β-D-*erythro*-furanoside so as not to specify the configuration at $C_{4'}$ as formerly done by us: T. Sasaki, K. Minamoto, and K. Hattori, *J. Amer. Chem. Soc.*, **95,** 1350 (1973). On the other hand, compounds **6** are cyclo nucleosides formally produced by 2,4′-dehydrogenation of the corresponding derivatives of α-L-lyxofuranosyl nucleosides and are certainly different from the hitherto known pyrimidine 2-anhydro nucleosides which usually form by elimination of a molecule of ROH (R = H or leaving groups). The hydrogenolysis of **6b** to **9** also seems to justify this treatment. In this sense, we correct the nomenclature of cyclo nucleosides of type **6** as in the text.
(27) G. E. Hilbert, E. F. Jansen, and S. B. Hendricks, *J. Amer. Chem. Soc.*, **57,** 552 (1935).
(28) I. L. Doerr and J. J. Fox, *J. Amer. Chem. Soc.*, **89,** 1760 (1967).
(29) The mobilities of the 2,4′-cyclo nucleosides on tlc are usually remarkably lower than their precursors in various solvent systems described in the Experimental Section.
(30) G. T. Rogers and T. L. V. Ulbricht, *Biochem. Biophys. Res. Commun.*, **39,** 414 (1970).

Notes

Preparation of *cis*- and *trans*-4-*tert*-Butylcyclohexane-*1*-d_1 and Their Identification by Infrared Spectra and ^{2}H Nuclear Magnetic Resonance[1]

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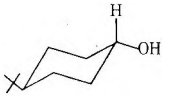
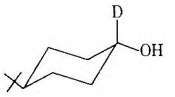
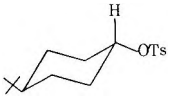
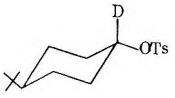
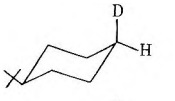
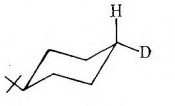
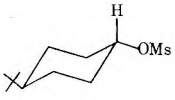
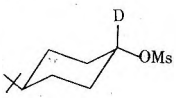
It is generally accepted that when the bulky *tert*-butyl group is introduced into a cyclohexane ring, it assumes a favored equatorial position and stabilizes the resulting conformation.[2] If a reducible function and deuterium are introduced in the 1 position of 4-*tert*-butylcyclohexane, the resulting compound has considerable potential for studying the stereochemistry and mechanism of reductions involving secondary carbon atoms. In those cases where *cis*- and *trans*-4-*tert*-butylcyclohexane-1-d_1 (**5** and **6**, respectively) are possible final products, it is necessary that distinguishing features of these compounds be recognized and identified. It was necessary, therefore, to synthesize **5** and **6** for subsequent comparison. Table I lists all of the compounds prepared together with the physical data used in their identification.

cis- and *trans*-4-*tert*-butylcyclohexane-*1*-d_1 of suitable purity for this study were prepared readily and in good yield from 4-*tert*-butylcyclohexanone. 4-*tert*-Butylcyclohexanone was reduced using a $LiAlH_4$–$AlCl_3$ mixture according to the method of Eliel–Martin–Nasipuri[3] to give *trans*-4-*tert*-butylcyclohexanol (**1**). Compound **1** was allowed to react with *p*-toluenesulfonyl chloride in dry pyridine at 0° to give an 89% yield of the *p*-toluenesulfonyl ester (**3**). Compound **3** when heated at 90° with an excess of $NaBD_4$[4] in hexamethylphosphoramide gave a better than 70% yield of **5**. Approximately 10% of **3** was found on work-up to have been converted to **1**, presumably by $NaBD_4$ attack on sulfur. If the above procedure is modified by using a $LiAlD_4$[5]–$AlCl_3$ mixture for the initial reaction and $NaBH_4$ in the final reduction, the isolated product is **6** in equally good yields. Both **5** and **6** were purified by elutriation with pentane through a column packed with 10%

Table I

No.	Compd	Data[a]
1		Mp 82.0–82.5° (lit.[b] mp 82.5–83.0°); ir 3615, 3440 cm^{-1} (OH); ^{1}H nmr δ 0.82 (s, 9 H, *tert*-butyl), 3.12–3.54 (m, 1 H, H–C–O–), 2–4 varies with concn (s, 1 H, OH)
2		Mp 81–82°; ir 3615, 3440 cm^{-1}(OH), 2090 cm^{-1} (C–D); ^{1}H nmr δ 0.82 (s, 9 H, *tert*-butyl), 2–4 varies with concn (s, 1 H, OH)
3		Mp 88–89° (lit.[c] mp 89.4–90°); ir 1601, 1165, 1180 cm^{-1} (tosylate); ^{1}H nmr δ 0.80 (s, 9 H, *tert*-butyl), 2.38 (s, 3 H, benzylic), 3.92–4.26 (m, 1 H, H–C–O–), 7.00–7.67 (m, 4 H, aryl)
4		Mp 89–91°; ir 2185 cm^{-1} (C–D), 1601, 1165, 1180 cm^{-1} (tosylate); ^{1}H nmr δ 0.80 (s, 9 H, *tert*-butyl), 2.38 (s, 3 H, benzylic), 7.00–7.67 (m, 4 H, aryl)
5		Bp[d] 171–172° (737 mm); n^{25}D[d] 1.4483; ir[e] 2120–2140 cm^{-1} (C–D), 804, 818 cm^{-1}; ^{2}H nmr +5.98 ppm relative to $CDCl_3$
6		Bp[f] 170–171° (737 mm); n^{25}D[f] 1.4444; ir[e] 2140–2160 cm^{-1} (C–D), 1130 cm^{-1}; ^{2}H nmr +5.42 ppm relative to $CDCl_3$
7		Mp 72–73° (lit.[g] mp 74–75°); ir 1345, 1325, 1165 cm^{-1} (mesylate); ^{1}H nmr δ 0.82 (s, 9 H, *tert*-butyl), 2.83 (s, 3 H, –S–CH_3), 4.08–4.70 (m, 1 H, H–C–O–)
8		Mp 72–73°; ir 2165 cm^{-1} (C–D), 1345, 1325, 1165 cm^{-1} (mesylate); ^{1}H nmr δ 0.82 (s, 9 H, *tert*-butyl), 2.83 (s, 3 H, –S–CH_3)

[a] Solids were recrystallized from pentane before melting point determinations. Unless otherwise specified, ir spectra were made on a Beckman IR-10 using 0.1–0.2-g samples/ml of $CHCl_3$. ^{1}H nmr were taken on a Varian T-60 using CCl_4 as solvent. [b] Reference 2. [c] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, 77, 5562 (1955). [d] The mass spectrum of this material indicates that it is a mixture of 90% of **5** and 10% *tert*-butylcyclohexane. [e] Spectrum taken on a neat sample in a cavity cell (NaCl) with 0.1-mm path length. [f] The mass spectrum of this material indicates that it is a mixture of 97% **6** and 3% *tert*-butylcyclohexane. [g] D. S. Noyce, B. E. Johnson, and B. Weinstein, *J. Org. Chem.*, 34, 463 (1969).

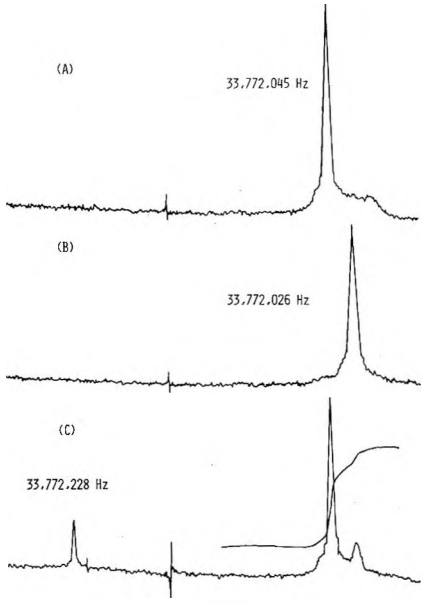


Figure 1. ^{2}H nmr spectra of (A) *trans*-4-*tert*-butylcyclohexane-*1*-d_1, (B) *cis*-4-*tert*-butylcyclohexane-*1*-d_1, and (C) Li–NH_3–EtOH reduction product of the methanesulfonate ester of *trans*-4-*tert*-butylcyclohexanol-*1*-d_1. The resonance peak at 33,772,228 Hz results from $CDCl_3$ used as an internal reference.

$AgNO_3$–SiO_2. The pentane was removed subsequently by careful distillation.

Products **5** and **6** were examined on a CEC-21-110B mass spectrometer to determine their composition and isotopic purity. The mass spectra indicate that **5** is a mixture of 90% monodeuterated *tert*-butylcyclohexane and 10% *tert*-butylcyclohexane and that **6** is a mixture of 97% monodeuterated *tert*-butylcyclohexane and 3% *tert*-butylcyclohexane.

Both **5** and **6** were examined by ir methods. A characteristic feature of **6** is a doublet of medium intensity between 2140 and 2160 cm^{-1} due to symmetric and asymmetric stretching of the equatorial C–D bond. The doublet component of lower wave number is the more intense of the two. These results are in agreement with the spectrum obtained by Glaze and Selman[6] from a product obtained by the deuterolysis of 4-*tert*-butylcyclohexyllithium and assumed by them to be **6**. This doublet also agrees with the expected absorption of equatorial C–D bonds in cyclohexane as predicted by Corey, *et al.*[7] Other identifying features of the spectrum for **6** are weak absorption at 1130 cm^{-1} and no absorption between 800 and 820 cm^{-1}.

The ir spectrum for **5** shows a doublet of moderate intensity between 2120 and 2140 cm^{-1} with the component of higher wave number being the more intense. Two moderately strong absorptions occur at 804 and 818 cm^{-1}, respectively. No characteristic absorptions were noted for **5** between 1100 and 1140 cm^{-1}.

To ensure that the ir absorptions selected for identifying **5** and **6** did not arise from *tert*-butylcyclohexane, its spectrum was taken for comparison. This spectrum confirms that the absorptions assigned to **5** and **6** do result in each case from the deuterated product. In summary, **5** and **6**, singly or in combination, are indicated and are differentiated readily by the presence or absence of ir absorptions in the 800–820- and 1100–1140-cm^{-1} regions.

The ^{2}H nmr spectra of both **5** and **6** were examined. Although limited examples of the use of ^{2}H nmr have appeared in the literature,[8-14] its potential has not been exploited probably because of the limited availability of equipment needed to resolve and enhance the relatively insensitive deuterium signal. It was found that ^{2}H nmr can readily distinguish both qualitatively and quantitatively between **5** and **6**. Using a Varian HR-220 and utilizing free Fourier transform techniques,[15] **5** and **6** gave broad singlets sufficiently separated for easy identification and integration. Relative to $CDCl_3$ as an internal reference, the chemical shifts of **5** and **6** were found to be +5.98 and +5.42 ppm,[16] respectively.

To substantiate that ir and ^{2}H nmr spectra could be used to follow the course of a chemical reduction, the methanesulfonate ester of *trans*-4-*tert*-butylcyclohexanol-*1*-d_1 (**8**) was prepared by allowing **2** to react with methanesulfonyl chloride in pyridine at 0°. Recrystallized **8** was reduced with a Li–NH_3–EtOH mixture according to the modified Birch reduction procedure of Wilds and Nelson.[17] Ir analysis of the isolated reduction product clearly indicated the presence of both **5** and **6**. ^{2}H nmr analysis of the product substantiated the presence of two products, and integration of the peak areas indicated that approximately 80% of the product underwent inversion while 20% retained its original configuration. The previous statement does not imply that the reduction necessarily occurs by a typical SN2 mechanism. There is some evidence that such reductions may involve intermediate carbanions and that the ratio of products reflects the ratio of pyramidal carbanions and/or their protonation rather than the stereochemistry of the process.[18,19]

In Figure 1, the ^{2}H nmr spectra of both **5** and **6** as well as the Birch reduction product are reproduced for inspection and comparison.

Acknowledgments. The author is indebted to Indiana University for use of its Varian HR-220 spectrometer and to Purdue University for use of its CEC-21-110B mass spectrometer. Thanks specifically to A. O. Clouse and A. R. Garber for their assistance in obtaining the ^{2}H spectra and to R. G. Cooks and W. O. Perry for their help with the mass spectra.

Registry No.—**1**, 21862-63-5; **2**, 30461-17-7; **3**, 7453-05-6; **4**, 53042-75-4; **5**, 53042-76-5; **6**, 17553-36-5; **7**, 18508-90-2; **8**, 53111-68-5; *tert*-butylcyclohexane, 3178-22-1; 4-*tert*-butylcyclohexanone, 98-53-3.

References and Notes

(1) Presented in part at the 1972 Fall Meeting of the Indiana Academy of Science.
(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N.Y., 1965, p 50.
(3) E. L. Eliel, R. J. L. Martin, and D. Nasipuri, *Org. Syn.*, **47**, 16 (1967).
(4) Sodium borodeuteride-d_4 (99% D) from Stohler Isotope Chemicals.
(5) Lithium aluminum deuteride-d_4 (99% D) from Stohler Isotope Chemicals.
(6) W. H. Glaze and C. M. Selman, *J. Organometal Chem.*, **11**, 3 (1968).
(7) E. J. Corey, R. A. Sneen, M. G. Dancher, R. L. Young, and R. L. Rutledge, *Chem. Ind. (London)*, 1294 (1954).
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(9) R. C. Dougherty, G. D. Norman, and J. J. Katz, *J. Amer. Chem. Soc.*, **87**, 5801 (1965).
(10) L. K. Montgomery, A. O. Clouse, A. M. Crelier, and L. E. Applegate, *J. Amer. Chem. Soc.*, **89**, 3453 (1967).
(11) R. Wylde and J. Grinaud, *C. R. Acad. Sci., Ser. C*, **271**, 597 (1970).
(12) E. Casadevall and P. Metzger, *Tetrahedron Lett.*, 4199 (1970).
(13) R. E. Santini, *Anal. Chem.*, **43**, 801 (1971).
(14) W. R. Moore, P. D. Mogolesko, and D. Traficante, *J. Amer. Chem. Soc.*, **94**, 4753 (1972).
(15) Data pertaining to the ^{2}H nmr spectra include the following: FFT, 128 scans/1.4 sec repetition rate, t_0 = 33,772,280 Hz, neat samples of approximately 200 mg.
(16) Upfield chemical shifts from $CDCl_3$ are reported as + shifts.
(17) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5360 (1953).
(18) M. Smith in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1968, p 112.
(19) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962, p 385.

Effects of Substituents on the Nucleophilic Ring Opening of Activated Cyclopropanes

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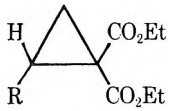
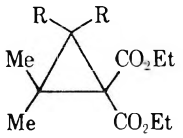
Received May 16, 1974

The propensity of suitably activated cyclopropanes to suffer ring opening upon reaction with nucleophiles has been recognized since the studies of Bone and Perkin.[1a-d] Ordinarily, this type of reaction requires two geminal activating groups.[2-4]

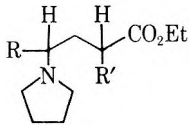
To our knowledge, there has been no systematic study of the effect of alkyl substitution on the direction or rate of opening of activated cyclopropanes. Such information could be of importance in extending this reaction to more complex synthetic objectives. Accordingly, we have prepared compounds **1**, **2**, and **3** and investigated their reactions with pyrrolidine.



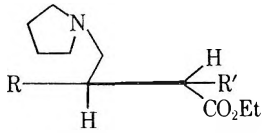
1, R = Et
4, R = CH_2=CH



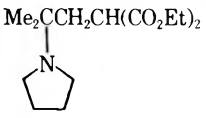
2, R = H
3, R = Me



6, R = Et; R′ = H
8, R = Et; R′ = CO_2Et
9, R = CH_2=CH; R′ = CO_2Et



5, R = Et; R′ = H
7, R = Et; R′ = CO_2Et
10, R = CH_2=CH; R′ = CO_2Et



11

Compound **1** was prepared by catalytic reduction (H_2, Pd/C) of diethyl 2-vinylcyclopropane-1,1-dicarboxylate (**4**).[5] Competing hydrogenolysis was not a problem with ethyl acetate as the solvent.[5,6] Compounds **2** and **3** were prepared by photochemically induced reactions of diethyl diazomalonate with isobutylene and tetramethylethylene, respectively, according to the procedure of Jones.[7]

Reaction of **1** with pyrrolidine at 110° for 50 hr gave a 40% yield of a mixture of four basic products. Starting **1** was recovered to the extent of 46%. The acid-soluble products, obtained in a ratio of 1:1.5:10:14.7 (analytical glc), were identified as **5**, **6**, **7**, and **8**, respectively. It seems reasonable that the decarbethoxylation reaction leading to **5** and **6** occurs after ring opening.[2]

Authentic **8** was prepared by catalytic hydrogenation of the known **9**,[8,9] obtained from the reaction of pyrrolidine with **4**. Hydrolysis, decarboxylation and reesterification converted **8** into authentic **6**. Compound **7** was obtained in pure form by regeneration from its picrate derivative, mp 113–113.5°, which was prepared by fractional crystallization from the mixture of amine picrates.

Since the mixture of **5**, **6**, **7**, and **8** was not amenable to preparative separation, the total basic fraction was subjected to hydrolysis–decarboxylation–reesterification. The resulting two-component mixture of **5** and **6** was separable by column chromatography on Florisil. Final purification of **5** was effected by preparative glc.

For the case of pyrrolidine as the nucleophile, there is a striking difference in the responses of the two cyclopropanes **1** and **4**. Thus, the vinyl compound, **4**, reacts with pyrrolidine to give exclusive substitution at the secondary carbon. No products corresponding to **10** were observed by two groups of workers.[8,9] Compound **1**, under the same circumstances, gives a 3:2 ratio of secondary (**6** + **8**); primary (**5** + **7**) modes of attack. These results can be construed as reflecting substantial dipolar character[10] in the ring opening of such activated cyclopropanes. Vinyl substitution would be expected to exert a considerably stronger directing influence due to allylic delocalization of the incipient positive charge. The finding that the rate of ring opening with pyrrolidine is very much faster[11] for **4** than for **1** is in accord with such a formulation.

Reaction of **2** with pyrrolidine occurred quite slowly. After 40 hr at 120°, a 13% yield of adduct **11** was obtained. Starting **3** was recovered to the extent of 60%. The preferential attack at the tertiary center is again consistent with carbonium ion character[10] in the transition state for ring opening. However, the overall reaction at both the primary and tertiary centers is substantially retarded relative to **1**, presumably for reasons involving steric hindrance to attack. Another factory could be the general stabilization of ring structures with increasing substitution (Thorpe–Ingold effect).[12]

Either or both of these factors may be involved in the nonreaction of **3** with pyrrolidine. After the two components were heated at 120° for 42 hr, the recovery of **3** was 76%. No basic products were detected.

Further studies into nucleophilic opening of activated cyclopropanes are in progress.

Experimental Section[13]

Diethyl 2-Ethylcyclopropane-1,1-dicarboxylate (1). This compound was prepared in quantitative yield by catalytic (10% Pd/C) hydrogenation of **4**[8,9] in ethyl acetate. Compound **1** was obtained as a free-flowing oil: bp 58–60° (0.025 mm); λ (CCl_4) 5.79, 8.30, 8.85, 9.62, 9.82 μ; τ (CCl_4) 5.86 (2 H, q, J = 7 Hz), 5.88 (2 H, q, J = 7 Hz), 7.8–9.3 (14 H, m, containing t at 8.75, J = 7 Hz); *m/e* 214 (parent), 122 (base peak).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.40. Found: C, 61.94; H, 8.60.

Reaction of 1 with Pyrrolidine. Formation of 5, 6, 7, and 8. A solution of compound **1** (2.0 g, 9.33 mmol) and pyrrolidine (1.34 g, 18.9 mmol) was heated in a Fisher borosilicate pressure bottle at 110° for 50 hr. The product was diluted with ether and extracted with 5% aqueous HCl. Evaporation of the organic fraction gave 0.92 g of essentially pure **1**.

The acidic aqueous fraction was neutralized (cautious addition of solid sodium carbonate) and extracted with ether. Evaporation gave a residue of 0.92 g of basic material. Analytical glc (5 ft, 3% SE-30 column at 160°) indicated the presence of **5**, **6**, **7**, and **8** in a ratio of 1:1.5:10:14.7 using authentic samples as described below.

The total amine mixture was dissolved in 95% ethanol and treated with a saturated solution of picric acid. After heating and slow cooling, platelets were collected which were purified by recrystallization from absolute ethanol. Regeneration of amine **7** from this picrate (see below) indicated the crystals to be the ammonium picrate corresponding to **7**.

Anal. (for picrate) Calcd for $C_{21}H_{30}N_4O_{11}$: C, 49.02; H, 5.88; N, 10.89. Found: C, 48.76; 5.81; N, 10.80.

A suspension of this picrate in ether was shaken with dilute aqueous sodium acetate. The ether solution was dried and concentrated *in vacuo* to afford a residue of pure **7**: λ (CCl_4) 3.56, 5.71 (sh), 5.77 μ; τ (CCl_4) 5.87 (2 H, q, J = 7 Hz), 5.89 (2 H, q, J = 7 Hz), 6.58 (1 H, d, J = 7 Hz), 7.2–9.2 (14 H, m, containing t at 8.75, J = 7 Hz); *m/e* 285 (parent), 112 (base peak).

Purification 5 and 6. To 5 ml of 10% aqueous HCl was added 1.55 g of the crude amine mixture described above. The solution was heated under reflux for 3 hr and maintained at room temperature overnight. The solution was neutralized with aqueous KOH and the water removed *in vacuo*. The residue was thoroughly

triturated with methylene chloride. Evaporation of the methylene chloride left a residue of 1.34 g. This was heated at 170° until cessation of gas evolution (~30 min). The crude mixture of amino monoacids (1.0 g) was dissolved in 10 ml of absolute ethanol, saturated with HCl, and heated under reflux overnight. Neutralization with aqueous KOH followed by extraction with ether gave 0.70 g (62%) of amino ester mixture **5** and **6**.

Chromatography of 250 mg of this mixture on 10 g of Florisil gave 27 mg of essentially pure **5** (eluted with 1:1 ether–hexane): λ (CCl_4) 3.58, 5.78, 8.50, 9.66 μ; τ (CCl_4) 5.97 (2 H, q, J = 7 Hz), 7.3–9.4 (21 H, m, containing t at 8.77, J = 7 Hz); m/e 213 (parent), 84 (base peak).

Further elution with ether provided 63 mg of pure **6**, whose infrared, nmr, and mass spectra were identical with those of the same compound when obtained from pure **8** (see below).

Preparation of Pure Amino Diester 8 by Hydrogenation of 9. A solution of 1.003 g (3.53 mmol) of 9[8,9] in ethanol was hydrogenated at atmospheric pressure with an uptake of 88 ml of gas (theoretical, 82 ml) in 1 hr. Filtration and removal of the solvent at reduced pressure gave 0.992 g of **8** distilling at 80° (0.005 mm): λ (CCl_4) 3.55, 5.71, 5.76 μ; τ (CCl_4) 5.87 (4 H, q, J = 7 Hz), 6.57 (1 H, t, J = 7 Hz), 7.2–9.3 (22 H, m, containing t at 8.77, J = 7 Hz); m/e 285 (parent), 112 (base peak).

Anal. (of picrate, mp 63–64°) Calcd for $C_{21}H_{30}N_4O_{11}$: C, 49.02; H, 5.88; N, 10.89. Found: C, 49.10; H, 6.03; N, 10.75.

Conversion of 8 to 6. A solution of 460 mg (1.62 mmol) of **8** in 2 ml of 20% aqueous HCl was heated under reflux for 20 hr. The residue remaining after removal of the water *in vacuo* was heated at 170° until cessation of gas evolution. This residue of crude amino monoacid was dissolved in absolute ethanol. The solution was saturated with anhydrous HCl and heated under reflux overnight. The ethanol solution was neutralized with 20% aqueous KOH. Extraction with methylene chloride followed by evaporation afforded a residue of 161 mg of crude amino ester. Distillation *in vacuo* at 100–110° (0.005 mm) gave 80 mg (24%) of **6**: λ (CCl_4) 3.59, 5.79, 8.51 μ; τ (CCl_4) 5.95 (2 H, q, J = 7 Hz), 7.3–9.3 (21 H, m, containing q at 8.84, J = 7 Hz); m/e 213 (parent), 112 (base peak).

Preparation of Diethyl 2,2-Dimethycyclopropane-1,1-dicarboxylate (2). To a 150-ml quartz immersion type photolysis cell, equipped with a Vycor filter and a Dry Ice condenser, was added 125 ml of isobutylene (bp −6°) and 3.6 g (0.0193 mmol) of diethyl diazomalonate. The system was purged with nitrogen and attached to a bubble counter. The solution was maintained at ±5° (circulating pump using ethanol coolant cooled by Dry Ice–acetone bath) and irradiated with a Hanovia 500-W high-pressure mercury immersion lamp until cessation of gas evolution (*ca.* 5 hr). The solution was concentrated by warming to room temperature and the residue was vacuum distilled to give 3.0 g (0.014 mol, 72%) of **2** collected at 46° (0.005 mm): λ (CCl_4) 5.79, 8.1, 9.1 μ; τ (CCl_4) 5.88 (4 H, J = 7 Hz), 8.71 (3 H, s), 8.79 (11 H, s and t, J = 7 Hz); m/e 214 (parent), 122 (base peak).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.74. Found: C, 61.84; H, 8.34.

Reaction of Compound 2 with Pyrrolidine. Formation of 11. To a 100-ml glass pressure flask was added 3.0 g (14.1 mmol) of **2** and 1.0 g (14.1 mmol) of pyrrolidine. The vessel was purged with nitrogen, sealed, and heated at 120° for 40 hr. The solution was diluted with ether and extracted with 5% aqueous HCl. The organic fraction was dried and concentrated *in vacuo* to give 1.82 g (60%) of recovered **2**. The aqueous fraction was carefully made basic with solid Na_2CO_3 and extracted with ether. The ether fraction was dried and concentrated *in vacuo*. The residue was distilled at 80–87° (0.005 mm) to give 0.47 g (1.65 mmol, 13%) of **11**: λ (CCl_4) 3.53, 5.72, 5.78 μ; τ (CCl_4) 5.95 (4 H, q, J = 7 Hz), 6.40 (1 H, t, J = 6 Hz), 7.3–7.8 (4 H, m), 8.0–8.9 (12 H, m, containing t, J = 7 Hz at 8.9), 9.04 (6 H, s); m/e 285 (parent), 112 (base peak).

Anal. (of methiodide, mp 92–94°) Calcd for $C_{16}H_3NO_4I$: C, 44.97; H, 7.07. Found: C, 44.68; H, 7.31.

Formation of Diethyl Tetramethylcyclopropane-1,1-dicarboxylate (3). To a 150-ml quartz immersion type photolysis cell, equipped with a reflux condenser, was added 125 ml of tetramethylethylene and 2.0 g (10.7 mmol) of diethyl diazomalonate. The system was purged with nitrogen and attached to a bubble counter. The solution was maintained at 18° (tap water) and irradiated until cessation of gas evolution (6 hr) with a Hanovia 500-W high-pressure mercury immersion lamp. The solution was concentrated under reduced pressure and distilled to give 1.9 g (7.75 mmol, 73%) of **3**: bp 64° (0.02 mm); λ (CCl_4) 5.79, 8.15 μ; τ (CCl_4) 5.91 (4 H, q, J = 7 Hz), 8.78 (t, J = 7 Hz), and 8.79 (s) (total = 18 H; m/e 242 (parent), 227 (base peak).

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.84; H, 9.26.

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Registry No. —**1**, 16783-06-5; **2**, 16783-05-4; **3**, 53166-31-7; **4**, 7686-78-4; **5**, 53166-32-8; **6**, 53166-33-9; **7**, 53166-34-0; **7** picrate, 53166-35-1; **8**, 53166-36-2; **8** picrate, 53166-37-3; **9**, 53166-38-4; **11**, 53166-39-5; **11** methiodide, 53166-40-8; pyrrolidine, 123-75-1; isobutylene, 115-11-7; diethyl diazomalonate, 5256-74-6; tetramethylethylene, 563-79-1.

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(11) In the case of **1** 46% is recovered after 50 hr at 110°. In the case of **1** only 7% is recovered after 50 hr at 100°. However, a precise ratio for the relative rates of ring opening is complicated by the formation of decarbethoxylation products **5** and **6** from **1** and some deterioration of starting materials under these forcing conditions.
(12) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962, pp 197–202, and references therein.
(13) Boiling points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 infracord spectrophotometer. Nmr spectra were obtained from a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained from an LKB-9000 system *via* direct insertion. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Ring-Opening Reactions of 2-Benzoylcyclopropane Isocyanate

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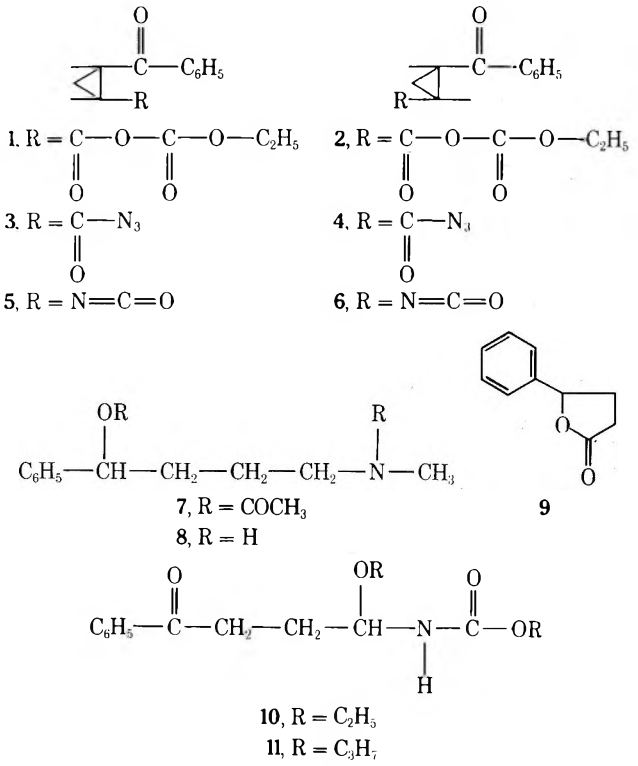
In an extension of some previous work it was felt that the mixed carbonic anhydrates of *cis*- (**1**) and *trans*-2-benzoylcyclopropanecarboxylic acid (**2**)[1] could be used to prepare the benzoylcyclopropane isocyanates, **5** and **6**. These latter materials were required as intermediates in the synthesis of the benzoylcyclopropylamines which were to serve as models for the preparation of a series of azabicyclic compounds.

The anhydrides, **1** and **2**, were smoothly converted to the isomeric carboxazides, **3** and **4**, respectively, by reaction with sodium azide. These carboxazides rearranged to give the isomeric isocyanates, **5** and **6**, on refluxing in toluene.

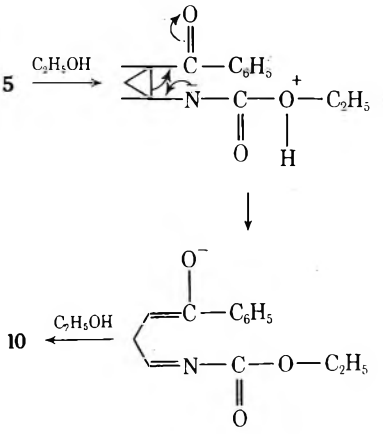
Reduction of either **5** or **6** with lithium aluminum hydride gave the same amino alcohol as shown by chromatographic and spectral comparisons of the two reduction products. The nmr spectrum of the diacetate of this compound was consistent with structure **7**, which was confirmed by direct synthesis. Reaction of phenylbutyrolactone (**9**) with methyl amine gave a hydroxyamide which on reduction with lithium aluminum hydride gave an amino alcohol, **8**, identical with that obtained on reduction of either **5** or **6**. Treatment of **8** with acetic anhydride gave **7**. This ring opening of **5** or **6** by lithium aluminum hydride was not unexpected since it had been shown previously that reaction of phenylcyclopropylamines with either lithium aluminum hydride[2] or base[3] caused ring cleavage. It was thought, though, that a phenyl substituent must be present on the cyclopropane ring in order for these reactions to occur.



However, ring opening did not occur when either 2-phenoxycyclopropyl isocyanate[4] or 2-(2′,3′-methylenedioxyphenyl)cyclopropyl carboxazide[5] were converted to the corresponding carbamates on heating in alcohol. It was considered, then, that a similar reaction should be successful in converting either the carboxazide, **3** and **4**, or the isocyanates, **5** and **6**, into the corresponding cyclopropyl carbamates. When the carboxazide, **3**, was refluxed in ethanol a carbamate was obtained but the elemental analysis indicated that two molecules of alcohol were incorporated into the product. The nmr spectrum of this carbamate showed that the cyclopropane ring was no longer present but rather that the product was **10**. This was verified by lithium aluminum hydride reduction to the amino alcohol **8**. **10** was also obtained when either **4**, **5**, or **6** was refluxed in ethanol. The propyloxy carbamate, **11**, was obtained when the azides, **3** or **4**, or the isocyanates, **5** or **6**, were refluxed in *n*-propyl alcohol.

In contrast to the previous reports of ring stability during the reactions of cyclopropyl isocyanates[5] and carboxazides[4] with alcohol, this facile ring cleavage is due to the stabilization of the ring-opened anion by the carbonyl group as shown in Scheme I.

Scheme I



Experimental Section

All melting points are uncorrected. The infrared spectra were recorded using a Beckman IR-10 spectrophotometer and the nmr spectra were obtained using a Varian A-60A spectrometer with TMS as an internal standard.

***cis*-1-Benzoyl-2-cyclopropane Isocyanate (5).** *cis*-1-Benzoyl-2-cyclopropanecarboxylic ethylcarbonic anhydride (**1**) was prepared as previously described[1] from 4.08 g of *cis*-1-benzoyl-2-cyclopropanecarboxylic acid, 2.55 g of triethylamine, and 3.0 g of ethyl chloroformate in 75 ml of acetone. **1** was not isolated but was treated directly at 0° with a solution of 2.1 g of sodium azide in 8 ml of water. The resulting suspension was stirred for 1 hr at 0° and 1 hr at room temperature and then poured into cold water and extracted with ether. The dried ethereal solution ($MgSO_4$) was concentrated under reduced pressure to give *cis*-1-**benzoyl-2-cyclopropane carboxazide, (3)**, as an oily residue: ir (toluene) 2140 cm^{-1} (CON_3).

A toluene solution of **3**, previously dried over $MgSO_4$, was slowly added to a flask heated on a steam bath. Decomposition was noted immediately with nitrogen being profusely evolved. The solution was heated until gas evolution ceased and then the toluene was removed under reduced pressure to give about 4 g of a red oil shown to be primarily **5** by its spectral properties: ir (neat) 2285 (N=C=O) and 1675 cm^{-1} (PhCO); no other carbonyl bands present.

***trans*-1-Benzoyl-2-cyclopropane isocyanate (6)** was prepared in very good yield from *trans*-1-benzoyl-2-cyclopropanecarboxylic ethylcarbonic anhydride (**2**)[1] using the procedure described for the preparation of the cis isomer, **5**: ir of **4** (toluene) 2140 cm^{-1} (CON_3).

The oil obtained from the decomposition of the carboxazide, **4**, was distilled and the product, **6**, collected at 103° (0.1 mm). Extensive decomposition occurred during the distillation. This distillate had an infrared spectrum identical with that of the crude material before distillation and was different from that of the cis isomer, **5**: ir (neat) 2280 cm^{-1} (N=C=O); nmr ($CDCl_3$) aromatic CH at δ 7.92 (m, 2) and 7.45 (m, 3) cyclopropyl CH at 3.28 (m, 1), 2.83 (m, 1), and 1.40 (m, 1).

***N*-Methyl-4-hydroxy-4-phenylbutylamine (8). Method A.** A solution of 17.0 g (0.073 mol) of **10** in 175 ml of tetrahydrofuran was added dropwise under an atmosphere of nitrogen to a suspension of 5.7 g (0.15 mol) of powdered lithium aluminum hydride in 300 ml of anhydrous ether at 0°. The reaction mixture was allowed to stir at room temperature overnight and for 3 hr at reflux. Twenty-five milliliters of water was then added dropwise and the resulting suspension was stirred for 0.5 hr and filtered. The filtrate was concentrated to an oil under reduced pressure, and the oil was dissolved in ether, dried ($MgSO_4$), and distilled to give 7.4 g (57.2%) of **8**: bp 99–108° (0.02 mm); ir (film) 3300 cm^{-1} (broad) (NH and OH).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.56; H, 9.50; N, 7.64.

8 was also obtained when **5**, **6**, or **11** was reduced with lithium aluminum hydride as described above.

Method B. Phenylbutyrolactone (**9**) was prepared according to the procedure described by Julia,[6] bp 97–98° (0.02–0.03 mm [lit,[6] bp 122° (0.1 mm)] ir (Nujol), 1780 cm^{-1} (lactone C=O). A solution

of 3.6 g (0.02 mol) of **9** in 50 ml of dry ether was saturated with gaseous methylamine in a pressure bottle and the stoppered bottle was kept at room temperature for 5 days. The solvent was removed under reduced pressure and the oily residue was dissolved in chloroform, washed with dilute hydrochloric acid and water, and then dried ($MgSO_4$). Removal of the solvent under reduced pressure left 3.0 g (67%) of *N*-methyl-4-hydroxy-4-phenylbutyramide (**12**) as an oily residue: ir (neat) 3300 (broad) (NH and OH), 1640 (amide C=O), and 1510 cm^{-1} (amide II).

A solution of 3.0 g (0.015 mol) of **12** in 50 ml of tetrahydrofuran was slowly added to a suspension of 3.8 g (0.01 mol) of powdered lithium aluminum hydride in 85 ml of tetrahydrofuran under an atmosphere of nitrogen. The reaction mixture was refluxed for 20 hr and then treated cautiously with 16 ml of water. The suspension was filtered and the filtrate was concentrated *in vacuo* to give an oily residue which was then dissolved in ether and extracted with dilute hydrochloric acid, and the acid solution was made basic with aqueous sodium bicarbonate. Extraction with ether followed by drying and removal of the solvent left an oily residue which gave an infrared spectrum and glpc identical in every respect with **8** prepared by method A.

***N*-(4-Acetoxy-4-phenylbutyl)-*N*-methylacetamide (7).** A solution of 7.0 g (0.04 mol) of **8** in 20 ml of pyridine and 25 ml of acetic anhydride was heated on a steam bath overnight. The reaction mixture was poured into water and extracted with ether. The ether solution was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, and water and then dried ($MgSO_4$). Removal of the ether under reduced pressure left 5.8 g (56%) of an oily residue: ir (neat) 1740 (ester C=O) and 1645 cm^{-1} (amide C=O); nmr ($CDCl_3$), δ 7.28 (s, 5, ArH), 5.77 (t, 1, Ph-CH), 3.28 (q, 2, CH_2-N), 2.83 (d, 3, $NHCH_3$), 2.02 (s, 3, $COCH_3$), 1.98 (s, 3, $COCH_3$), and 1.70 (m, 4, O-C-CH_2CH_2).

3-Benzoyl-1-ethoxypropylurethane, (10). A solution of 300 g of **3** was refluxed overnight in 100 ml of absolute ethanol and the excess ethanol was removed under reduced pressure. The red oily residue was extracted with three 250-ml portions of petroleum ether (30–60°) and the combined extracts were cooled in a Dry Ice–acetone bath to give the product as a pale yellow solid in 43% yield. Recrystallization from petroleum ether (60–110°) gave **10** as a white solid melting at 105–105.5°: ir ($CHCl_3$) 3440 and 3360 cm^{-1} (NH), 1720 (carbamate C=O), and 1688 (ketonic C=O); nmr ($CDCl_3$) δ 7.92 (m, 2, ArH), 7.62 (m, 3, ArH), 4.10 (q, 2, O-CH_2CH_3), 3.58 (m, 2, O-CH_2CH_3), 3.08 (t, 2, $COCH_2$), 2.08 (q, 2, CH_2), 1.20 (t, 3, O-CH_2CH_3), and 1.15 (t, 3, O-CH_2CH_3).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.49; H, 7.47; N, 5.22

Substituting compounds **4**, **5**, or **6** for **3** in the above reaction also gave **10** as the product. Yields ranged from 30 to 50%.

Propyl 3-Benzoyl-1-propoxypropyl Carbamate, (11). A solution of 30.0 g of **3** was refluxed overnight in 100 ml of propanol. The excess propanol was removed under reduced pressure at 60° (15 mm) leaving a red oil which crystallized on standing. The product was separated from an insoluble red oil by trituration with three 250-ml portions of petroleum ether (30–60°). The combined extracts were cooled in a Dry Ice–acetone bath to give a pale yellow solid in 20% yield which was recrystallized twice from petroleum ether (60–110°) to give **11** as a white solid melting at 66–67°: ir (Nujol) 3440 and 3360 (NH), 1720 (carbamate C=O), and 1688 cm^{-1} (keto C=O).

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.45; H, 8.20; N, 4.56. Found: C, 66.43; H, 8.09; N, 4.72.

The same product, **11**, was obtained, as evidenced by an identical mp and ir spectrum, when **4**, **5**, or **6** was substituted for **3** in the above reaction. Yields ranged from 20 to 40%.

Registry No.—**1**, 15982-16-8; **2**, 15982-30-6; **3**, 53166-42-0; **4**, 53166-43-1; **5**, 53166-44-2; **6**, 53166-45-3; **7**, 24316-62-9; **8**, 4266-01-7; **9**, 1008-76-0; **10**, 53166-46-4; **11**, 53166-47-5; **12**, 53166-48-6.

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Thermal [2 + 2] Cycloaddition of 1,1-Dimethoxyethene to the Carbonyl of 2-Ethoxy-3-indolone

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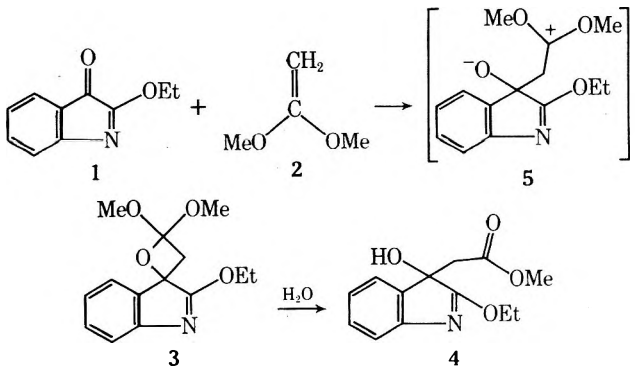
Although the photochemical [2 + 2] cycloaddition reaction of ketones and aldehydes to olefins (the Paterno–Büchi reaction) is a general reaction for the preparation of oxetanes,[1] analogous thermal cycloadditions are relatively rare. An exception is the thermal cycloadditions of cumulated systems (ketenes and ketenimines) to carbonyl compounds.[2] A few examples of thermal cycloadditions to strongly polarized ketones such as hexafluoroacetone[3] and carbonyl cyanide[4] have also appeared.

We wish to report on the thermal [2 + 2] cycloaddition of 2-ethoxy-3-indolone (**1**) to 1,1-dimethoxyethene (**2**). When a deuteriochloroform solution of **1** and **2** was heated at 40° in the probe of an nmr spectrometer for 2 hr, new peaks were observed in the nmr spectrum. The nmr absorptions (Experimental Section) indicated that the product was a [2 + 2] cycloadduct of **1** and **2**, either an oxetane or an azetidine. A solution containing the product and approximately 10% residual starting materials was then examined by infrared spectroscopy. The ir spectrum revealed that the product possessed a carbon–nitrogen double bond (1600 cm^{-1}) but not a carbon–oxygen double bond. Hence the product was assigned an oxetane structure. The regiochemistry of the cycloadduct was tentatively predicted as shown in structure **3** from the chemical shifts of the ring methylene protons, δ 2.78 and 3.29 ppm, and the polarities of the carbonyl group of **1** and the double bond of **2**. Although the cycloadduct could be separated from solvent by rotary evaporation, it was not stable to any standard methods of purification such as sublimation, glpc, or tlc.

The regiochemistry and overall structure of **3** was subsequently confirmed by a hydrolysis experiment. When a chloroform solution of **3** was extracted with water, methyl 3-(2-ethoxy-3-hydroxyindoleninyl)acetate (**4**) was isolated in 40% yield. The indoleninylacetate (**4**) was identified from OH, C=O, and C=N stretching bands at 3480, 1720, and 1625 cm^{-1}, respectively, in the ir spectrum, the nmr data reported in the Experimental Section, and a strong mass spectral parent ion at *m/e* 249. Oxetanes with regiochemistry identical with **3** from photochemical [2 + 2] cycloaddition of ketones to 1,1-diethoxyethene are similarly unstable with respect to hydrolysis.[5]



Symmetry considerations[6] suggest that this cycloaddition occurs *via* an intermediate or *via* the 2s + 2a mode. The need for a strongly polar olefin capable of stabilizing charge and the regiochemistry of the cycloaddition are consistent with initial formation of a dipolar intermediate such

as 5. 2-Ethoxy-3-indolone (1) was not thermally reactive with less polar olefins such as styrene even at higher temperatures.

Experimental Section

The nmr spectra were obtained using Varian A-60A and HA100 spectrometers, and ir spectra were recorded with a Perkin-Elmer 337 spectrophotometer. Elemental analysis was performed by Atlantic Microlabs, Atlanta, Georgia.

2-Ethoxy-3-indolone (1). 2-Ethoxy-3-indolone was prepared by the reaction of ethyl iodide with the silver salt of isatin. Silver nitrate (200 g, 1.18 mol) was dissolved in 500 ml of water and added with stirring to 128 g (1.2 mol) of sodium carbonate dissolved in 500 ml of water. The yellow precipitate was collected by suction filtration, washed with water, and dried at 140° in the dark until the weight was constant. Isatin (160 g, 1.09 mol), the dry silver carbonate (156 g, 1.13 equiv of silver), 2 g of silver nitrate and 3 l. of ethanol were placed in a 5-l. three-neck flask equipped with a mechanical stirrer and condenser and refluxed for 14 days. The silver salt of isatin was then removed by vacuum filtration and washed several times with ethanol. The salt was dried at ambient temperature under vacuum to a constant weight of 214 g. Evaporation of the ethanol washes gave 89 g (0.6 mol) of recovered isatin.

The dried silver salt (125 g) and 2 l. of chloroform were placed in a 5 l. three-neck flask equipped as above and brought to reflux for 1 hr. The mixture was cooled and 79 g (0.5 mol) of ethyl iodide was added. The reaction was stirred for 10 days at ambient temperature, the precipitate was removed by vacuum filtration through Celite, and the red chloroform filtrate was evaporated to give 29.5 g of crude 2-ethoxy-3-indolone. The precipitate collected on Celite was dried as before and allowed to react with an additional 48 g (0.3 mol) of ethyl iodide under the same conditions as described above. Work-up gave an additional 29 g of crude product. The crude material was sublimed four times at 50° (0.01 mm) to yield 32 g (38% based on isatin consumed), mp 61–62° (lit.[7] 52°). The purified 2-ethoxy-3-indolone gave the following spectral absorptions: nmr ($CDCl_3$) δ 1.49 (t, J = 7 Hz, 3 H), 4.53 (q, J = 7 Hz, 2 H), 7.01–7.42 ppm (m, 4 H); ir ($CHCl_3$) 1750 and 1600 cm^{-1}.

Thermal Reaction of 2-Ethoxy-3-indolone (1) with 1,1-Dimethoxyethene (2) in an Nmr Tube. 1,1-Dimethoxyethene (40 mg, 0.45 mmol) and 0.5 ml of deuteriochloroform were placed in an nmr tube and the 100-MHz spectrum was recorded, δ 3.06 (s, 2 H) and 3.59 ppm (s, 6 H). Then 60 mg (0.34 mmol) of 2-ethoxy-3-indolone was added to the above solution. Three minutes after the addition, the spectrum was taken and consisted simply of the sum of the spectra of 1,1-dimethoxyethene and 2-ethoxy-3-indolone. After 10 min at 40° shoulders appeared on the low-field side of each of the peaks of the methylene quartet of 2-ethoxy-3-indolone. After 30 min at 40° each peak of the methylene quartet appeared as distinct doublets, a shoulder appeared to the high-field side of the methoxy peak at 3.59 ppm, a new singlet appeared at 3.42 ppm, and an AB pattern appeared at 2.78 and 3.29 ppm (J = 12 Hz). After 2 hr in the probe of the spectrometer, these new peaks, along with the methyl triplet and aromatic proton absorptions, were the only significant peaks in the spectrum, discounting the residual 1,1-dimethoxyethene absorptions.

Thermal Reaction of 2-Ethoxy-3-indolone (1) with 1,1-Dimethoxyethene (2) Observed in an Ir Cell. 2-Ethoxy-3-indolone (120 mg, 0.68 mmol), 1,1-dimethoxyethene (60 mg, 0.68 mmol), and 0.51 ml of chloroform were placed in an nmr tube and the thermal cycloaddition was followed by nmr until the reaction reached 90% completion as judged by observation of the change in the methylene quartet pattern of the spectrum at δ 4.53 ppm. An aliquot was then withdrawn from the nmr tube and diluted to a suitable concentration with chloroform. The ir spectrum contained a small absorbance at 1650 cm^{-1} (A = 0.1) due to residual 1,1-dimethoxyethene in addition to the carbonyl absorbance at 1750 cm^{-1} (A = 0.15) and the carbon–nitrogen double bond stretching band at 1600 cm^{-1} (A = 0.80) from residual 2-ethoxy-3-indolone and the cycloadduct (3). Thus, the ratio of the absorbances in the reaction mixture (C=O:C=N) was 0.19, whereas the ratio of absorbances (C=O:C=N) was 0.45 for pure 2-ethoxy-3-indolone in chloroform solution.

Thermal Reaction of 2-Ethoxy-3-indolone (1) with 1,1-Dimethoxyethene (2). A 100-ml three-neck flask equipped with a magnetic stirrer, condenser, and nitrogen inlet was charged with 0.50 g (2.9 mmol) of 2-ethoxy-3-indolone, 0.40 g (4.5 mmol) of 1,1-dimethoxyethene, and 50 ml of chloroform. The flask was heated at 40° for 12 hr and an additional 0.40 g of 1,1-dimethoxyethene was added. After the solution was heated for an additional 12 hr, it was transferred to a separatory funnel, 50 ml of water was added, and the mixture was shaken vigorously. The organic layer was separated and dried with magnesium sulfate, and the chloroform was removed by rotary evaporation. The residue solidified and was sublimed at 110° (0.01 mm). The sublimate was then recrystallized twice from ether–petroleum ether (bp 30–40°) to give 0.28 g of white crystals (40%), mp 108–110°. The product was identified as methyl 3-(2-ethoxy-3-hydroxyindoleninyl)acetate (4) from the following spectral absorptions: nmr ($CDCl_3$) δ 1.40 (t, J = 7 Hz, 3 H), 2.83 (s, 2 H), 3.71 (s, 3 H), 4.42 (q, J = 7 Hz, 2 H), 4.55 (broad, 1 H), and 7.25 ppm (m, 4 H); ir ($CHCl_3$) 3480, 1720, 1625, and 1590 cm^{-1}; mass spectrum (70 eV) m/e 249 (41), 220 (4.9), 219 (15), 190 (6), 188 (6), 176 (21), 162 (10), 161 (14), 148 (21), 146 (base), 134 (6), 119 (8), 90 (23); (12 eV) m/e 250 (18), 249 (base).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.62; H, 6.11; N, 5.51.

Acknowledgment. The authors wish to thank the National Institutes of Health (GM-18349) and The American Cancer Society for generous support of this work.

Registry No.—1, 53153-60-9; **2,** 922-69-0; **3,** 53153-61-0; **4,** 53153-62-1; ethyl iodide, 75-03-6; isatin silver salt, 5711-07-9.

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Bis Homologation of a Naphthalene to a Dihydroheptalene *via* Carbenoid Addition[1a]

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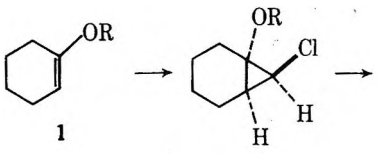
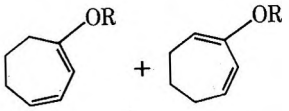
The homologation of a bicyclo[4.4.0]decane, with simultaneous enlargement of both rings to a bicyclo[5.5.0]dodecane, was first demonstrated by Anderson and Barlow[2] and subsequently was exploited by Dauben and Bertelli in their elegant synthesis of heptalene.[3] In a search for alternate approaches to heptalene derivatives, we have found that this double-ring expansion can be accomplished conveniently by a bis addition of dibromocarbene to a tetrahydronaphthalene.

Parham, *et al.*, have shown that ring enlargement of a 1-alkoxycyclohexene (1) to alkoxycycloheptadienes **3a** and **3b** occurs when the derived *endo*-chlorocyclopropane **2** is heated in the presence of pyridine.[4] The rigid requirement for the endo halide in this reaction implies firm control of the electrocyclic opening (disrotatory) of the cyclopropyl cation by orbital symmetry constraints.[5] Application of this

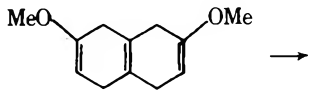


1 2



3a 3b

approach to 2,7-dimethoxy-1,4,5,8-tetrahydronaphthalene (4), prepared by Birch reduction of 2,7-dimethoxynaphthalene,[6] required selective addition of dibromocarbene to the two enol ether functions of 4, and this was achieved by the use of 2.2 equiv of bromoform in the presence of potassium *tert*-butoxide, which led to a mixture of syn (5) and anti (6) adducts in *ca.* 80% yield.[7] Mono- and tris(dibromocarbene) adducts were produced in only very minor amounts in this reaction, as determined by mass spectrometry and ascertained by thin-layer chromatography, but these were not separated.



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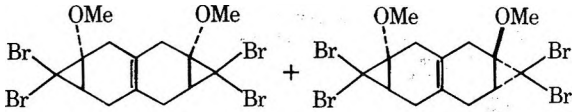
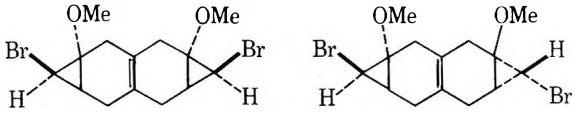


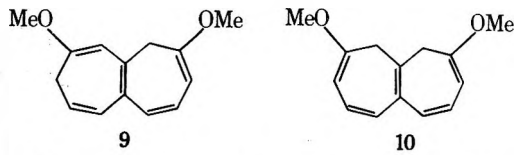
5 6

Stereoselective, reductive removal of the two exo halogens in 5 and 6 parallels similar results in related systems[4,8] and in the present case was most easily accomplished (on a 1-mmol scale) by electrolysis at a stirred mercury cathode in LiCl–DMF.[9] For larger scale reductions, transmetalation of 5 and 6 with 2 equiv of butyllithium at −78°, followed by methanolysis, proved to be the method of choice.[10] In both cases, virtually the sole products were the endo,syn,endo and endo,anti,endo dibromides (7 and 8, respectively), separable by thin-layer chromatography and characterized in each case by a coupling constant of 9 Hz between cis hydrogens on the cyclopropane rings.[11]

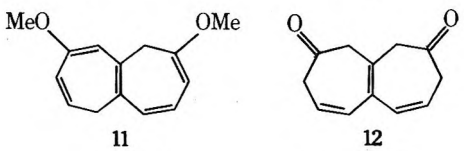


7 8

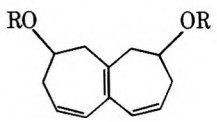
Upon heating at 100° in pyridine for 1 hr, the mixture of 7 and 8 was smoothly transformed to dihydroheptalene 9, isolated in pure form after column chromatography. In contrast, treatment of 7 and 8 with silver salts under a variety of conditions led to a large number of decomposition products.[12] Support for structure 9 comes from the uv spectrum, which reveals an extended chromophore (342 nm), and from the nmr spectrum, which shows nonequivalent methoxyl protons and six olefinic hydrogens. From the nmr data, the symmetrical dihydroheptalene 10 (but not 11) is eliminated. Gentle hydrolysis of 9 with aqueous oxalic acid gave the crystalline diketone 12, shown by ir (1710 cm^{-1}) to possess nonconjugated carbonyl groups. Although 12 is evidently the thermodynamically stable isomer, since no rearrangement to an α,β-unsaturated ketone could be induced under acidic conditions,[13] the mild hydrolysis of 9 probably does not provoke a shift of non-enol double bonds.



9 10



11 12



13, R = H
14, R = $COCH_3$

The approach described here provides a potential route to various substituted heptalenes which is under investigation. In an attempt to bring our scheme into convergence with Dauben and Bertelli's synthesis of the parent heptalene,[3] 12 was reduced with sodium borohydride to diol 13 which was converted to diacetate 14. However, neither dehydration of 13 nor pyrolysis of the surprisingly stable 14 produced useful quantities of dihydroheptalene.

Experimental Section

Mass spectra were determined on an AEI MS-9 double-focusing spectrometer, using a standard ionizing potential of 70 eV. All compounds subjected to mass spectrometric molecular weight determination were of high purity, as determined by nmr analysis and by homogeneity in thin-layer chromatography where applicable. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates T-60 or HA-100 spectrometer, in either the frequency sweep or Fourier transform mode. Absorptions are reported relative to an internal tetramethylsilane standard (0.00 ppm). Infrared spectra were obtained on a Perkin-Elmer Model 137, 237, or 457 spectrophotometer, and ultraviolet spectra were determined on a Cary Model 14 spectrometer. Elemental analysis was performed by Dr. Susan Rottschaefer, Department of Chemistry, University of Oregon. Melting points were determined on a Kofler hot-stage microscope, and all melting points and other temperatures are reported in degrees Celsius (uncorrected).

2,7-Dimethoxy-1,4,5,8-tetrahydronaphthalene (4). To a solution of 15 g (0.077 mol) of 2,7-dimethoxynaphthalene (mp 137–138°) in 400 ml of anhydrous *tert*-butyl alcohol, 400 ml of anhydrous THF, and 1 l. of liquid ammonia was added lithium wire (22 g, 3.1 mg-atoms) in small amounts over a 40-min period. The dark blue solution was stirred for 8 hr, after which the reaction was quenched with 400 ml of methanol. One liter of water was added, and the aqueous layer was extracted three times with methylene chloride. The combined methylene chloride washings were washed twice with water and once with saturated NaCl solution. Evaporation of solvent followed by crystallization of the residue from methanol at −40° gave 12.9 g (0.066 mol, 87%) of 4, mp 61–62° (lit.[6] mp 69–69.5°): ir (KBr) 1012, 1152, 1221, 1373, 1458, 1680, 1725 cm^{-1}; nmr ($CDCl_3$) δ 2.58 (8 H, s), 3.52 (6 H, s), 4.60 (2 H, s).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.26; H, 8.35.

1,5-Dimethoxy-6,6,12,12-tetrabromotetracyclo[9.1.0^{3,9}.0^{5,7}]-dodec-3(9)-ene (5 and 6). A solution of 0.38 g (1.9 mmol) of 4 and 0.77 g (8.0 mmol) of potassium *tert*-butoxide in 16 ml of benzene and 10 ml of *tert*-butyl alcohol was cooled to 0°, and a solution of 0.7 ml (2.0 g, 8.0 mmol) of bromoform in 6 ml of benzene was added with stirring over a 0.5-hr period. The solution was then stirred for 1 additional hr at 0°. Approximately 20 ml of water and 20 ml of diethyl ether were added, and the layers were separated. The aqueous layer was extracted several times with ether, and the ether layers were combined, washed with water, dried over $MgSO_4$, and evaporated to yield 0.95 g of the crude tetrabromide. A rapid column chromatography (activity II alumina, eluted with methy-

lene chloride) afforded 0.8 g (1.5 mmol) of **5** and **6** as a clear, light yellow oil. Precipitation from chloroform–hexane gave 0.6 g (1.1 mmol, 58%) of **5** and **6** as an amorphous yellow solid: ir (film) 570, 663, 754, 863, 980, 1030, 1115, 1157, 1207, 1220, 1258, 1383, 1428, 1608, 1677, 1692, 1710, 2830, 2885, 2935, 2995 cm^{-1}; nmr ($CDCl_3$) δ 1.7–2.8 (10 H, m), 3.50 (6 H, s); mass spectrum *m/e* 536 (parent, pentuplet of spacing 2 mass units).

1,5-Dimethoxy-6,12-dibromotetracyclo[9.1.0^{3,9}.0^{5,7}]dodec-3(9)-ene (7 and 8). A. Electrochemical Reduction. A three-compartment electrolysis cell was constructed from a vigorously stirred mercury pool cathode, a platinum gauze anode, a catholyte consisting of 30 ml of 1.0 *N* LiCl in 96% DMF–4% water, and anolyte consisting of 4 ml of 1.0 *N* LiCl in 86% DMF–4% water–10% hydrazine, and a Ag–AgCl standard reference electrode. The cathode and anode chambers were separated by a fine-porosity fritted disk, and the standard electrode was isolated by a cracked-glass tube filled with the catholyte solution. All solutions were deoxygenated using argon, and argon was bubbled through the cell continuously during the electrolysis. The cell was positioned in an ice bath and operated for 15 min at a cathode potential of −2.00 V with respect to the reference electrode. A solution of 265 mg (0.5 mmol) of **5** and **6** in 4 ml of DMF was then added, and electrolysis was allowed to proceed (*ca.* 0.75 hr) until the cell current approached the previously determined background current of *ca.* 10 mA. The catholyte was poured into a mixture of 100 ml each of water and pentane, and the pentane layer was washed with water and evaporated to give 190 mg (0.5 mol, 100%) of **7** and **8**.

B. *Via* Halogen–Metal Exchange. A solution of 265 mg (0.5 mmol) of tetrabromides **5** and **6** in 2 ml of THF was cooled to −80° and treated with 0.7 ml (1.1 mmol) of *n*-butyllithium (Foote, 1.6 *N*). The mixture was stirred at −80° for 15 min and then quenched by the addition of 0.5 ml of methanol. Approximately 10 ml each of ether and water were added, and the ether layer was washed, dried over $MgSO_4$, and evaporated to yield crude dibromide. Preparative-layer chromatography (silica gel, eluted with $CHCl_3$) yielded 160 mg (0.42 mmol, 85%) of **7** and **8**: ir ($CDCl_3$) 605, 870, 1032, 1044, 1147, 1197, 1230, 1326, 1357, 1397, 1430, 1720, 2833, 2905, 2950, 3005, 3050, 3070 cm^{-1}; nmr ($CDCl_3$) δ 1.60 (2, H, d, J = 9 Hz), 1.65 (2 H, d, J = 9 Hz), 1.92 (2 H, s), 2.44 (6 H, broad s), 3.42 (6 H, s); mass spectrum *m/e* 377 (parent, triplet of spacing 2 mass units). This material was identical in all respects with the two dibromides prepared by method A above.

2,9-Dimethoxy-1,8-dihyroheptalene (9). A solution of 2.62 g (6.93 mmol) of **7** and **8** in 50 ml of anhydrous pyridine was stirred for 1 hr at 100°. The mixture was evaporated *in vacuo*, and the residue was taken up into ether, washed with 1 *N* $CuSO_4$ solution, dried over $MgSO_4$, and evaporated to yield 0.9 g of crude pyrolysate. Column chromatography (silica gel, eluted with $CHCl_3$) gave 0.53 g (2.46 mmol, 28%) of pure **9**: ir 1020, 1170, 1204, 1225, 1268, 1423, 1544, 1620, 2840, 2963, 3010 cm^{-1}; nmr ($CDCl_3$) δ 2.50 (2 H, d, J = 7 Hz), 2.67 (2 H, s), 3.55 (3 H, s), 3.71 (3 H, s), 5.1–6.5 (6 H, m); uv (EtOH) λ_{max} 342 nm (ϵ 6000); mass spectrum *m/e* 216.114 (parent, calcd for $C_{14}H_{16}O_2$ 216.115).

Bicyclo[5.5.0]dodeca-1,9,11-triene-4,7-dione (12). A solution of 100 mg of **9** in 3 ml of acetone, 0.6 ml of water, and 0.3 ml of concentrated hydrochloric acid was stirred for 25 min at room temperature. The reaction mixture was poured into saturated $NaHCO_3$ solution, which was extracted three times with ether. The ether layers were combined, washed with water, dried over $MgSO_4$, and evaporated to yield 86 mg (0.46 mmol, 100%) of nearly pure **12**. Recrystallization from EtOH–water gave 81 mg (0.43 mmol, 93%) of **12**, mp 107–109°: ir 790, 972, 1143, 1188, 1240, 1405, 1574, 1707, 2920, 3015, 3400 cm^{-1}; nmr ($CDCl_3$) δ 3.06 (4 H, d, J = 6 Hz), 3.26 (4 H, s), 5.89 (2 H, d of t, J = 5.5, 6 Hz), 6.33 (2 H, d, J = 11 Hz); uv (EtOH) showed end absorption only; mass spectrum *m/e* 188.085 (parent, calcd for $C_{12}H_{12}O_2$ 188.084).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.21; H, 6.37.

Bicyclo[5.5.0]dodeca-1,9,11-triene-4,7-diol (13). A solution of 130 mg (0.69 mmol) of **12** and 50 mg (1.3 mmol) of sodium borohydride in 10 ml of anhydrous EtOH was stirred for 1 hr at 0°. The reaction mixture was poured into water and extracted three times with ether. The combined ether layers were washed with water, dried over $MgSO_4$, and evaporated to yield 125 mg of crude diol. Preparative-layer chromatography gave 110 mg (0.58 mmol, 84%) of pure **13**: ir ($CDCl_3$) 910, 1018, 1082, 1262, 1444, 2910, 2950, 3005, 3440, 3608 cm^{-1}; nmr ($CDCl_3$) δ 2.01 (2 H, broad s), 2.2–2.5 (2 H, m), 2.51 (4 H, d, J = 6 Hz), 4.39 (2 H, quintet, J = 6 Hz), 5.89 (4 H, s); mass spectrum *m/e* 192.118 (parent, calcd for $C_{12}H_{16}O_2$ 192.115).

Bicyclo[5.5.0]dodeca-1,9,11-triene-4,7-diacetate (14). A solution of 20 mg (0.104 mmol) of **13**, 75 mg of acetic anhydride, and 135 mg of 4-(*N*,*N*-dimethylamino)pyridine in 2 ml of CH_2Cl_2 was stirred for 15 min at room temperature. The reaction mixture was cooled to 0°, 0.5 ml of methanol was added, and all volatiles were evaporated. The residue was taken up into ether, which was washed with 2 *N* HCl and then with saturated $NaHCO_3$ solution. The ethereal solution was dried over $MgSO_4$ and evaporated to give 27 mg (0.98 mmol, 94%) of pure **14**: ir ($CHCl_3$) 1022, 1100, 1260, 1378, 1443, 1734, 2962 cm^{-1}; nmr ($CDCl_3$) δ 2.04 (6 H, s), 2.1–2.4 (4 H, m), 2.49 (4 H, d, J = 6 Hz), 5.28 (2 H, m), 5.89 (4 H, d, J = 2 Hz); mass spectrum *m/e* 276 (parent), 216 (loss of HOAc), 156 (base peak, loss of 2 HOAc).

Acknowledgment. We are grateful to Professor David Dolphin for assistance with electrochemical aspects of this work and to Professor Weston Borden for helpful discussions.

Registry No.—**4**, 1614-82-0; **5**, 53165-97-2; **6**, 53187-74-9; **7**, 53165-98-3; **8**, 53187-75-0; **9**, 53165-99-4; **12**, 53166-00-0; **13**, 53166-01-1; **14**, 53166-02-2; 2,7-dimethoxynaphthalene, 3469-26-9.

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A New Fragmentation Reaction and Its Application to the Synthesis of (±)-Grandisol

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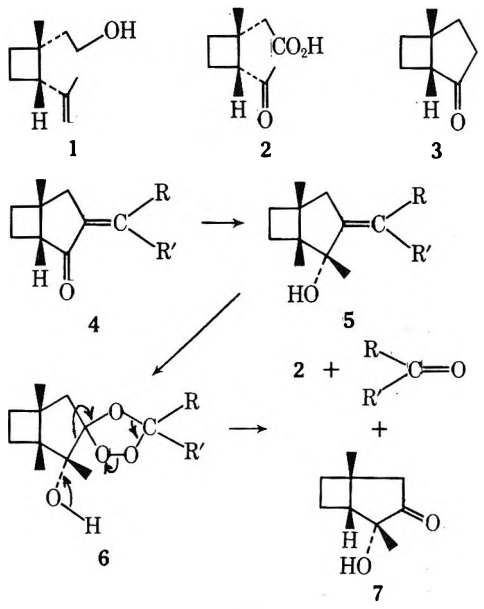
Grandisol (**1**), a component of the pheromone released by the male boll weevil, *Anthonomus grandis* Boehman,[1] has been synthesized by a variety of routes.[2] We report here a convenient synthesis of racemic **1** that involves a novel fragmentation of an ozonide.

Condensation of **3** with benzaldehyde, furfural, or acetone provided an alkylidine derivative **4**. Reaction of **4** with methyllithium yielded the corresponding tertiary alcohol **5**. Ozonolysis of **5** at −70° in methylene chloride followed by decomposition of the presumed ozonide **6** in aqueous sodium bicarbonate gave keto acid **2** in an overall yield of 40–50% from **3**. Conversion of **2** into **1** has been reported.[2]

Although all three alkylidine derivatives **5a–c** gave **2** in acceptable yields, **5c** is the preferred intermediate. Ozonol-



a, R = Ph; R′ = H
b, R = Fu; R′ = H
c, R = R′ = CH_3

ysis decomposition of **5a** always gave some benzoic acid whose separation from **2** was difficult. Neither of the furfurylidine compounds **4b** or **5b** was obtained sufficiently pure for complete characterization, but **5b** was converted cleanly into **2**. In one case, when decomposition of ozonide **6c** was carried out at *ca.* 25°, keto acid **2** was obtained in only 34% yield, and it was accompanied by the "normal" ozonolysis product **7**.

Decomposition of the ozonide **6** presumably occurs *via* the electronic change indicated. This fragmentation[3] provides a convenient method for the cleavage of ketones (as the derived alcohols) between the carbonyl carbon and an adjacent methylene group.[4]

Experimental Section[5]

5-Methylbicyclo[3.2.0]heptan-2-one (3). A solution of 9.96 g (104 mmol) of 3-methylcyclopentenone in 250 ml of reagent grade methylene chloride was irradiated (Pyrex) with a 450-W mercury arc at −70° with a continuous flow of ethylene (Matheson CP) through the solution. The Pyrex probe was cooled by circulating ethanol (cooled to −70°) through it, and the vessel was suspended in a Dewar flask containing a −70° bath. Reaction progress was followed by vpc (10% Carbowax 1000, 8 ft × 0.25 in., 135°). The addition was complete in 29 hr. The vessel was allowed to warm to room temperature in a hood so that the excess ethylene could escape. Removal of solvent yielded 10.16 g (85%) of **3**: bp 88–90° (36 Torr); ir (CCl_4) 1735 cm^{-1} (C=O); nmr (CCl_4) δ 1.25 ppm (s, 3, CH_3).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74, Found: C, 77.19; H, 9.76.

3-Benzylidene-5-methylbicyclo[3.2.0]heptan-2-one (4a). To a solution of 6.19 g (50 mmol) of **3** in 75 ml of 95% ethanol was added 8 ml of freshly distilled benzaldehyde, then 2 ml of 15% NaOH solution. The flask was stoppered and the mixture was stirred overnight. The solvent was removed *in vacuo* the residue dissolved in ether, and the resulting solution was washed with saturated sodium *m*-bisulfite solution. After the ethereal solution was dried ($MgSO_4$) and filtered, the solvent was removed leaving a yellow solid. Recrystallization from hexane yielded 8.06 g (76%) of **4a**: mp 72–73°; ir (CCl_4) 1695 cm^{-1} (C=O); nmr (CCl_4) δ 1.36 (s, 3, CH_3), 7.5–7.0 ppm (m, 6, vinyl and aromatic).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.74; H, 7.61.

3-Furfurylidene-5-methylbicyclo[3.2.0]heptan-2-one (4b) was prepared from **3** as described for the preparation of **4a** except that freshly distilled furfural was substituted for benzaldehyde. The yield of **4b**, a yellow oil, was 72%: ir (CCl_4) 1700 cm^{-1} (C=O); nmr (CCl_4) δ 1.38 (s, 3, CH_3), 6.42 (d of d, 1, $J_{4'5'}$ = 2 Hz, $J_{3'4'}$ = 3 Hz, 4′-H), 6.57 (d, 1, $J_{3'4'}$ = 3 Hz, 3′-H), 7.08 (t, 1, J = 3 Hz, vinyl), and 7.47 ppm (d, 1, $J_{4'5'}$ = 2 Hz, 5′-H); mass spectrum (70 eV) *m/e* 202 (M^+).

3-Isopropylidene-5-methylbicyclo[3.2.0]heptan-2-one (4c). A dry 250-ml round-bottomed flask, flushed with nitrogen, and equipped with a reflux condenser and a magnetic stirrer was charged with 50 ml of dry methanol (commercial absolute methanol distilled from magnesium). To the methanol was added 2 g (87 mg-atoms) of sodium. When the solution had cooled, the mixture was further cooled to −10°. To the stirred solution was added 2.35 g (18.9 mmol) of **3** in 25 ml of reagent grade acetone. The mixture was stirred at −10° for 48 hr, and then stirred at room temperature for 12 hr. The dark brown solution was poured into 75 ml of water and acidified with concentrated HCl. The resulting solution was extracted four times with 50-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and concentrated. Fractional distillation at aspirator pressure (removal of acetone and mesityl oxide) and then at vacuum pump pressure yielded 2.39 g (77%) of **4c**: bp 80–85° (1.25 Torr); ir (CCl_4) 1700 (C=O), 1625 cm^{-1} (C=C); nmr (CCl_4) δ 1.30 (s, 3, CH_3), 1.83 (m, 3, CH_3C=C), 2.20 ppm (m, 3, CH_3C=C).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44, H, 9.83. Found: C, 80.59; H, 9.86.

2,5-Dimethyl-3-benzylidenebicyclo[3,2.0]heptan-2-ol (5a). A solution of 7.21 g (34 mmol) of **4a** in 50 ml of dry ether was prepared in a 250-ml round-bottomed flask equipped with a magnetic stirrer. A few milligrams of *o*-phenanthroline was added to act as an indicator for excess alkyllithium. A solution of 2.0 *M* methyllithium in ether was added to the above solution until an excess of methyllithium was indicated by the dark brown color of the solution. The flask was stoppered and the solution was stirred for 2 hr. Water was added dropwise to the dark brown solution until the dark color faded and then a further 50-ml portion of water was added. The layers were separated, the aqueous phase extracted with 25 ml of ether, and the ether layers were combined. The ethereal solution was dried ($MgSO_4$) and concentrated and the crude product was chromatographed on 150 g of Alcoa F-20 alumina (hexane) yielding 7.99 g (100%) of **5a** as a yellow oil: nmr (CCl_4) δ 1.25 (s, 3, CH_3) 1.32 (s, 3, CH_3-COH), 6.56 (m, 1, vinyl), and 7.25 ppm (m, 5, aromatic).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.34; H, 8.69.

2,5-Dimethyl-3-furfurylidenebicyclo[3.2.0]heptan-2-ol (5b) was prepared as described above for the preparation of **5a**. The yield of **5b**, a yellow oil, was 90%: nmr ($CDCl_3$) δ 1.22 (s, 3, CH_3), 1.28 (s, 3, CH_3COH), 2.10 (b, s, 1, OH), 6.15 (d, 1, $J_{3'4'}$ = 3 Hz, 3′-H), 6.40 (m, 2,4′-H and vinyl), and 7.30 ppm (d, 1, $J_{4'5'}$ = 2 Hz, 5′-H); mass spectrum (70 eV) *m/e* 218 (M^+).

2,5-Dimethyl-3-isopropylidenebicyclo[3.2.0]heptan-2-ol (5c) was prepared from **4c** as described above for the preparation of **5a**. The yield of **5c**, mp 64–65° (recrystallized from pentane), was 85%: nmr (CCl_4) δ 1.18 (s, 3, CH_3), 1.24 (s, 3, CH_3COH), 1.65 (s, 3, CH_3C=C), 1.91 ppm (s, 3, CH_3C=C).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.71; H, 10.94.

General Procedure for Ozonolysis of the Alcohols 5a–c. The alcohol was dissolved in ethyl acetate (50 ml for each 5 g of alcohol) and cooled to −70°. Ozone (about 2% in oxygen) was bubbled through the cold solution until the solution turned a bright blue color, indicating that an excess of ozone was present. The solution was allowed to warm to near room temperature and the solvent was removed by use of a rotary evaporator. (The flask containing the solution was not heated in any way as the solvent was removed.) Then, 25 ml of saturated aqueous $NaHCO_3$ was added for each 5 g of alcohol used. The mixture was stirred overnight, washed with ether, acidified, saturated with salt, and extracted with ether. The ether extract of the acidic solution was dried ($MgSO_4$) and filtered, and the ether was removed leaving the crude keto acid **2**: ir ($CDCl_3$) 1730 (acid C=O), 1710 cm^{-1} (ketone C=O); nmr ($CDCl_3$) δ 1.40 (s, 3, CH_3), 2.09 (s, 3, CH_3C=O), 2.47 (s, 2, CH_2COOH), and 8.6 ppm (COOH).

(A) ozonolysis following the above procedure of 4.91 g (22 mmol) of **5a** in 50 ml of ethyl acetate yielded 3.06 g of a yellow oil. Nmr analysis of this oil showed it to be a mixture of 13 mol % benzoic acid and 87 mol % **2** (78% yield).

(B) Ozonolysis as above of 5.15 g (23.5 mmol) of **5b** in 50 ml of ethyl acetate yielded the desired keto acid **2** in 72% yield.

(C) Ozonolysis of 1.06 g (6 mmol) of **5c** in 25 ml of ethyl acetate as above gave keto acid **2** in 71% yield. In this case it is imperative that the temperature of the ozonide be kept below 10–20°. In an

experiment using 2.56 g (14.2 mmol) of **5c** in which the ozonide was allowed to warm to *ca.* 25° the yield of **2** was reduced to 0.87 g (34%). Examination of the ether wash of the basic aqueous solution yielded 0.75 g of a keto alcohol identified as **7**: mp 53–54°; ir (CCl_4) 1745 cm^{-1} (C=O); nmr (CCl_4) δ 1.16 (s, 3, CH_3), 1.33 (s, 3, CH_3COH), and 2.85 ppm (s, 1, OH); mass spectrum (70 eV) *m/e* 154 (M^+).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.31; H, 9.23.

Registry No.—(±)-**1**, 28117-21-7; **2**, 53166-10-2; **3**, 50459-35-3; **4a**, 53166-11-3; **4b**, 53166-12-4; **4c**, 53166-13-5; **5a**, 53166-14-6; **5b**, 53166-15-7; **5c**, 53166-16-8; **7**, 53166-17-9; methyllithium, 917-54-4; 3-methylcyclopentenone, 2758-18-1; ethylene, 74-85-1; benzaldehyde, 100-52-7; furfural, 98-01-1; acetone, 67-64-1.

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(3) For a review of fragmentation reactions see (a) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967); (b) J. A. Marshall and J. L. Belletire, *Tetrahedron Lett.*, 871 (1971).

(4) The conversion, **3** → **2** *via* **4** and **5**, may be viewed as being catalyzed by the carbonyl reagent (benzaldehyde, *etc.*).

(5) Microanalyses were performed by Afred Bernhardt, Microanalytisches Laboratorium, Elbach über Engelskirchen, Mülheim (Ruhr), West Germany.

Synthesis of 2,5-Dihydroxy-2,5-dihydrofurans by Anodic Oxidation of Furans

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During synthetic work on *Lactarius* sesquiterpenes, we needed an efficient method of converting furans into maleic acid derivatives. Hydrolysis of 2,5-dimethoxy-2,5-dihydrofurans[1] followed by Jones oxidation[2] gave only a low yield of anhydride, partly because of the formation of lactones and polymeric material in the hydrolysis step.[3] Direct oxidation of the 2,5-dimethoxy-2,5-dihydrofurans with Jones reagent[2] according to Marei and Raphael[4] gave the desired maleic acid derivative but with significant amounts of γ-methoxy-α, β-unsaturated γ-lactones (up to 35%) and polymeric material.

In order to avoid the hydrolysis step we examined the oxidation of 2,5-dihydroxy-2,5-dihydrofurans to maleic anhydrides. Remarkably, no preparative route to this type of compound has been reported other than a hydroxylation of furan with osmium tetroxide–hydrogen peroxide to 2,5-dihydroxy-2,5-dihydrofuran which was obtained only as the corresponding bis(phenylhydrazone).[5] We now wish to report a preparatively useful route to 2,5-dihydroxy-2,5-dihydrofurans by anodic oxidation of furans. Table I shows the results obtained.

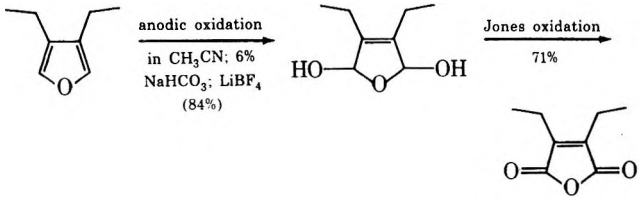
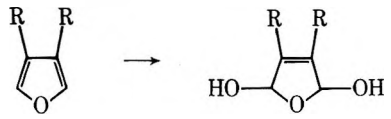
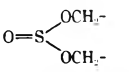
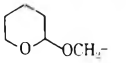


Table I
Anodic Oxidations



Starting material	R	Product	Yield, %	Current yield, %
1[a]	CH_3CH_2-	8	84	100
2		9	78	87
3[6]	CH_3COOCH_3-	10	86	100
4[7]		11	77	75
5[8]	Cl-CH_2-	12	*ca.* 70[b]	90
6	H-		*c*	
7[6]	CH_3CH_2OOC-		*d*	

[a] Peak potential relative to saturated calomel electrode: E_p = 1.62 V (cyclic voltammetry in MeCN). [b] **12** was unstable and decomposed on SiO_2 chromatography. EtOAc extraction gave a fairly pure crude product: nmr ($CDCl_3$) δ 6.00, 5.74 (s, 2, HO-CH), 4.30 (s, 4, Cl-CH_2). [c] Low yield of undefined material. [d] No reaction.

The electrolysis product (**8**) is conveniently oxidized further to anhydride by standard Jones oxidation.

Experimental Section

3,4-Diethylfuran (**1**). Methyllithium in ether (0.36 mol) was added to cuprous iodide (14.5 g, 0.165 mol) in ether (100 ml) at 0°. 3,4-Bis(chloromethyl)furan[8] (**5**) (6.9 g, 0.056 mol) in ether (50 ml) was added dropwise at 0° with stirring (continued for 12 hr).[9] Addition of water (300 ml), extraction with ether, drying (Na_2SO_4), and distillation gave 3,4-diethylfuran (**1**) (3.65 g, 70%): bp 39–40° (11 mm); $n^{21}D$ 1.4500; ir (neat) 3160, 1555, 1475, 1060, 887, 805 cm^{-1}; nmr ($CDCl_3$) δ 7.13 (s, 2), 2.36 (q, 4, J = 7.5 Hz), 1.17 (t, 6, J = 7.5 Hz).

Anal. Calcd for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.4; H, 9.8.

2-Oxofuro[5,6-c]-1,3,2-dioxathiepane (**2**). 3,4-Bis(hydroxymethyl)furan[8] (25.6 g, 0.2 mol) and triethylamine (40.4 g; 0.4 mol) were dissolved in dry methylene chloride (400 ml). Thionyl chloride (47.2 g, 0.4 mol) in methylene chloride (130 ml) was added dropwise at 0° with stirring (continued for 30 min) (*cf.* ref 10). The reaction mixture was poured into cold water (300 ml) and the methylene chloride phase was separated. Drying (Na_2SO_4), evaporation, and distillation gave 3,4-bis(chloromethyl)furan (**5**)[8] (1.5 g, 5%) and 2-oxofuro[5,6-c]-1,3,2-dioxathiepane (**2**) (17.0 g, 49%): bp 56–57° (0.2 mm); $n^{23}D$ 1.5210; ir (neat) 3140, 1565, 1460, 1185, 1053, 885, 813 cm^{-1}; nmr ($CDCl_3$) δ 7.35 (s, 2), 5.72, 4.56 (AB q, 4, J = 14.0 Hz).

Anal. Calcd for $C_6H_6SO_4$: C, 41.4; H, 3.5; S, 18.4. Found: C, 41.5; H, 3.5; S, 18.2.

General Hydroxylation Procedure. The anodic oxidation was performed at constant current (100 mA) in a water-jacketed beaker (100 ml) equipped with magnetic stirrer, Pt anode (120 × 40 × 0.1 mm) and Ni cathode (helical wire, 400 × 1.6 mm). The furan (*ca.* 5 mmol) was dissolved in acetonitrile (50 ml) and saturated sodium bicarbonate solution (3 ml) was added together with lithium tetrafluoroborate (*ca.* 10 mg as supporting electrolyte). After complete oxidation of the furan (tlc: SiO_2/CH_2Cl_2) the reaction mixture was evaporated and the residue chromatographed (35 g SiO_2/EtOAc) to give a mixture of *cis*- and *trans*-2,5-dihydroxy-2,5-dihydrofurans.

3,4-Diethyl-2,5-dihydroxy-2,5-dihydrofuran (**8**): yield, 84%; $n^{21}D$ 1.4889; ir (neat) 3400 cm^{-1}; nmr ($CDCl_3$) δ 6.05, 5.71 (s, broad, 2, HO-CH), 2.20 (q, broad, 4, J = 8.0 Hz), 1.06 (t, broad, 6, J = 8.0 Hz).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found C, 60.9; H, 8.2.

2-Oxo-(2,5-dihydroxy-2,5-dihydrofuro)[5,6-c]-1,3,2-dioxathiepane (**9**): yield, 78%; $n^{23}D$ 1.5180; ir (neat) 3400, 1200 cm^{-1}; nmr (D_2O; sodium 4,4-dimethyl-4-silapentane-1-sulfonate[11]) 6.11, 5.82 (s, 2, HO-CH), 4.45–5.50 (m, 4, CH_2) ppm.

Anal. Calcd for $C_6H_8SO_6$: C, 34.6; H, 3.9. Found: C, 35.0; H, 4.1.

3,4-Bis(acetoxymethyl)-2,5-dihydroxy-2,5-dihydrofuran (10): yield, 86%; n^{27}D 1.4831; ir (neat) 3440, 1740 cm^{-1}; nmr (acetone)d_6) δ 5.60–6.15 (mm 2, HO–CH), 4.96, 4.60 (AB q, broad, 4, J = 13.0 Hz, CH_2), 2.04 (s, 6; CH_3).

Anal. Calcd for $C_{10}H_{14}O_7$: C, 48.8; H, 5.7. Found: C, 49.2; H, 5.7.

3,4-Bis[(2-tetrahydropyranyl)oxymethyl]-2,5-dihydroxy-2,5-dihydrofuran (11): yield, 77%; n^{23}D 1.4938; ir (neat) 3390 cm^{-1}; nmr ($CDCl_3$) δ 6.19, 5.84 (s, 2, HO–CH), 4.73 (s, broad, 4, =C–CH_2–O), 4.40 (t, 2, J = 7.0 Hz; CH_2O–CH–O), 3.25–4.20 (m, 4, O–CH_2), 1.20–2.20 (m, 12, pyranyl-CH_2).

Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.2; H, 7.9. Found: C, 57.9; H, 7.8.

Diethylmaleic Anhydride (13).[12] 3,4-Diethyl-2,5-dihydroxy-2,5-dihydrofuran (217 mg) in acetone (10 ml) was cooled to 0° and Jones reagent[2] (0.6 ml: 10 g CrO_3/8.5 ml concentrated H_2SO_4/30 ml H_2O) was added dropwise (magnetic stirring). After 30 min the reaction mixture was filtered, the filtrate was evaporated, and the residue was partitioned between water and ether. After extraction with ether, drying (Na_2SO_4), and evaporation, the residue was dissolved in dry methylene chloride and treated (4 hr) with molecular sieve (Linde 3 A). Filtration and distillation gave diethylmaleic anhydride (13) (150 mg, 71%): bp 102–104° (10 mm) (lit.[12] bp 115° (13 mm)); n^{21}D 1.4640; ir (neat) 1852, 1773 cm^{-1}; nmr ($CDCl_3$) δ 2.54 (q, 4, J = 7.5 Hz), 1.23 (t, 6, J = 7.5 Hz).

Acknowledgment. We thank Professor Börje Wickberg for stimulating discussions. This work was in part supported by the Swedish Natural Science Research Council.

Registry No.—**1**, 53059-82-8; **2**, 14496-25-4; **3**, 30614-73-4; **4**, 52618-12-9; **5**, 6372-18-5; *cis*-**8**, 53059-83-9; *trans*-**8**, 53059-84-0; *cis*-**9**, 53059-87-3; *trans*-**9**, 53109-80-1; *cis*-**10**, 53059-85-1; *trans*-**10**, 53059-86-2; **11**, 53059-40-8; *cis*-**12**, 53059-41-9; *trans*-**12**, 53059-42-0; **13**, 28843-39-2; 3,4-bis(hydroxymethyl)furan, 14496-24-3; thionyl chloride, 7719-09-7.

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Assay and Methylation of 2-Methyl-1,2-dihydroisoquinoline

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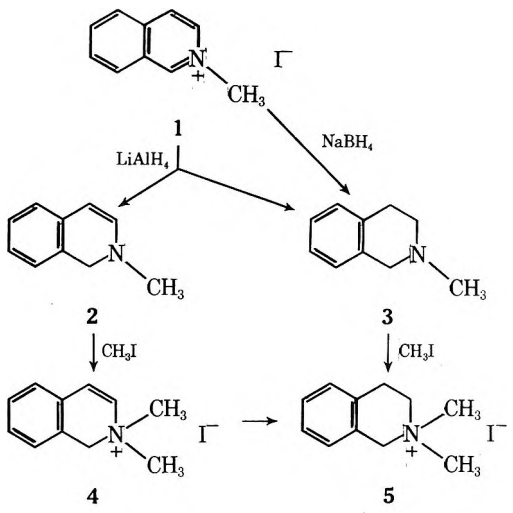
This note describes a procedure for the quantitative determination of 2-methyl-1,2-dihydroisoquinoline (2) and the course of its alkylation with methyl iodide. Dihydroisoquinoline **2** was obtained by reducing isoquinolinium methiodide (1) with lithium aluminum hydride by an optimization of the Schmid–Karrer method.[1] None of the other preparations tried were satisfactory.[2]

To determine the composition of the routinely distilled product, or more specifically the extent of overreduction to 2-methyl-1,2,3,4-tetrahydroisoquinoline (3), we developed a straightforward procedure involving dehydrogenation with excess iodine followed by iodimetric back-titration. Since the dihydroisoquinoline **2** requires 2 equiv of iodine



for aromatization while the tetrahydroisoquinoline **3** requires 4 equiv, the amount of iodine absorbed provides a reliable basis for assay. In an exploratory manner, we also investigated a spectroscopic method, which suggested that either or both of the 2-methyl-1,2-dihydroisoquinoline absorption maxima at λ_{max} (absolute C_2H_5OH) 234 and 329 nm[5] might serve as the basis for quantitative analysis. Quantitative gas–liquid chromatography was also tried but was found unreliable.

According to the iodimetric assay, the Schmid–Karrer preparation gives rise to mixtures of di- and tetrahydroisoquinoline (**2** and **3**), with the latter compound comprising as much as 35% of the product. One run that could not be repeated gave an exceptionally low concentration, 2%, of the tetrahydroisoquinoline. Accordingly, the tacit assumption that the Schmid–Karrer product is free of tetrahydro impurity is not warranted.[10] Whether the tetrahydroisoquinoline develops before or during the work-up was not determined. It is pertinent to note, however, that the conditions we employed, which avoided exposure to strong acid and high temperatures,[12] would not be expected to favor disproportionation of the dihydroisoquinoline.

Using starting material whose content of 2-methyl-1,2-dihydroisoquinoline (**2**) had been measured, we examined the reaction with methyl iodide. Only the N-alkylation product **4** was isolated. Hydrogenation of this product furnished 2,2-dimethyl-1,2,3,4-tetrahydroisoquinoline iodide (**5**), the same as the material obtained by methylating 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3**).[11] Our results with the simplest alkyl group and the parent dihydroisoquinoline, therefore, agree with the tendency noted before for eneamine alkylation with alkyl halides to favor nitrogen rather than carbon.[12,13]

Experimental Section

2-Methyl-1,2-dihydroisoquinoline (2). 2-Methylisoquinolinium iodide (8.1 g; 0.030 mol) was added in one portion to a stirred suspension of lithium aluminum hydride (1.2 g; 0.030 mol) in 150 ml of ether protected with a blanket of nitrogen. The mixture was stirred at room temperature for 30 min and then quenched over 200 g of crushed ice layered with 50 ml of ether. The ether layer was separated, the solids in the aqueous phase were washed thoroughly with ether, and the combined ether layers were rinsed with portions of saturated possium chloride solution and dried. Fractional distillation gave yellow oily 2-methyl-1,2-dihydroisoquinoline (**2**), bp 50–60° (0.1–0.2 mm) [lit.[1,4] 60–65° bath temperature (0.03 mm); 69° (0.8 mm)], which decomposed quickly in contact with air and was stored routinely under nitrogen. The product, obtained in 70% yield, contained 65–80% dihydro- and 35–20% tetrahydroisoquinoline **3** by iodimetric analysis. Variations in these directions improved neither the yield nor the content of the desired dihydroisoquinoline.

2-Methyl-1,2,3,4-tetrahydroisoquinoline (3).[11] 2-Methylisoquinolinium iodide (5.4 g; 0.020 mol) was reduced with sodium borohydride (5.0 g; 0.13 mol) in 500 ml of methanol plus 10 ml of water essentially as described in the literature.[11] 2-Methyl-1,2,3,4-tetrahydroisoquinoline (2.5 g; 86%) was obtained as a colorless oil, bp 55–58° (0.5 mm). The hydrochloride melted at 226–228° [lit.[14] 228°].

Iodimetric Analysis for Dihydroisoquinoline. Freshly distilled material was used routinely for the assay, which was done under nitrogen. A carefully weighed sample (50–100 mg) of the reduced isoquinoline was dissolved in 10 ml of absolute alcohol and was transferred quantitatively with the help of several 2-ml volumes of solvent to 20.0 ml of a standardized solution of iodine (0.5–1.0 g) in absolute ethanol. The mixture in a stoppered flask was stirred magnetically for 40 min at room temperature. Solid potassium iodide (1.0 g) and sodium bicarbonate (0.5 g) were then introduced followed by 100 ml of water and an excess of standard 0.1 *N* sodium thiosulfate. After 10 min of stirring, the colorless solution was back-titrated with standard iodine to a pale-blue starch end point.

When pure 2-methyl-1,2,3,4-tetrahydroisoquinoline was analyzed with this procedure, it required 2.02 ± 0.01 mol of iodine per mole of substrate. Pure 2-methyl-1,2-dihydroisoquinoline, if available, would consume 1.00 mol of iodine per mole. One exceptional batch of dihydroisoquinoline required 1.02 ± 0.03 mol and so was practically homogeneous. All other samples absorbed between 1 and 2 mole of iodine per mole, from which result the composition could be directly obtained.

2,2-Dimethyl-1,2-dihydroisoquinolinium Iodide (4). Methyl iodide (3.0 g; 0.02 mol) was added slowly to a stirred solution of 2-methyl-1,2-dihydroisoquinoline (1.5 g) in 5 ml of acetonitrile. The mixture was stirred under nitrogen at room temperature for 1 day. The yellow precipitate was collected, washed with a little alcohol, and dried to give the 2,2-dimethyl compound **4** (1.0 g), mp 158.5–159.5°. Crystallization from ethanol did not change the melting point.

Anal. Calcd for $C_{11}H_{14}IN$: C, 46.01; H, 4.91; I, 44.19; N, 4.88; $(CH_3)_2N$, 10.45. Found: C, 46.00; H, 5.00; I, 44.35; N, 5.00; *N*-methyl, 10.43.

2,2-Dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (5) from Tetrahydroisoquinolinium Iodide (3). A solution of 2-methyltetrahydroisoquinoline (0.3 g) and methyl iodide (0.35 g) in benzene (5 ml) was refluxed for 5 min. The solid deposited from the cooled mixture was crystallized from alcohol to give yellow crystals of 2,2-dimethyltetrahydroisoquinolinium iodide (**5**), mp 188–189° (sinter 183°) [lit.[15] mp 189°].

Anal. Calcd for $C_{11}H_{16}IN$: C, 45.69; H, 5.58. Found: C, 45.77; H, 5.58.

2,2-Dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (5) from Dihydroisoquinolinium Iodide 4. A solution of dihydro compound **4** (71 mg; 0.25 mmol) in 15 ml of 1:1 water–alcohol was stirred under hydrogen at room temperature with the catalyst prereduced from 60 mg of platinum oxide. After 4 hr, 0.25 mmol of hydrogen had been absorbed; continued stirring resulted in no further uptake. Removal of catalyst and solvent left 70 mg of 2,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium iodide (**5**), mp 179–180°. Crystallization from alcohol gave material with mp 186–187° (sinter 174°). The mixture melting point with the same material prepared from the tetrahydroisoquinoline was 186–187° (sinter 175°); the infrared absorption spectra of the two iodides were identical.

Acknowledgment. We wish to thank American Cancer Society for Grant T-300A in support of this work.

Registry No.—**1**, 3947-77-1; **2**, 14990-40-0; **3**, 1612-65-3; **3 HCl**, 53112-33-7; **4**, 53112-34-8; **5**, 1637-45-2.

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(5) Values in the literature include the following: λ_{max} 235[6] and 328,[7] and in cyclohexane 240 and 330 nm.[4] 2-Butyl-1,2-dihydroisoquinoline in alcohol shows λ_{max} 235, 282, and 330 nm.[1] The unsubstituted 1,2-dihydroisoquinoline has been reported with λ_{max} ($CHCl_3$) 265, 280, and 320 nm; no 230 nm maximum appears in alcohol solvent.[8] 2,4-Dimethyl-1,2-dihydroisoquinoline shows λ_{max} (C_2H_5OH) 202, 241, and 334.[9] Since in protic solvent the immonium form of the dihydroisoquinolines could be present, it would be desirable to study the effect of solvent on the ultraviolet absorption spectrum.
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Chemistry of Azoethenes and Azoethynes. I. Synthesis of Phenylazoethynylbenzene and Its Derivatives

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1-(2-Hydroxynaphthylazo)hexyne was suggested as a reaction intermediate by Robson and Tedder.[1] Later Sladkov and coworkers reported the synthesis of electron-withdrawing-group-bearing arylazoethynylbenzenes by the reaction of arenediazonium chlorides in aqueous solution with silver acetylides.[2] Their procedure gave only poor to fair yields of the azoethynes among difficult-to-separate reaction product mixtures. The simplest compound of the series, phenylazoethynylbenzene (**1**) and the electron-donating-group-bearing *p*-methoxyphenylazoethynylbenzene (**2**) cannot be obtained by their method. We have now successfully synthesized **1**, **2**, and other arylazoethynylbenzenes (**3–10**) in fair to good yields (Table I) by a new procedure.

Our method involved the reaction of purified arenediazonium salts (chlorides or bromides) with silver phenylacetylide in alcohol–chloroform (eq 1). Compounds **1–10** thus obtained were easily purified by column chromatography.

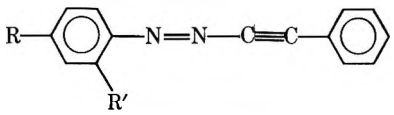
$$ArN_2^+X^- + AgC{\equiv}CPh \longrightarrow ArN{=}NC{\equiv}CPh + AgX \quad (1)$$

1–10

Compounds **1–10** exhibit ir signals in the range 2160–2165 cm^{-1} and nmr signals expected for the structures.[3] The mass spectra of these compounds all show a common fragmenation pattern (Scheme I), in agreement with the assigned structures.[3]

The uv spectra of **1–10** (Table I) show absorption in ethanol λ_{max} 360–384 nm (with log ϵ ~4) attributed to the $-N{=}NC{\equiv}C-$ group.[2] The insertion of the $-C{\equiv}C-$ group

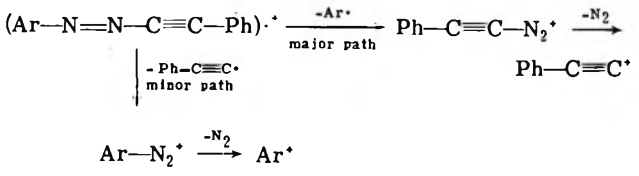
Table I
Arylazoethynylbenzenes[a]



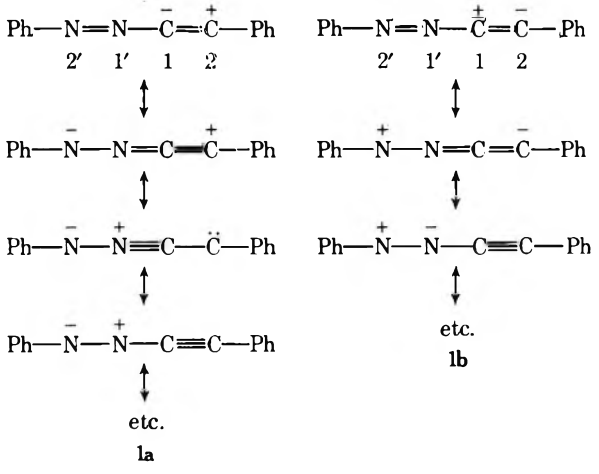
Compd	R	R'	% yield	Mp, °C	λ_{max}, nm[b]	Mol wt[c]
1	H	H	65	64–66	360	206
2	CH_3O	H	33[d]	52–54	384	236
3	Cl	H	70[e]	115	370	240 242
4	Br	H	70[e]	110	371	284 286
5	I	H	60	118–120	372	322
6	NO_2	H	72[e]	140	362	251
7	COOEt	H	81	80–82	363	278
8	CN	H	55	136	363	231
9	Cl	COOMe	60	87–88	380	298
10	H	PhCO	87	99–100	380 sh	310

[a] Satisfactory analytical data (±0.4%) for C, H, and N were obtained for all compounds listed in this table. [b] In ethanol. [c] By mass spectrometry. [d] 2 decomposes rapidly. [e] Sladkov and coworkers prepared 3 in 39%, 4 in 24%, and 6 in 26% yield.[2]

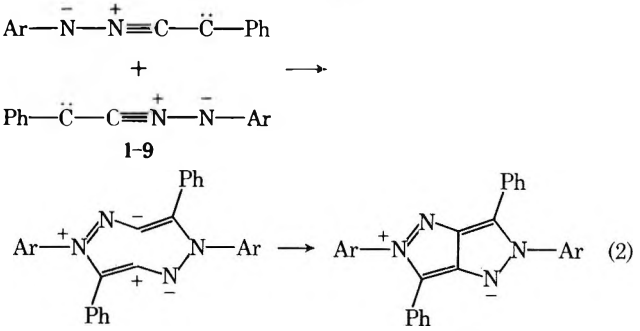
Scheme I



into the arylazobenzene structure produces a strong bathochromic shift (*trans*-azobenzene has λ_{max} 318 in ethanol[4]). The introduction of a group with +M effect produces a bathochromic shift whereas the introduction of a group with −M effect produces little change on the λ_{max} of 1. Qualitatively one expects the polarization of the -N=NC≡C- group in the direction represented by structure **1a** rather than by structure **1b** for 1. The Hammett σ_p constants for the PhN=N group and the Ph group are 0.64 and −0.01 ± 0.05, respectively;[5] the PhN=N group is stronger electron-withdrawing (stabilizes a negative charge better) than the Ph group. This should result in a higher electron density at C_1 (the carbon on which the PhN=N group is attached) than at C_2 (the carbon on which the Ph group is attached). Also, the Shoolery's effective nmr shielding constants for the Ph group and the PhC≡C group are 1.82 and 1.65, respectively; the Ph group is stronger electron withdrawing than the PhC≡C group. This should result in higher electron density at N_2' (the nitrogen on which the Ph group is attached) than N_1' (the nitrogen on which the PhC≡C group is attached). Whether this extended conjugation results in a linear structure for the -N=NC≡C- group or not is not certain at the present time.



Compounds **1–9** show a tendency to undergo thermal dimerization to give 2,5-diaryl-3,5-diphenyl-1,2,4,5-tetraazapentalenes, **D1–D9**, as reported by Simamura and coworkers.[6] A mechanism has been proposed by Grundman and coworkers for the dimerizations of arylazoethynylbenzenes and bis(arylazo)acetylenes, as shown in eq 2 for the dimerization of **1–9** to **D1–D9**.[7] Attempts to obtain dimer from the highly hindered **10** failed.



The reduction of **1–10** to arylazoethenylbenzenes will be reported in a separate article.[8]

Experimental Section

Melting points were taken on a Köfler hot-stage apparatus and were corrected. The ir spectra were measured on a Perkin-Elmer Infrachord 137 spectrophotometer. The nmr spectra were determined using a Varian A-60 spectrometer. The uv spectra were determined using a Beckman DB spectrophotometer. Mass spectra were obtained on an AEI MS-9 mass spectrometer. Analyses were performed by Baron Consulting Co., Orange, Conn. Thin-layer chromatography was performed on 0.25-mm layers using silica gel GF 254 and PF 254 (Merck), Darmstadt, Germany. The silica gel used for column chromatography was obtained from Gerbrüder Herman, Köln, Germany. All solvents and reagents were purified according to standard procedures before use.

Compounds **1–10** were prepared and purified according to the general procedure described below.

Arylazoethynylbenzenes (1–10). To a solution of 10 mmol of silver nitrate in 250 ml of aqueous ethanol (75% by volume) at room temperature was added slowly with vigorous stirring a solution of 10 mmol of phenylacetylene in 25 ml of ethanol. The white silver phenylacetylide precipitated out was filtered, washed with water, and dried *in vacuo*. Meanwhile the arenediazonium halide (chloride or bromide) was prepared by slowly adding 12 mmol of *n*-butyl nitrite into a solution of 10 mmol of the corresponding aniline hydrohalide in 20 ml of ethanol at 0 to −5° with vigorous stirring. The mixture was stirred for 15 min and was diluted with ether. The arenediazonium halide that crystallized out was filtered and washed with ether and then redissolved in 25 ml of ethanol. The dried silver phenylacetylide was suspended in 100 ml of chloroform at room temperature with vigorous stirring and the ethanolic arenediazonium halide was added dropwise. The orange mixture was stirred for 30 min and was filtered with the aid of a filter cell. The filtrate (tlc of which generally showed a major yellow-orange spot for **1–10** followed by a more polar fluorescent spot for **D1–D9**) was evaporated *in vacuo* and separated on a 300-g silica gel or Florisil column eluted with benzene and chloroform. The major yellow-orange fraction was collected and evaporated to give the arylazoethynylbenzenes **1–10.** The melting point, molecular weight, and spectroscopic data are listed in Table I.[3]

A more polar fraction eluted from the column generally gave small amounts of **D1–D9.** Long time lag between preparation and separation resulted in the increased yields of **D1–D9** at the expense of the yields of **1–9.**

Dimers D1–D9. Solutions of **1–9** in cyclohexane were heated to reflux and the reactions were followed by tlc at regular time intervals. At the end of 24 hr, evaporation of solvent and separation on

a silica gel column gave pure **D1–D9**.[3,6] The yields of **D1–D9** ranged from 15% for **D2** to 60% for **D1**. No dimer could be obtained by heating **10** under the same conditions.

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Registry No.—**1**, 53198-79-1; **2**, 53198-80-4; **3**, 5076-51-7; **4**, 5076-52-8; **5**, 53198-81-5; **6**, 5076-53-9; **7**, 53198-82-6; **8**, 53198-83-7; **9**, 53198-84-8; **10**, 53198-85-9; phenylacetylene, 536-74-3.

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A Convenient, High-Yield Conversion of Aldehydes to Nitriles

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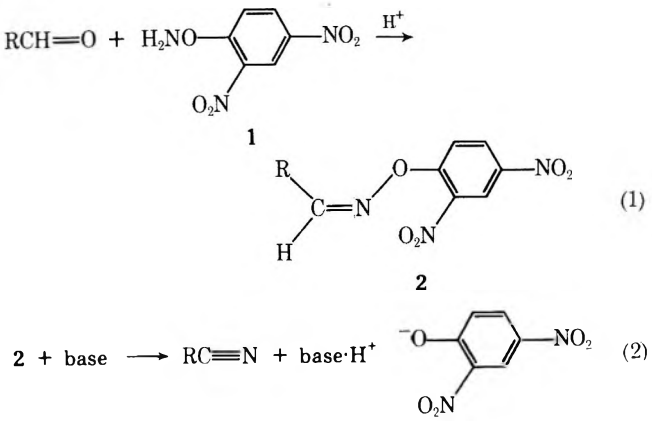
We wish to report a new method for accomplishing the conversion of aldehydes to nitriles. There have been a number of methods reported for this transformation;[1-6] ours differs from these in the fact that the experimentalist need not isolate and purify the intermediate oxime or related aldehyde derivative, although he may do so if he wishes; the method therefore saves one step in the aldehyde-to-nitrile conversion. The method additionally features relatively mild reaction conditions as well as a convenient internal indicator for the extent of reaction.

The development of efficient amino protecting groups has facilitated the synthesis of a variety of sensitive compounds, including O-substituted hydroxylamines.[7] Although a number of these are highly unstable,[8] others have significant synthetic utility. Their electrophilic character has been exploited in their increasing use as aminating agents.[9,10] Their nucleophilicity has been demonstrated by their reaction with ketones to form substituted oximes which undergo facile Beckmann and Neber rearrangements.[11]

Our method makes use of one of these reagents, *O*-2,4-dinitrophenylhydroxylamine (**1**), and proceeds according to eq 1 and 2.



The *O*-2,4-dinitrophenyloxime is formed by simply warming an alcoholic suspension of equivalent amounts of the aldehyde and **1** until the solution becomes homogeneous, followed by the addition of a few drops of mineral acid. The *O*-2,4-dinitrophenyloximes of aromatic aldehydes immediately precipitate from the reaction mixture and can be isolated by filtration after cooling. High yields of these materials have been obtained; their sharp melting points indicate that only one isomer is probably formed. Others have reported similar observations, and have presented evidence that the isomer formed is the *Z* isomer (syn isomer) about the C=N bond.[12] Higher yields of **2** can often be obtained by the addition of 1 vol of water to the reaction mixture before cooling. Elimination to form the nitrile is accomplished by warming a suspension of the O-substituted oxime in alcohol with excess base until the mixture becomes homogeneous (method **A**). The development of a deep, yellow-to-red color of the 2,4-dinitrophenolate ion indicates the extent of completion of the reaction.

The aliphatic oxime derivatives in our hands do not precipitate from the reaction mixture; however, subsequent

Table I
Results of Synthesis of *O*-2,4-Dinitrophenyloximes of Various Aldehydes and Their Conversion to Nitriles

		Oxime 2					Nitrile				
Aldehyde (method)	Registry No.	Solvent	Mp, °C	Lit. mp,[a] °C	Yield, %	Registry No.	Solvent	Mp, °C	Lit. mp,[a] °C	Yield, %	Registry No.
Benzaldehyde (A)	100-52-7	EtOH	143–145	145	93	53188-15-1	MeOH			84	100-47-0
p-Methoxybenzaldehyde (A)	123-11-5	EtOH	185–187	187	91	53188-16-2	MeOH	61–62	60–62	91	874-90-8
p-Bromobenzaldehyde (A)	1122-91-4	EtOH	213–214	207	85	53188-17-3	MeOH	110–113	113	89	623-00-7
p-Nitrobenzaldehyde (A)	555-16-8	EtOH	215–216	216	91	53188-18-4	EtOH	147–150	147–148	94	619-72-7
Piperonal (A)	120-57-0	EtOH	194–195	196	98	53188-19-5	EtOH	92–93	92–93	81	4421-09-4
Heptaldehyde (B)	111-71-7	MeOH					MeOH			91[b]	629-08-3
Undecylenic aldehyde (B)	112-45-8	EtOH					EtOH			93	53179-04-7

[a] For oximes, the melting point data are from ref 12a; for nitriles, the data are from Beilstein. [b] The product contained a trace of the starting aldehyde, as shown by infrared and by the diagnostic reaction with 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole.[13]

addition of base to the reaction mixture gives the nitrile directly (method B).

The choice of base for the elimination reaction to form nitriles is arbitrary, except for that of the oxime derived from *p*-nitrobenzaldehyde. In this case, potassium or sodium hydroxide gives a mixture of products, among which are the desired nitrile to the extent of about 50%, and smaller amounts of *p*-nitrobenzaldehyde and *N*-*p*-nitrophenylformamide. The use of triethylamine in absolute ethanol, however, affords *p*-nitrobenzonitrile cleanly.

The results of execution of these procedures with various aldehydes are given in Table I.

Experimental Section

The melting points were determined on a Büchi melting point apparatus and are corrected. The infrared spectra were taken on a Perkin-Elmer infracord spectrophotometer, and in all cases were identical with those of melting points of various derivatives are listed in Table I.

Synthetic Procedures. *O*-2,4-Dinitrophenylhydroxylamine was prepared either by the method of Sheradsky[9d] or that of Tamara;[10b] we found the latter method more convenient for our purposes.

Nitrile Preparation. Method A. *O*-2,4-Dinitrophenylhydroxylamine (0.995 g, 5 mmol) was dissolved in 50 ml of ethanol by warming on a steam bath. Piperonal (0.75 g, 5 mmol) was added, and the solution swirled until it was homogeneous. Two drops of concentrated HCl were added. A precipitate began to form immediately. Cooling followed by filtration gave a light yellow solid (1.3 g, mp 193–195°). Cooling the filtrate in a freezer (−23°) overnight gave, after filtration, 0.33 g of fine needles, mp 194–195°. The total yield of piperonal *O*-2,4-dinitrophenyloxime was 98%.

This oxime derivative (0.5 g, 1.51 mmol) was suspended in 50 ml of 95% ethanol. KOH (20 ml, 0.2 *N* in 95% ethanol) was added and the solution heated slowly to a gentle reflux. Reflux was maintained for 3 hr, although the color of the phenolate ion developed instantaneously, and the solution was concentrated to 15 ml under reduced pressure. Water (75 ml) and 5% NaOH (15 ml) were added and the resulting suspension extracted with chloroform. Drying, evaporation, and recrystallization from hexanes yielded a white solid in 81% yield; mp 91.5–93.5°; ir 2270 cm^{-1}.

In another preparation of the same material, warming of the solution (to effect dissolution of the *O*-2,4-dinitrophenyloxime) for 10 min followed by work-up as described above afforded essentially the same yield of nitrile. Stirring the O-substituted oxime with triethylamine in tetrahydrofuran for 12 hr, however, gave no reaction.

Method B. *O*-2,4-Dinitrophenylhydroxylamine (0.199 g, 1 mmol) was dissolved in 30 ml of ethanol by warming on a steam bath. 10-Undecylenic aldehyde (Aldrich, 0.168 g, 1 mmol) was added followed by one drop of concentrated HCl. The solution was allowed to cool, and it was stirred at room temperature for 30 min. Two equivalents of triethylamine was added, and the solution was heated to gentle reflux; a dark yellow color developed. After 5 min the solution was poured into 75 ml of 5% aqueous sodium bicarbonate and extracted with ether. Drying and evaporation of the ethereal solution left a light yellow liquid. Bulb-to-bulb distillation gave a colorless liquid (153 mg, 93%): ir 2260 cm^{-1}.

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Registry No.—1, 17508-17-7.

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A Reagent for the α,β Reduction of Conjugated Nitriles

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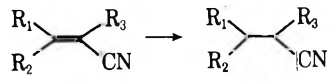
The reduction of α,β-unsaturated nitriles **1** to saturated nitriles **2** often proceeds with concomitant reduction of the nitrile moiety,[1] decyanation,[2] hydrodimerization,[3] and polymerization.[4] Those procedures reported to afford predominantly the nitrile **2** suffer from poor yields[5] and limited[6] or uncertain[7] scope. We now wish to report a general procedure for effecting the transformation **1** → **2** in high yield.



1 **2**

The reduction of **1** to **2** using magnesium in methanol was compatible with various substitution patterns and, in the limited cases examined, with other functional groups (see Table I). A particular advantage of this method over catalytic hydrogenation was the regioselective reduction of a conjugated double bond in the presence of a nonconjugated double bond. The principal side reaction observed in only a few instances was decyanation to afford olefins.[8]

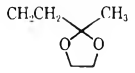
Experimental Section

Infrared spectra were determined on a Perkin-Elmer Infracord spectrometer. Nmr spectra were determined on a Varian A-60A spectrometer. Mass spectra were determined on a Varian-Mat CH5 mass spectrometer. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga.

The following is a typical experimental procedure.

3-Phenylbutyronitrile. To 188 mg (1.31 mmol) of 3-phenyl-2-butenitrile[9] (*E*/*Z* = 9/1) in 13.1 ml of methanol was added 1.27 g (52.4 mmol, 40 equiv) of magnesium turnings. The exothermic reaction which ensued after 10 min was moderated with an ice bath. The reaction was stirred 1 hr at 0° and 5 hr at 25°. To the reaction at 0° was added 24 ml of 6 *N* hydrochloric acid over a 1-hr period to afford a clear solution which was extracted with three 20-ml portions of ether. The ether solutions were combined, washed with 20 ml of brine, dried over anhydrous magnesium sulfate, and evaporated to afford 196 mg of oil. The oil was chromatographed on a 20 × 20 cm preparative layer Merck silica gel F254 plate in 1:9 ether–hexane to afford 183 mg (96%) of 3-phenylbutyronitrile (R_f 0.20): ir (TF) 4.48 (CN) and 6.25 μ (arom); nmr (CCl_4) δ 1.42 (d, J = 7 Hz, 3, $CHCH_3$), 2.35–2.55 (m, 2, CH_2CN), 2.80–3.35 (m, 1, $CHCH_3$), and 7.23 (5, s, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 51 (12), 77 (32), 78 (8), 79 (16), 103 (15), 104 (6), 105 (100), 106 (11), and 145 (22).

Table I
The Magnesium in Methanol Reduction of α,β-Unsaturated Nitriles $R_1R_2C{=}CR_3CN$

R_1	R_2	R_3	Registry No.	Isolated[a] yield of nitrile 2, %	Registry No.
i-C_3H_7	CH_3	CH_3	4786-38-3	72	53153-89-2
i-C_3H_7	CH_3	CH_2CH_3	53153-63-2	77	53153-90-5
i-C_4H_9	CH_3	CH_3	53153-64-3	75	53153-91-6
i-C_4H_9	CH_3	CH_2CH_3	53153-65-4	84	53193-92-7
n-C_6H_{13}	CH_3	H	53153-66-5	68	42144-33-2
n-C_6H_{13}	CH_3	CH_3	53153-67-6	100	53153-93-8
n-C_6H_{13}	CH_3	CH_2CH_3	53153-68-7	95	53153-94-9
Ph	H	H	4360-47-8	85	645-59-0
Ph	CH_3	H	14799-78-1	96	20132-76-7
Ph	Ph	H	3531-24-6	67	2286-54-6
Ph	CH_3	CH_3	53153-69-8	95	53153-95-0
Ph	CH_3	CH_2CH_3	53153-70-1	95	53153-96-1
CH_2Ph	CH_2Ph	H	50400-28-7	73	53153-97-2
CH_2Ph	CH_2Ph	CH_3	53153-71-2	92	53153-98-3
CH_2Ph	CH_2Ph	CH_2CH_3	53153-72-3	70	53153-99-4
$-(CH_2)_4-$		CH_3	53153-73-4	77	53154-00-0
$-(CH_2)_4-$		CH_2CH_3	53153-74-5	83	29770-74-9
$-(CH_2)_4-$		i-C_3H_7	53153-75-6	66	53154-01-1
$-(CH_2)_5-$		H	4435-18-1	74	4435-14-7
$-(CH_2)_5-$		CH_3	53153-76-7	91	53154-02-2
$-(CH_2)_5-$		CH_2CH_3	53153-77-8	95	4634-62-2
$-(CH_2)_5-$		i-C_3H_7	53153-78-9	87	53154-03-3
$-(CH_2)_6-$		CH_3	53153-79-0	90	53154-04-4
$-(CH_2)_6-$		CH_2CH_3	53153-80-3	100	53154-05-5
$-CH(CH_3)CH_2CH_2CH_2CH_2-$		H	53153-81-4	84	53154-06-6
$-CH(CH_3)CH_2CH_2CH_2CH_2-$		CH_3	53153-82-5	93	53154-07-7
$-CH(CH_3)CH_2CH_2CH_2CH_2-$		CH_2CH_3	53153-83-6	78	53154-08-8
$(CH_2)_2CH{=}C(CH_3)_2$	CH_3	H	5146-66-7	75	51566-62-2
$CH_2CH_2CO_2CH_3$	CH_3	H	53153-84-7	65	
CH_2CH_2COOH	CH_3	H	53153-85-8	90[b]	53154-09-9
$CH_2CH_2CHOHCH_3$	CH_3	H	53153-86-9	93	53154-10-2
$CH_2CH_2CH(OnBu)CH_3$	CH_3	H	53153-87-0	74	53154-11-3
	CH_3	H	53153-88-1	74[c]	18214-14-7

[a] All products were isolated by preparative layer chromatography on Merck silica gel F254 and had infrared, nmr, and mass spectral data in accord with assigned structures. [b] Isolated as the methyl ester. [c] Isolated as the ketone.

Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64. Found: C, 82.64; H, 7.67.

Acknowledgment. We (J.A.P. and D.S.W.) wish to thank the Research Corporation for their generous support.

Registry No.—(*Z*)-3-Phenyl-2-butenenitrile, 14799-79-2.

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(8) For example, **1** ($R_1 = R_2 = CH_2Ph$; $R_3 = CH_3$) afforded 1,1-dibenzylethylene in 27% yield.

(9) Most α,β-unsaturated nitriles used in this study were prepared by the modified Wittig reaction of R_1R_2CO with $(RO)_2POCHR_3CN$ according to W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

Tetrafluorodithiosuccinyl Difluoride

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Contribution No. 2091 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

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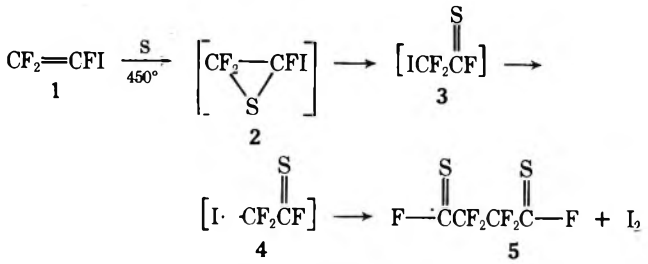
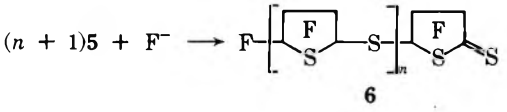
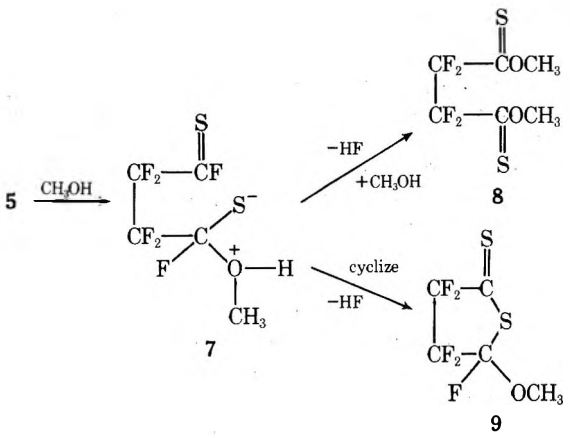
Earlier, we reported that the reactions of chlorotrifluoroethylene and bromotrifluoroethylene with sulfur vapors give high yields of chloro- and bromodifluorothioacetyl fluoride, respectively.[1] Our attempts to prepare the corresponding iododifluorothioacetyl fluoride (**3**) from the reaction of iodotrifluoroethylene (**1**) with sulfur vapors at 450° were unsuccessful. Instead, a 60% yield of tetrafluorodithiosuccinyl difluoride (**5**) was formed. The expected product, **3**, probably does form but is unstable at the high temperature of the reaction and dissociates into an iodine radical and the resonance stabilized radical **4**, which dimerizes to give **5**.



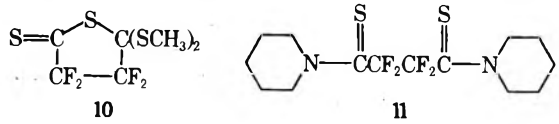
Like other thioacyl fluorides, **5** is easily polymerized at low temperatures by initiation with basic catalysts.[2] Since the polymer is not highly cross-linked and contains no reactive CSF groups, it is believed to be composed of cyclic units as illustrated by structure **6**. Its slight pink color is due to the dithiolactone chromophore at the end of the chain.



Tetrafluorodithiosuccinyl difluoride (**5**) reacts with excess methanol to give two products, the orange-red diester **8** and the purple-red dithiolactone **9**. The diester **8** was always obtained as the major product, but when the reaction was carried out at lower temperatures (−20°), appreciable amounts of **9** were also formed. The increased stability at low temperatures of an intermediate such as **7** might explain these results. At higher temperatures, **7** could eliminate HF easily and go on to the diester **8**, but at lower temperatures, **7** could exist long enough to cyclize and give **9**.



Reaction of **5** with ethyl and isopropyl alcohol gave only the dithio esters. An attempt to prepare the tetrathio ester by reaction of **5** with methanethiol gave instead the dimethylthiodithiolactone **10**. The ester **8** reacts with piperidine to give the expected dithioamide **11**.



Experimental Section[3]

Tetrafluorodithiosuccinyl Difluoride (5). A stream of nitrogen gas was bubbled into a flask containing 150 g (0.72 mol) of freshly distilled trifluoroiodoethylene, and the entrained vapors were then passed through a 500-ml flask fitted with 6 in. side arms containing 150 g of sulfur heated to reflux and then through a 12 in. horizontal wide-bore air condenser into an ice-cooled trap. Iodine crystals deposited in the air condenser, and a dark liquid condensed in the trap. The rate of nitrogen flow was adjusted so that the entire sample of trifluoroiodoethylene was added in about 2 hr. The condensate in the trap was distilled to give 41.32 g (61%) of **5** as a red-brown liquid: bp 84–85.5°; λ_{max} 428 (ϵ 46.5), 294 (ϵ 171), and 220 mμ (ϵ 11,300); ^{19}F nmr (CCl_3F) δ +66.2 (m, 2 F), −109.1 ppm (m, 4 F).

Anal. Calcd for $C_4F_6S_2$: C, 21.24; F, 50.41; S, 28.35. Found: C, 21.34; F, 50.47; S, 28.47.

Dimethyl Tetrafluorodithionosuccinate (8). A 62.5-g (0.275 mol) sample of **5** was added dropwise to 125 g of methanol cooled to 10°. The temperature of the reaction was kept between 10 and 20°. Distillation of the reaction mixture gave 51.51 g (75%) of **8** as an orange-red liquid, bp 86–88° (5 mm). Gas chromatography indicated the sample was about 95% pure. It was combined with similar samples and redistilled to give **8** as an orange-red liquid: bp 97–98° (96 mm); n^{25}D 1.4606; uv (isooctane) λ_{max} 243 (ϵ 14,000) and 399 mμ (ϵ 31); ^{19}F nmr (CCl_3F) δ −109.2 ppm (s); ^{1}H nmr (CCl_3F) δ 4.18 ppm (s).

Anal. Calcd for $C_6H_6F_4O_2S_2$: C, 28.80; H, 2.42; F, 30.37; S, 25.62. Found: C, 29.04; H, 2.44; F, 30.41; S, 25.64.

2,2,3,3,4-Pentafluoro-4-methoxydithiobutyrolactone (9) and 8. A 27.5-g (0.12 mol) sample of **5** was added dropwise to 50 ml of methanol cooled to −20°. The reaction mixture was warmed to room temperature and then distilled to give 12.66 g (42%) of **8**, bp 87–88° (5.0 mm), and 5.34 g (19%) of **9** as a deep red liquid: bp 50–51° (5.0 mm); λ_{max} (isooctane) 520 (ϵ 17) and 302 mμ (ϵ 7,500); ^{19}F nmr (CCl_3F) δ −97.4 (m, $-CFOCH_3$), −110.0 and 110.9 (AB of m, $-CF_2CS-$), and 131.3 ppm (m, $-CF_2CFOCH_3$); ^{1}H nmr (CCl_3F) δ 3.78 ppm (d, J = 1.2 Hz of t, J = 0.4 Hz).

Anal. Calcd for $C_5H_3F_5OS_2$: C, 25.21; H, 1.27; F, 39.88; S, 26.92. Found: C, 24.85; H, 1.48; F, 39.86; S, 26.81.

Diethyl and Diisopropyl Tetrafluorodithionosuccinate. A 16.0-g (0.07 mol) sample of **5** was added dropwise to 50 ml of ethyl alcohol cooled to 15°. The reaction mixture was passed through a column containing 100 g of Al_2O_3 and then distilled to give 14.37 g (74%) of the ester as an orange liquid: bp 76° (0.55 mm); n^{25}D 1.4545; uv (isooctane) λ_{max} 400 (ϵ 38.6), 308 (ϵ 292), and 244 mμ (ϵ 14,100); ^{19}F nmr (CCl_3F) δ −109.2 ppm (s); ^{1}H nmr (CCl_3F) δ 1.48 (t, J = 7 Hz, 6 H) and 4.68 ppm (q, J = 7 Hz, 4 H).

Anal. Calcd for $C_8H_{10}F_4O_2S_2$: C, 34.53; H, 3.62; F, 27.31; S, 23.04. Found: C, 34.84; H, 3.63; F, 27.50; S, 23.12.

The diisopropyl ester was obtained in a similar manner and was obtained as an orange liquid: bp 77–80° (0.75 mm); uv (isooctane) λ_{max} 400 (ϵ 54.8), 302 (ϵ 410), and 248 mμ (ϵ 13,200); ^{19}F nmr (CCl_3F) δ −107.2 ppm (s); ^{1}H nmr (CCl_3F) δ 1.42 (d, J = 6 Hz, 12 H) and 5.67 ppm (septet, J = 6 Hz, 2 H).

Anal. Calcd for $C_{10}H_{14}F_4O_2S_2$: C, 39.21; H, 4.51; F, 24.81; S, 20.93. Found: C, 38.91; H, 4.21; F, 25.03; S, 20.77.

2,2,3,3-Tetrafluoro-4,4-di(methylthio)dithiobutyrolactone (10). A 16-g (0.08 mol) sample of **5** was added dropwise to 50 g of methanethiol cooled in an ice bath. Ether, 25 ml, and then 6.7 g (0.16 mol) of powdered sodium fluoride were added to the reaction mixture, and the reaction mixture was filtered and then distilled. Several products that were not cleanly separated were formed. One fraction, 4.7 g (21%) of deep purple red oil, appeared to be pure by gc and was identified as **10**: bp 100–103° (0.75 mm); n^{25}D 1.5896; uv (CH_3CN) λ_{max} 513 (ϵ 13.5) and 320 mμ (ϵ 7300); ^{19}F nmr (CCl_3F) δ −103.3 (t, J = 9.5 Hz, 2 F) and −116.8 ppm (t, J = 9.5

Hz of septets, J = 0.8 Hz 2 F); ^{1}H nmr (CCl_3F) δ 2.35 ppm (t, J = 0.8 Hz).

Anal. Calcd for $C_6H_6F_4S_4$: C, 25.52; H, 2.14; F, 26.91; S, 45.42. Found: C, 25.08; H, 2.21; F, 26.45; S, 45.63.

1,1,2,2-Tetrafluoro-1,2-bis(piperidinothiocarbonyl)ethane (11). A 3.5-g (0.014 mol) sample of 8 was added dropwise to a solution of 2.55 g (0.03 mol) of piperidine in 25 ml of ether at room temperature. The reaction mixture was evaporated to dryness under nitrogen, and the yellow residue was recrystallized from hexane–benzene to give 3.0 g of the diamide as yellow crystals: mp 129–132°; uv (ethanol) λ_{max} 365 (ϵ 161) and 296 mμ (ϵ 20,900); ^{19}F nmr (CCl_3D) δ −95.0 ppm (s); ^{1}H nmr (CCl_3D) δ 1.77 (m, 18 H), 4.04 (m, 4 H), and 4.28 ppm (m, 4 H).

Anal. Calcd for $C_{14}H_{20}F_4N_2S_2$: C, 47.18; H, 5.66; F, 21.32; N, 7.86; S, 17.99. Found: C, 47.03; H, 5.89; F, 21.11; N, 7.73; S, 17.60.

Poly(tetrafluorodithiosuccinyl fluoride) (6). A solution of 4.5 g of 5 in 50 ml of ether was cooled to −78°, and 1 drop of dimethylformamide was added. Cooling was continued for 2 hr, and then the reaction mixture was warmed to room temperature. The precipitated polymer was collected on a filter, washed with ether, and dried in air. There was obtained 2.3 g of the polymer as a light pink powder, mp 242–267° (viscous melt). No solvent was found for the polymer, but an opaque, brittle pink film was pressed at 150° (10,000 lb/in.^{2}).

Anal. Calcd for $(C_4F_6S_2)_n$: C, 21.24; H, 0.0; F, 50.40; S, 28.35. Found: C, 21.31; H, 0.36; F, 50.15; S, 28.97.

Registry No.—**1**, 359-37-5; **5**, 53128-98-6; **6**, 53128-99-7; **8**, 53129-20-7; **9**, 53129-21-8; **10**, 53129-22-9; **11**, 53129-23-0; diethyl tetrafluorodithionosuccinate, 53129-24-1; diisopropyl tetrafluorodithionosuccinate, 53129-25-2; methanol, 67-56-1; ethyl alcohol, 64-17-5; isopropyl alcohol, 67-63-0; methanethiol, 74-93-1; piperidine, 110-89-4.

References and Notes

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(3) All boiling points are uncorrected.

Rôle of Water in the Proton Transfer Step of Addition of Water to 1-Alkynyl Thioethers

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Our detailed study of the acid-catalyzed hydration of 1-alkynyl ethers,[2] thioethers,[3] and amines[4] revealed that the

$$RC{\equiv}CX + H_2O \longrightarrow RCH_2{-}COX$$

$$X = OR', SR', NR_2'$$

rate-determining step involves proton transfer to carbon.

$$RC{\equiv}CX + HA \longrightarrow RCH{=}C^+X + A^- \quad \text{(slow)}$$

Since the triple bond is highly asymmetrically substituted, in the transition state the proton probably is much closer to C_β than to C_α. The proton transfer step is endothermic and its transition state will resemble the intermediate carbocation.

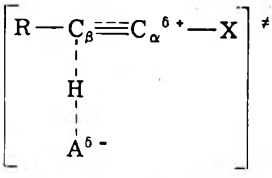
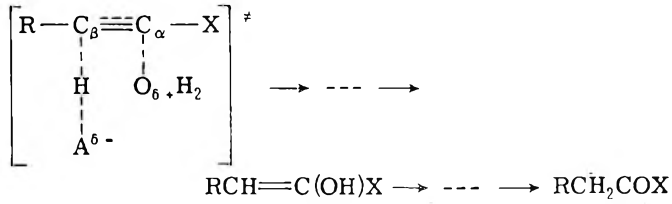


Table I
First-Order Rate Constants, k_1,[a] of Addition of Water to 1-Alkynyl Thioethers RC≡C—S—R'[b] in Aqueous Perchloric Acid at 25°. Ionic Strength 6.00 M by Addition of Sodium Perchlorate

R = H, R' = C_2H_5[c]		R = CH_3, R' = C_2H_5[d]		R = C_2H_5, R' = C_2H_5[e]		R = CH_3, R' = $C(CH_3)_3$[f]	
$HClO_4$ mol/l.	k_1 sec^{-1}	$HClO_4$ mol/l.	k_1 sec^{-1}	$HClO_4$ mol/l.	k_1 sec^{-1}	$HClO_4$ mol/l.	k_1 sec^{-1}
0.49	5.0	0.96	1.05	0.50	0.64	0.44	0.50
1.00	10.6	1.51	1.92	0.96	1.39	0.88	1.02
1.48	18.1	2.05	3.1	1.51	2.23	1.33	1.78
2.50	37	2.54	4.7	2.05	4.0	1.77	2.19
3.02	59	3.04	6.3	2.54	5.2	2.21	3.2
				3.04	7.2	2.65	3.9

[a] From spectrophotometry at 234 nm; standard deviation of the mean of at least three measurements ≤5%. Helpful assistance by Dr. R. W. Stephany is gratefully acknowledged. [b] Synthesized by Dr. J. Meijer and Mr. R. A. van der Welle following instructions by Brandsma.[6] [c] Registry no.—7299-53-8. [d] Registry no.—13597-15-4. [e] Registry no.—24298-52-0. [f] Registry no.—1595-36-4.

The question remains whether a water molecule is covalently attached to C_α already in this transition state and therefore also in the intermediate cation or later on.



Entropies of activation and rates in alcohol–water mixtures[3] indicated the absence of water in the transition state of the slow step. However, none of these arguments is very strong. Also it must be emphasized that the two possibilities, either covalently or not covalently bound, will be the extremes of a range of possibilities.

Generally, an answer to this question is sought from measurements in solutions at least 1 N in acid. Until now the fast rate of reaction of these hetero substituted acetylenes prevented us from extending our measurements to high acidity except for the relatively slow vinylthioethyne. For this compound in aqueous perchloric acid up to 3.5 N at 25°, a linear correlation was observed[3] between log k and the Hammett acidity function, $-H_0$, with a slope of 1.07.

Recently, we were able to measure the rates of 1-alkynyl thioethers in up to 3 N perchloric acid by stopped flow spectrophotometry. The results are presented in order to contribute to the complex problem of reaction kinetics in concentrated acids.

Rate constants at different perchloric acid concentrations and a constant ionic strength are given in Table I. Hammett's acidity function, H_0, and the water activity, a_w, have been determined by Perrin.[5]

When log k_1 was plotted *vs.* the acidity function $-H_0$, straight lines appeared of which the slopes, z, are given in Table II. These slopes are of the same order of magnitude or slightly higher than the slopes of 0.96–1.13 found by Noyce, *et al.*,[7] for the hydration of phenylpropiolic acids and phenylacetylenes. From a $\rho\sigma^+$ correlation for phenylpropiolic acids, it was concluded that C–OH_2 bond formation lags appreciably behind proton transfer. From a comparison of the H_0 correlation slopes, we tend to believe that

Table II
Slopes of the Zucker–Hammett Plots, z, and Bunnett's w Parameters

Compound	z	w
$HC{\equiv}C{-}S{-}C_2H_5$	1.16 ± 0.04	−2.4 ± 0.3
$CH_3C{\equiv}C{-}S{-}C_2H_5$	1.31 ± 0.04	−3.4 ± 0.5
$C_2H_5C{\equiv}C{-}S{-}C_2H_5$	1.16 ± 0.04	−2.4 ± 0.5
$CH_3C{\equiv}C{-}S{-}C(CH_3)_3$	1.03 ± 0.03	−0.2 ± 0.5

also in the acid catalyzed hydration of acetylenic thioethers covalent bonding of water is not of much importance in the transition state of the proton transfer step.

As a matter of completeness, in Table II we have given the slopes w of plots of (log k + H_0) *vs.* log a (H_2O) according to Bunnett.[8] These negative values are in the range believed to be characteristic for reactions in which water is not involved in the rate-determining step.

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Cuprous Trimethylsilylacetylide. Preparation and Reaction with Acid Chlorides

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The title compound, cuprous trimethylsilylacetylide (1), is of interest in that (1) trimethylsilyl protected acetylenes can be readily cleaved[1] to regenerate the terminal acetylenic function, (2) cuprous acetylide, itself, does not undergo the reactions of other cuprous acetylides, and (3) it represents the simplest Castro coupling reagent.[2] To the best of our knowledge acetylide 1 has not been prepared.[1,3]

In this paper we wish to report the preparation of 1 and its reaction with acid chlorides. Treatment of trimethylsilylacetylene in tetrahydrofuran (THF) with cuprous *tert*-butoxide[4,5] afforded a solution containing 1. Although an orange-red solid can be isolated from this solution upon dilution with ether, it is unstable and readily decomposes, even at −20°. We have tentatively assigned the structure of 1 to the orange-red solid based upon the infrared (Nujol mull) absorption bands at 1890 (C≡C), 1250 ($SiMe_3$), and 855 cm^{-1} ($SiMe_3$). The insolubility and instability of this precipitated material have precluded further characterization. The THF solutions of 1 are relatively stable at 0° provided they are not allowed to stand for extended periods of time. Thus 1 is best prepared in solution and used immediately without isolation. Furthermore, when preparing 1 it was found essential for cuprous iodide and trimethylsilylacetylene to be in excess of the lithium *tert*-butoxide, as 1 decomposed upon prolonged exposure to basic reagents. We have also prepared 1 from trimethylsilylacetylene by the butyllithium–cuprous iodide method,[6] but this method was not as satisfactory as the cuprous *tert*-butoxide procedure.

So far all attempts to obtain the Castro coupling product from 1 and the very reactive substrate methyl 2-iodobenzoate have been unsuccessful due to the instability of 1 under the reaction conditions. However, treatment of 1 with acid chlorides afforded the trimethylsilylethynyl ketones listed in Table I.

Table I
Trimethylsilylethynyl Ketones

R	Amt, mmol RCOCl	Amt, mmol 1[a]	$RCOC{\equiv}CSi(CH_3)_3$, % yield
CH_3	15	12.8	30
CH_3	15	25.6	24
$CH_3(CH_2)_4$	8	12.8	38
$CH_3(CH_2)_4$[b]	8	12.8	62
$(CH_3)_2CH$[b]	8	12.8	48
C_6H_5	15	12.8	66
C_6H_5	15	25.6	66
p-$CH_3C_6H_4$	8	12.8	48
p-ClC_6H_4	8	12.8	61

[a] Prepared *in situ* from $CuOC(CH_3)_3$ and $HC{\equiv}CSi(CH_3)_3$ with the assumption of a quantitative formation of 1. [b] The solution containing 1 was evaporated to dryness under reduced pressure and the residue redissolved in THF before the addition of RCOCl.

The data in Table I show that there is no advantage in using an excess of either 1 or the acid chloride. When aliphatic acid chlorides were used, the *tert*-butyl alcohol generated in the preparation of 1 had to be removed (evaporation under reduced pressure) prior to the acid chloride addition since it competed with 1 for the acid chloride. With aryl acid chlorides the competing side reaction with *tert*-butyl alcohol was negligible.

Trimethylsilylethynyl ketones have previously been prepared by the action of trimethylsilylethynylmagnesium bromide on acid anhydrides[7] and by the aluminum chloride catalyzed reaction of acid chlorides with bis(trimethylsilyl)acetylene.[8]

The present procedure is complementary to the above methods in that it uses acid chlorides instead of the less readily available anhydrides required by the former, and the reaction conditions are essentially neutral as compared to the strongly acidic conditions of the latter.

In summary, cuprous trimethylsilylacetylide proved to be too unstable for Castro coupling; however, it does react readily with acid chlorides to give trimethylsilylethynyl ketones.[9]

Experimental Section[10]

General Procedure. To a magnetically stirred suspension of cuprous iodide in 40 ml of THF at 0° under nitrogen was added 0.9 equiv of lithium *tert*-butoxide. The mixture was stirred for 45 min at 0° and then 1 equiv of trimethylsilylacetylene[11] dissolved in 10 ml of THF was added with the temperature being maintained at 0°. After 30 min, the acid chloride was added and the cooling bath was removed. The reaction mixture was stirred for 20 hr at room temperature and the solvent was then removed on a rotary evaporator. The residue was treated with ether and filtered, and the filtrate was evaporated on a rotary evaporator. The residue was chromatographed on a small column of silica gel eluting with hexane up to 0.5% ether–hexane. The products so collected were then distilled under reduced pressure. In each chromatography run a small forefraction, ranging from 12 to 18%, of bis(trimethylsilyl)-1,4-butadiyne was obtained as a coupling product from 1.

Phenyl trimethylsilylethynyl ketone was isolated as a pale

yellow liquid: bp 98–99° (1.0 mm) [lit.[7] bp 103–104° (2.5 mm)]; ir (CCl_4) 2165 (C≡C), 1640 (C=), 1250 ($Si(CH_3)_3$), 865 ($Si(CH_3)_3$), 855 cm^{-1} ($Si(CH_3)_3$); nmr (CCl_4) δ 0.32 (s, 9, $Si(CH_3)_3$), 7.50 (m, 3, Ar H), 8.05 (m, 2, Ar H).

***p*-Chlorophenyl trimethylsilylethynyl ketone** was isolated as a pale yellow liquid: bp 105–106.5° (0.5 mm) [lit.[8b] bp 80–84° (10^{-3} mm)]; ir (CCl_4) 2160 (C≡C), 1645 (C=O), 1250 ($Si(CH_3)_3$), 865 ($Si(CH_3)_3$), 855 cm^{-1} ($Si(CH_3)_3$); nmr (CCl_4) δ 0.32 (s, 9, $Si(CH_3)_3$), 7.15 (d, 2, J = 9 H_z, Ar H), 7.75 (d, 2, J = 9 Hz, Ar H).

***p*-Methylphenyl trimethylsilylethynyl ketone** was isolated as a pale yellow liquid: bp 110–112° (0.75 mm) [lit.[8b] bp 74–78° (10^{-3} mm)]; ir (CCl_4) 2170 (C≡C), 1640 (C=O), 1250 ($Si(CH_3)_3$), 865 ($Si(CH_3)_3$), 855 cm^{-1} ($Si(CH_3)_3$); nmr (CCl_4) δ 0.30 (s, 9, $Si(CH_3)_3$), 2.28 (s, 3, Ar CH_3), 6.92 (d, 2, J = 8 Hz, Ar H), 7.62 (d, 2, J = 8 Hz, ArH).

Methyl trimethylsilylethynyl ketone was isolated as a colorless liquid: bp 62–64° (28 mm) [lit.[7] bp 51.5° (12 mm)]; ir (CCl_4) 2160 (C≡C), 1675 (C=O), 1255 ($Si(CH_3)_3$), 870 ($Si(CH_3)_3$), 855 cm^{-1} ($Si(CH_3)_3$); nmr (CCl_4) δ 0.25 (s, 9, $Si(CH_3)_3$), 2.25 (s, 3, $C(O)CH_3$).

***n*-Pentyl trimethylsilylethynyl ketone**[12] was isolated as a colorless liquid: bp 74–75° (1.0 mm); ir (CCl_4) 2160 (C≡C), 1670 (C=O), 1250 ($Si(CH_3)_3$), 870 ($Si(CH_3)_3$), 855 cm^{-1} ($Si(CH_3)_3$); nmr (CCl_4) δ 0.24 (s, 9, $Si(CH_3)_3$), 0.70–1.90 (cm, 9), 2.38 (t, 2, J = 6 Hz, $C(O)CH_2$).

Isopropyl trimethylsilylethynyl ketone[12] was isolated as a colorless liquid: bp 78.2–81.8° (17 mm); ir (CCl_4) 2160 (C≡C), 1670 (C=O), 1255 ($Si(CH_3)_3$), 865 ($Si(CH_3)_3$), 855 cm^{-1} ($Si(CH_3)_3$); nmr (CCl_4) δ 0.28 (s, 9, $Si(CH_3)_3$), 1.16 (d, 6, J = 7 Hz, $CH(CH_3)_2$), 2.50 (heptet, 1, J = 7 Hz, $CH(CH_3)_2$).

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

Registry No.—**1**, 53210-13-2; RCOCl (R = CH_3), 75-36-5; RCOCl [R = $CH_3(CH_2)_4$], 142-61-0; RCOCl [R = $(CH_3)_2CH$], 79-30-1; RCOCl (R = C_6H_5), 98-88-4; RCOCl (R = p-$CH_3C_6H_4$), 874-60-2; RCOCl (R = p-ClC_6H_4), 122-01-0; cuprous *tert*-butoxide, 35342-67-7; trimethylsilylacetylacetylene, 1066-54-2; phenyl trimethylsilylethynyl ketone, 13829-77-1; *p*-chlorophenyl trimethylsilylethynyl ketone, 37166-46-4; *p*-methylphenyl trimethylsilylethynyl ketone, 37166-45-3; methyl trimethylsilylethynyl ketone, 5930-98-3; *n*-pentyl trimethylsilylethynyl ketone 53210-14-3; isopropyl trimethylsilylethynyl ketone, 53210-05-2.

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(3) R. Oliver and D. R. M. Walton, *Tetrahedron Lett.*, 5209 (1972), have suggested that **1** might be an intermediate in the formation of $Me_3Si(C{\equiv}C)_2SiMe_3$ from $LiC{\equiv}CSiMe_3$ and $IC{\equiv}CSiMe_3$ in the presence of cuprous halides.
(4) T. Tsuda, T. Hashimoto, and T. Saegusa, *J. Amer. Chem. Soc.*, **94**, 658 (1972).
(5) Cuprous *tert*-butoxide was not isolated as in ref 4 but was prepared *in situ* by the action of lithium *tert*-butoxide on cuprous iodide.
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(9) Trimethylsilylethynyl ketones are easily desilylated with an aqueous Borax solution to give ethynyl ketones; see ref 8b for details.
(10) All boiling points are uncorrected. Ir spectra were recorded on a Perkin-ElmerModel 257 spectrophotometer. Nmr spectra were recorded on a Hitachi Perkin-Elmer Model R-20A spectrometer with tetramethylsilane as an internal standard. All column chromatography was performed on Grace Davison 950 silical gel. The acid chlorides used, except for caproyl chloride, were commercial samples that were distilled prior to use. Tetrahydrofuran was distilled from $LiAlH_4$. Cuprous iodide was obtained from Alfa Inorganics and dried in *in vacuo* at 130°. Lithium *tert*-butoxide was prepared by the action of anhydrous *tert*-butyl alcohol on 1 equiv of lithium metal suspended in anhydrous ether followed by the removal of the ether on a rotary evaporator.
(11) N. V. Komarov and O. G. Yarosh, *Zh. Obshch. Khim.*, **37**, 264 (1967), *Chem. Abstr.*, **66**, 95126 (1967).
(12) A satisfactory combustion analysis could not be obtained due to contamination with a small amount of the desilylated ketone whose presence was detected by the appearance of 3300 and 2105 cm^{-1} bands in the ir spectrum. It appears that the trimethylsilyl group is partially removed during attempted purifications.

Alkyllithium Additions to Allylic Alcohols

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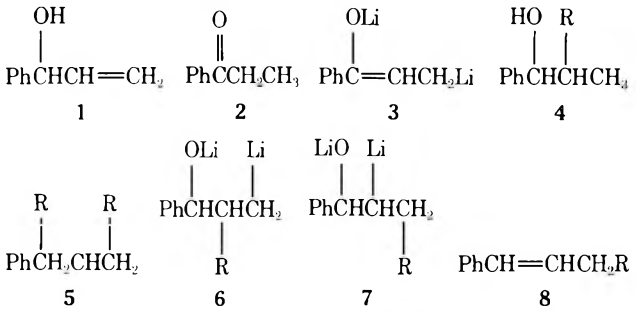
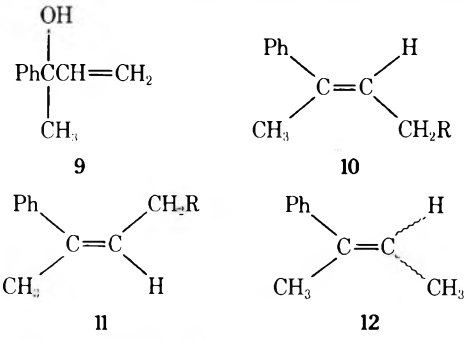
In some previous work, we had established that α-vinylbenzyl alcohol (**1**) can react in a variety of ways when treated with alkyllithium reagents. Treating **1** with *n*-butyllithium in tetrahydrofuran (THF) gave good yields of propiophenone (**2**), by way of a dianion intermediate (**3**).[2] In contrast to this result, the same starting materials in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and with hexane as the solvent gave the alcohol **4** (R = *n*-Bu) and saturated compound **5** (R = *n*-Bu) in a 3:1 ratio, and no ketone.[3] The alcohol, which is produced in a highly stereospecific manner, presumably arises by addition of *n*-butyllithium to the internal end of the double bond giving rise to intermediate **6** (R = *n*-Bu), which upon hydrolysis affords **4**. The saturated product **5** more than likely arises by way of addition of *n*-butyllithium to the terminal end of the double bond, giving rise to **7** (R = *n*-Bu) which eliminates Li_2O to **8** (R = *n*-Bu) and subsequently undergoes a second addition of *n*-butyllithium to the conjugated double bond.



Treatment of α-vinylbenzyl alcohol (**1**) with *tert*-butyllithium in the presence of TMEDA and hexane gave 23% ketone (**2**), 9% *cis*-**8** (R = *t*-Bu), 36% *trans*-**8** (R = *t*-Bu), and 32% **5** (R = *t*-Bu).[3] Consequently, in the case of *tert*-butyllithium the only addition products that result come from addition to the terminal end of the double bond and not the internal end. These differences led us to investigate the addition of *n*- and *tert*-butyllithium to two other homologous alcohols.

In our previous work, we reported that 2-phenyl-3-buten-2-ol (**9**) did not show any addition or rearrangement products when treated with excess *n*-butyllithium. However, it has now been found (after several trials) that overnight refluxing of a solution of **9**, 3 equiv of *n*-butyllithium,



and 1 equiv of TMEDA in the solvent hexane resulted in the production of two new compounds, together with a considerable amount of unreacted starting material remaining.

Table I
Spectral Data of Some Selected Substituted Styrenes

Compd	Uv (EtOH) λ_{max}	Uv (EtOH) ϵ_{max}	Nmr (CCl_4), [a] ppm =CH	α-CH_3	β- allylic	γ-CH_3	Other-CH_2-
12-*cis*	247	12,800	5.75 (q of q)	1.98 (pentet)	1.80 (CH_3) (q of d)		
12-*trans*	238	9,500	5.50 (q of q)	2.00 (pentet)	1.55 (CH_3) (q of d)		
10, R = *n*-Bu	244	9,500	5.70 (t)[b]	2.01 (s)	2.1 (CH_2) (m)	0.92 (t)[c]	1.1–1.8 (m)
11, R = *n*-Bu	235	5,300	5.40 (t)[b]	2.00 (d)	<2.0 (CH_2)	0.85 (t)[c]	1.0–2.0 (m)
10, R = *t*-Bu	244	10,100	5.80 (t)	2.01 (s)	2.08 (CH_2) (d)	0.98 (s)	
11, R = *t*-Bu	233	6,000	5.50 (q of t)	2.04 (d)	1.83 (CH_2) (d)	0.83 (s)	

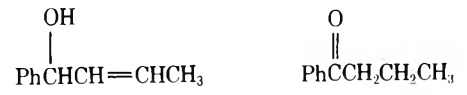
[a] All spectra integrated correctly, in accordance with the structural assignments. The aromatic signals were multiplets in the 6.8–7.5-ppm region in each case. [b] Complex. [c] Distorted.

The two new compounds were identified as *cis*- and *trans*-2-phenyl-2-octene (**10** and **11**, R = *n*-Bu), 15% and 10%, respectively.

The identity of the hitherto uncharacterized olefins rests on spectra data. The mass spectra of both compounds were very similar; both display molecular ions at *m/e* 188 and base peaks at *m/e* 131, corresponding to the allylic ion which would result upon cleavage of the C-4–C-5 bond. The nmr and uv data are given in Table I. A comparison to the values known for 2-phenyl-2-butene (**12**), cis and trans, is also presented.[4,5] As can be seen from the data, the nmr signals of β-alkyl groups cis to the phenyl group are shifted upfield, while the β-vinyl protons cis to the phenyl group are shifted downfield. The uv data are consistent with the general observation that a cis β-alkyl group produces a weaker, shorter wavelength maximum than the trans β-alkyl group.[6]

The reaction of *tert*-butyllithium with alcohol **9** gave results analogous to those of the *n*-butyllithium reaction. Treatment of **9** with 2 equiv of *tert*-butyllithium and 1.5 equiv of TMEDA in hexane afforded about 70% starting alcohol, 15% of *cis*-2-phenyl-5,5-dimethyl-2-hexane (**10**, R = *t*-Bu), and 15% of *trans*-2-phenyl-5,5-dimethyl-2-hexane (**11**, R = *t*-Bu). The mass spectra of both olefin products showed molecular ions at *m/e* 188, base peaks at *m/e* 131 (allylic carbonium ion), McLafferty rearrangement ions at *m/e* 132, and an abundance of low molecular weight aliphatic ions. The nmr and uv data were consistent with the proposed structures (Table I).

The reaction of *n*-butyllithium with 1-phenyl-2-buten-1-ol (**13**) produced only small amounts of butyrophenone (**14**), starting alcohol, and possibly polymerization products using either THF or hexane–TMEDA.



13 **14**

In summary, the reaction of alkyllithium reagents with 2-phenyl-3-buten-2-ol (**9**) produces olefins of the type **10** and **11**, which suggests initial attack of the RLi on the external end (C-4) of the allylic system, followed by elimination of Li_2O. Although the minor products in these reactions could not be isolated, it seems reasonable to conclude that little attack occurred at C-3, in comparison to C-4. The poor yields and change in the position of attack on the allylic systems (comparing *n*-butylation of **1** and **9**) seems to indicate that these reactions are influenced considerably by steric factors. While *n*-butyllithium adds in good yield to the simple alcohol **1** in hexane–TMEDA, the additional methyl present in allylic alcohol **13** seems to retard addition reactions in favor of a weak dianion reaction, giving ketone **14**.

Experimental Section

***n*-Butylation of 2-Phenyl-3-buten-2-ol (9).** To a small three-necked, round-bottomed flask fitted with a dropping funnel, nitrogen gas inlet, drying tube, and stirrer was added 2.6 g (17.5 mmol) of 2-phenyl-3-buten-2-ol (**9**),[7] about 25 ml of hexane, and 2.0 g (17.5 mmol) of TMEDA. The solution was cooled with ice, and 30 ml (66 mmol) of a 2.2 *M* solution of *n*-butyllithium in hexane was added in a rapid dropwise fashion. The reaction mixture was allowed to warm to room temperature and stirred at reflux overnight. After quenching with water, the organic phase was separated, dried ($MgSO_4$), and evaporated under vacuum at room temperature.

Analysis by vpc (6-ft SE 30 column (¼ in). at 140°) showed seven components, several of which were quite minor. An nmr spectrum of this crude product showed methyl signals in the δ 2.0 region and vinyl protons at δ 5.4 and 5.7, indicative of products 10 and 11. By use of preparative vpc (8-ft SE 30 column (1 in.) at 160°), three components were isolated. The first—low retention time—component (65%) was identical with the starting material **9** in its retention time and nmr and mass spectra. The second—moderate retention time—component (10%) was *trans*-2-phenyl-2-octene (**11**, R = *n*-Bu).[5] The third—long retention time—component (15%) was *cis*-2-phenyl-2-octene (**10**, R = *n*-Bu).[5]

***tert*-Butylation of 2-Phenyl-3-buten-2-ol (9).** Using a procedure similar to that above with 3.7 g (25 mmol) of **9**, 4.34 g (38 mmol) of TMEDA, 50 mmol of *n*-butyllithium, and about a total of 100 ml of hexane, the reaction mixture was refluxed overnight and worked up as before. The crude product was vacuum distilled, 75–85° (1.5 mm), and analyzed by both vpc (6-ft SE 30 column (¼ in.) at 140°) and nmr. The distilled product consisted of a mixture 70% starting alcohol **9** and 15% each of two other components of longer retention time.

The distilled product was separated by preparative vpc. The first component collected (70%) was identical in retention time and nmr and mass spectra with **9**. The second component (15%) was *trans*-2-phenyl-5,5-dimethyl-2-hexene (**11**, R = *t*-Bu).[5] The third—long retention time—component was *cis*-2-phenyl-5,5-dimethyl-2-hexene (**10**, R = *t*-Bu).[5]

Rearrangement of 1-Phenyl-2-buten-1-ol (13). In a procedure similar to above, 5.5 g (37 mmol) of **13**,[8] 4.3 g (37 mmol) of TMEDA, 80 mmol of *n*-butyllithium, and a total volume of about 100 ml of hexane were refluxed overnight. The crude product was analyzed by vpc at this point and showed only one major product—different from the starting material. The product was vacuum distilled and four fractions in the range 70° (1.5 mm)–140° (0.2 mm) were collected. The vpc traces of all the fractions were nearly the same, consisting of one major peak, which had the same retention

time as butyrophenone (14),[9] and several minor peaks of intensity of 10–20%. The nmr spectra of various fractions were also similar, showing the characteristic pentet at δ 1.65, triplet at δ 1.80, and ortho aromatic protons at δ 7.85 of butyrophenone together with variable strong absorptions in the aromatic (δ 7.0–7.4), aliphatic (δ 0.8–1.4), and vinyl (δ 5–6.3) regions. The clean-looking vpc trace yet a somewhat messy nmr could possibly be explained by the existence of polymeric products which might arise during reaction, distillation, and/or chromatography. The starting alcohol 13 is fairly susceptible to dehydration and polymerization, as we found out in some of our preparations. The butyllithium could promote a base-catalyzed elimination of water and polymerization of 13.

The reaction was repeated as before except the TMEDA was left out and THF was added in its place, so that the solvent system consisted of a mixture of hexane and THF. Analysis of the crude product by vpc (SE 30) showed, again, only one outstanding peak of retention time identical with that of authentic butyrophenone. However, the nmr of the crude product showed by overlapping comparisons to authentic samples that it was about a 1:1 mixture of alcohol 13 (which was not showing up to any great extent on the vpc possibly due to polymerization on the column) and ketone 14, together with additional aromatic and aliphatic signals.

Registry No.—9, 6051-52-1; 10 (R = *n*-Bu), 53109-16-3; 10 (R = *t*-Bu), 37887-25-5; 11 (R = *n*-Bu), 53109-17-4; 11 (R = *t*-Bu), 37887-26-6; *cis*-12, 768-00-3; *trans*-12, 767-99-7; 13, 3347-57-7; 14, 495-40-9.

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(1) To whom correspondence should be addressed at the Synthetics Department, Research Center, Hercules, Inc., Wilmington, Del. 19899.
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(4) Samples of these compounds were kindly supplied to us by Dr. M. A. McKinney (Marquette University). The olefins were prepared by dehydration of 2-phenyl-2-butanol according to the procedure of J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1469 (1969). The olefins, present in a 3:1 ratio, were separated by preparative vpc from the terminal olefin. The major olefin is reported to be the cis isomer: J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry," 3rd ed, McGraw-Hill, New York, N.Y., 1970, p 365. The major olefin possessed an ir spectrum identical with that of *cis*-2-phenyl-2-butene (Sadler, Vol. I, 1619).[5] The minor olefin possessed an ir spectrum identical with that of *trans*-2-phenyl-2-butene (Sadler, Vol. I, 1618).[5]
(5) Spectral data given in Table I.
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Zinc Chloride Catalysis in the Reaction of Thionyl Halides with Aliphatic Alcohols

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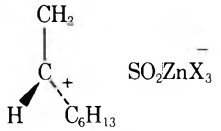
Since our report[2] that zinc chloride–thionyl chloride (1) easily converts 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (2) to 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (3), we have extended the use of reagent 1 to aliphatic systems. Since rapid, easy, high-yield, and high-purity synthesis of 3 was a significant breakthrough for carbohydrate chemists, we have documented the effectiveness of 1 with representative alcohols. We report here (1) clear proof that zinc chloride catalyzes the reaction of thionyl chloride with alcohols (Table I), (2) comparison of zinc chloride with pyridine as a catalyst, and (3) the yield and stereochemical result of converting optically active 2-octanol (4) to its chloride and bromide with the appropriate thionyl halide (Table II).

In addition to 4, the reagent 1 was allowed to react with the following alcohols: 1-butanol (5), 2-butanol (6), 2-methyl-2-propanol (7), and cyclohexanol (8). In Table I we show that reagent 1 readily converts each of these alcohols to product, under conditions where thionyl chloride alone gives little or no substitution. These data also document the synthetic utility of reagent 1 (runs 5, 8, 11, and 14). The yields of isolated products are acceptable, and no effort was made to optimize them.

The 2-chlorobutane produced from 5 (runs 4 and 5) is a primary reaction product, for 1-chlorobutane does not isomerize when treated with 1 for 2 days. This product mixture from 5 has been previously reported,[3] and led us to seek a catalyst to suppress the formation of the rearrangement product, 2-chlorobutane. Since pyridine has been widely used as a catalyst with thionyl chloride,[4] we investigated it with alcohols 5 and 6. With 5, pyridine was superior to zinc chloride; no rearrangement was detected by vpc (although 55% product formed in 2 days). With alcohol 6, pyridine gave lower initial and overall conversion than was attained with reagent 1. Attempts to combine zinc chloride and pyridine as a mixed catalyst were unsuccessful; lower conversion to product was generally observed than with either catalyst used alone.

For stereochemical studies (Table II), commercial 2-octanol (4) was resolved and purified according to the method of Kenyon.[5] Zinc chloride with either thionyl chloride or bromide in benzene or dioxane solution was an effective catalyst. At the concentration employed here, thionyl bromide slowly converts 4 to 2-bromooctane, but even this relatively easy reaction was greatly aided by zinc chloride. In every case where zinc chloride was used as a catalyst, the product was less optically pure than the starting 4 (*e.g.*, runs 15 and 16). This fact, along with the rearrangement product observed when reacting 5 with the reagent 1, suggests that, at some time during the reaction, at least partial symmetry is attained by the cation. Boozer and Lewis appear to be the first to propose that ions are involved in the mechanism of transforming alcohols to alkyl chlorides.[6] We find their mechanism compatible with our data, by assuming that zinc chloride complexes at one or more stages of the reaction, makes some reaction species more ionic, and in this manner speeds the reaction. The structure 9 is a representation of a possible intermediate



9, X = Cl or Br

when 1 converts 4 to the chloride. Solvation of such an intermediate could explain the effect of dioxane on the reaction of 1 with optically active 4. We can neither support nor reject the "ion pair" hypothesis of Sneen for solvolytic reactions.[7]

In conclusion, we have demonstrated that zinc chloride catalysis can be of value in converting alcohols to the corresponding chloride or bromide. As in the previously cited example of the conversion of 2 → 3,[2] this can be especially important when low acidity, mild temperature reaction conditions are desired.

Experimental Section

General Procedures. All boiling points are uncorrected. All reagents were the best commercial grade available, dried and/or distilled before use, and stored appropriately so as to prevent contamination. Reaction analysis was done on the Varian 90P-3 gas chromatograph (vpc) with the Model 244 disk–chart integrator for

Table I
Reaction of Selected Alcohols with Thionyl Chloride[a]

Run	Alcohol (mmol)	Equivalents of thionyl chloride	Mmol of zinc chloride	Hours to half-conversion	Maximum % conversion	Total hr for reaction
1	4 (22.0)	3.45	0		15[c]	161
2	4 (15.4)	3.25	1.8	~0.25[b]	100[b]	1.0
3	5 (55.0)	1.0	0		0	48
4	5 (55.0)	2.0	7.3		49[d]	48
5	5 (547)[e]	1.2	18.0	~2[b]	73[c,f]	30
6	6 (11.0)	1.0	0		~1	48
7	6 (11.0)	1.0	0.37	0.5	94	24
8	6 (437)[g]	1.2	14.5	~0.5[b]	73[c]	2.5
9	7 (2.7)	1.0	0	38	64	72
10	7 (2.7)	1.0	0.37	0.4	90	30
11	7 (533)[h]	1.2	18.0	~2[b]	78[c]	12
12	8 (9.5)	1.5	0		0	116
13	8 (9.5)	1.5	0.37	0.35	100	1.0
14	8 (473)[i]	1.2	18	~0.5[b]	75[c]	1.5

[a] All reactions were conducted under anhydrous conditions, at room temperature, and, except as noted, in 50 ml of benzene solvent. See Experimental Section for other details. [b] Estimated from vpc by disappearance of the starting alcohol. [c] Isolated by distillation. [d] Total chloride produced; 67% 1-chlorobutane and 33% 2-chlorobutane, by vpc on column B. [e] 100 ml of decane as solvent. [f] 73% 1-chlorobutane and 27% 2-chlorobutane by vpc on column B. [g] 180 ml of decane as solvent. [h] 250 ml of toluene as solvent. [i] 250 ml of benzene as solvent.

Table II
Reaction of *d*- or *l*-2-Octanol with Thionyl Halides

Run	$[\alpha]D$ alcohol	Solvent (50 ml)	Mmol of alcohol	Mmol of thionyl chloride	Mmol of thionyl bromide	Mmol of zinc chloride	Reaction time, hr	Yield	$[\alpha]D$ halide[a]	Stereochemical result,[b] %
15	+5.9	Benzene	22.0	76.0		0	161	15	−20.0	93 inversion
16	+5.9	Benzene	15.4	50.0		1.8	1.0	100	−10.3	48 inversion
17	−8.75	Dioxane	23.0	60.0		0	42	100	−25.7	82 retention
18	+5.9	Dioxane	15.4	50.0		1.8	1.0	100	− 0.4	98 racemization (2 inversion)
19	+5.9	Benzene	23.0		51.0	0	20	89	−13.5	64 inversion
20	−8.75	Benzene	11.4		36.6	1.8	1.0	100[c]	+17.7	59 inversion
21	+6.3	Dioxane	15.4		50.0	0	110	100	+10.0	48 retention
22	−8.75	Dioxane	11.4		36.6	1.8	1.0	100[c]	+ 4.90	84 racemization (16 inversion)

[a] Optically pure 2-chlorooctane has a rotation of 35.8°; 2-bromooctane, 34.2°. [b] Calculated relative to the optical purity of the starting alcohol. [c] Vpc analysis on column A showed no 2-chlorooctane, where the detection limit was 0.5 ± 0.5% (see Experimental Section).

the Varian Model 20 recorder. The columns used were A, 0.25 in. by 5 ft 20% SE-30 in 60–80 Chromosorb W; and, B, 0.25 in. by 10 ft 20% Apiezon-L on 45–60 mesh Chromosorb P. The column was operated between 80 and 145°, with 45–60 ml/min helium gas flow, and thermal conductivity detection. All products were identified by vpc comparison to authentic material and by comparing ir spectra on the Beckman IR 5-A.

The yields in Table I were determined, except as noted, on column B by the vpc method of internal standard.[8] In the runs without a standard solvent (**1**, **2**, **5**, **8**, **11**, and **14**), the reactions were terminated when the vpc showed either complete consumption of alcohol, or no further change. Column A was used for 1 and 2; column B, the others.

The resolved 2-octanol[5] for the experiments of Table II was considered acceptable if greater than 50% optically pure. Yields were determined by noting the vpc disappearance of the alcohol (column A). Optical rotations were measured in ethanol solution at 22°. The measurements were made with ~0.4 *M* solutions, on a Rudolph polarimeter with a sodium D lamp.

Typical Procedure for the Reactions Reported in Table I (Run 7). A 100-ml flask was fitted with a calcium chloride drying tube and a magnetic stirrer. A 50-ml pipet of standard solvent[8] (primarily benzene) was transferred into it, followed by 0.05 g (0.37 mmol) of zinc chloride, 1.00 ml (11 mmol) of **6**, and finally 0.80 ml (11 mmol) of freshly distilled thionyl chloride. The time of reaction was measured from the time of $SOCl_2$ addition. The reaction was monitored by quenching small aliquots in saturated sodium bicarbonate and then comparing the vpc area (column B) of the 2-butyl chloride peak with the internal standard. All reactions were conducted in duplicate, and all aliquots were analyzed at least three times. Runs 1 and 2 were similar, except that after quenching with saturated $NaHCO_3$, the chloride was additionally purified by filtration through silica gel.

Preparation of 2-Butyl Chloride (Run 8). A three-neck flask was protected from moisture, stirred magnetically, and equipped with a condenser and dropping funnel. The decane solvent (180 ml), 40 ml (0.437 mole) of **6**, and 2.0 g (14.5 mmol) of $ZnCl_2$ were added. Into this mixture was dropped 38 ml (0.524 mol) of $SOCl_2$, at a slow enough rate to keep the temperature below 30°. The reaction was stirred an additional 2.5 hr, following $SOCl_2$ addition, and then quenched carefully with 400 ml of saturated $NaHCO_3$. The organic layer was washed with 50 ml of water and dried over $MgSO_4$. The product was distilled through a short column and weighed 29.6 g (73%). Runs 5, 11, and 14 were done in a similar manner. All were analyzed on column B.

General Procedure for Preparation of 2-Octyl Halide from Optically Active 4. The optically active **4** was reacted with either $SOCl_2$ or $SOBr_2$ in the same manner as for run 7. The yields were determined by analysis of an aliquot on column A. The reactions were quenched with saturated $NaHCO_3$ and the product layers were separated (or extracted with benzene when dioxane was the solvent) and dried over $MgSO_4$. After distillation (and/or purification through Woelm Silica Gel), the 2-octyl halide was >98% pure (column A).

Control Experiments. In order to confirm that the 2-octyl halide did not react further after initial formation, a control was run with each experiment. A sample of *l*-4-bromide was treated with 40 ml of dioxane, 200 mg of $ZnCl_2$, and 1.0 ml of thionyl bromide.

After 22.5 hr, the recovered product was unchanged in optical rotation. Similarly, with *l*-4-chloride, the rotation was constant over 5 hr.

Acknowledgment. We appreciate the assistance, in the preparation of this work for publication, graciously given by Professor C. J. Collins, of the University of Tennessee and the Oak Ridge National Laboratory.

Registry No.—(+)-4, 5978-70-1; (−)-4, 6169-06-8; 5, 71-36-3; 6, 78-92-2; 7, 75-65-0; 8, 108-93-0; zinc chloride, 7646-85-7; thionyl chloride, 7719-09-7; thionyl bromide, 507-16-4.

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Oxymercuration of Nitrogen Heterocycles. II.[1] Syntheses of Novel Nitrogen Heterocycles and Cycloheptatriene Carboxaldehydes from *N*-Benzyldihydroazabullvalene and Dihydro-9-azabicyclo[4.2.2]deca-2,4,7-triene

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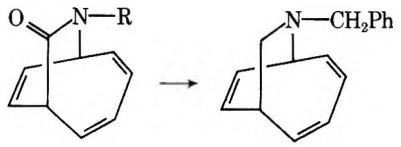
Solvomercuration–demercuration provides a convenient synthetic route for conversion of olefins into Markovnikov alcohols and ethers. An advantage of this synthetic approach is that additions generally occur without rearrangements.[2] However, there are a few alicyclic substrates which, because of their ground state strain or because they are precursors of stabilized carbonium ions, can rearrange either directly upon the addition of mercuric ions or following loss of free mercury from unstable hydroxymercurial ions. Most notably, rearranged oxymercurials are formed from bullvalene,[3,4] bicyclo[4.2.2]decatetraene,[4,5] and several 1-alkylidene-2-alkoxycyclopropanes,[6] while cyclobutene and 1-methylcyclobutene,[7] hexamethyl(Dewar benzene),[8] and cyclooctatetraene[9] undergo rearrangement with concomitant oxidative demercuration. Although mercuric acetate is capable of coordination with olefins in the presence of amines,[10,11] there have been no reports of rearrangements during the oxymercuration of heterocyclic structures. We here report two heterocyclic molecules **3** and **4** which can exhibit both of the above types of anomalous behavior during oxymercuation. In anhydrous media rearranged products of oxymercuration afford azabicyclic structures **5** and **6a** upon reduction, while in aqueous media, oxidative demercuration of hydroxymercurial product ions results in the synthesis of novel cycloheptatriene carboxaldehydes **7** and **8**.

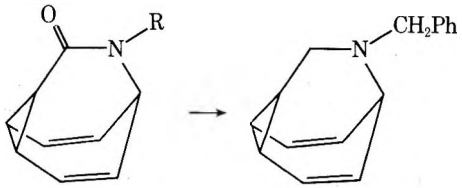
Discussion

The lactam **1a**[12] was benzylated with benzyl chloride–sodium hydride in dimethylformamide and the resulting *N*-benzyl lactam **1b** was treated with trimethyloxonium fluoroborate–sodium borohydride[13] to give amine **3**. Similar benzylation of lactam **2a** followed by aluminum hydride[14] reduction of **2b** afforded amine **4**. Detailed nmr analysis[15] of homotropilidene structure **4** has indicated the tautomeric structure is preferred in which nitrogen is not adjacent to cyclopropane.



1a, R = H
b, R = CH_2Ph

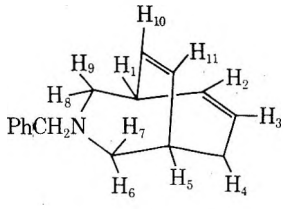
3



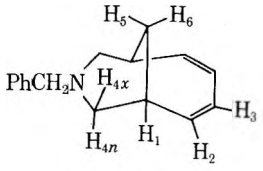
2a, R = H
b, R = CH_2Ph

4

Table I
Pmr Spectra of Azabicyclics 5 and 6a



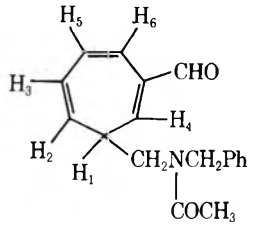
6a



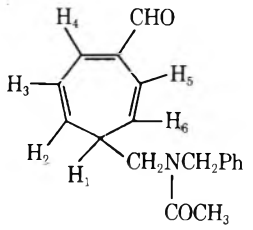
5

Proton	δ	Appearance, *J*, Hz	Proton	δ	Appearance, *J*, Hz
H_1	2.74	m, $J_{1,10} = 8.5$	H_1	2.54	m, $J_{1,4x} = 3.5$
H_2, H_3	5.72	m	H_{4x}	2.16	dd, $J_{4x,4n} = 11$
H_4, H_5	2.26	br	H_{4n}	2.84	dd, $J_{1,4n} = 1.0$
H_6, H_8	2.18, 2.30	d, $J_{8,9} = J_{6,7} = 11$	H_5, H_6	1.80	br
H_7, H_9	2.60, 2.84	dd, $J_{5,7} = J_{1,9} = 4$	H_2, H_3	5.86	br
H_{10}, H_{11}	5.90, 6.20	t, $J_{5,11} = 8.5$			
CH_2Ph	3.60, 7.30	s, br	CH_2Ph	3.46, 7.20	s, s

Table II
Pmr Spectra of Cycloheptatriene Carboxaldehydes 7b and 8b



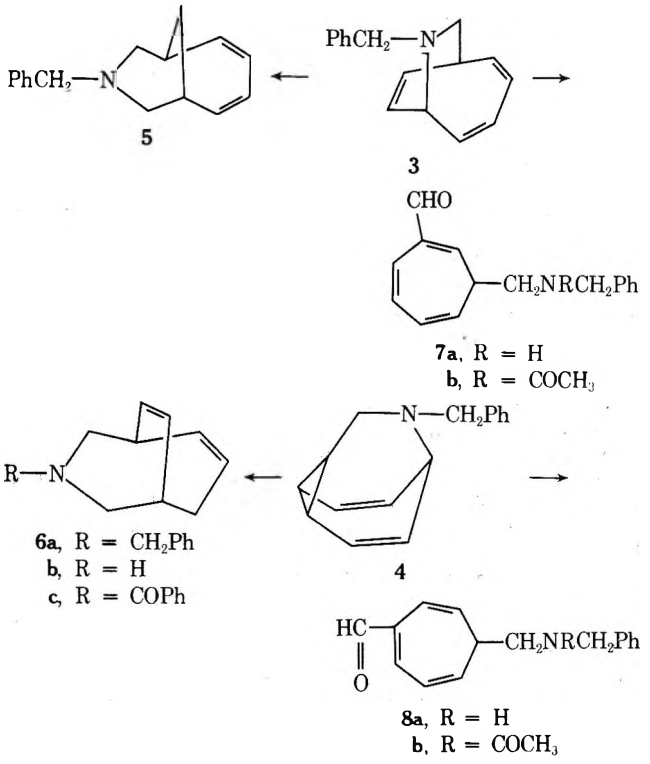
7b



8b

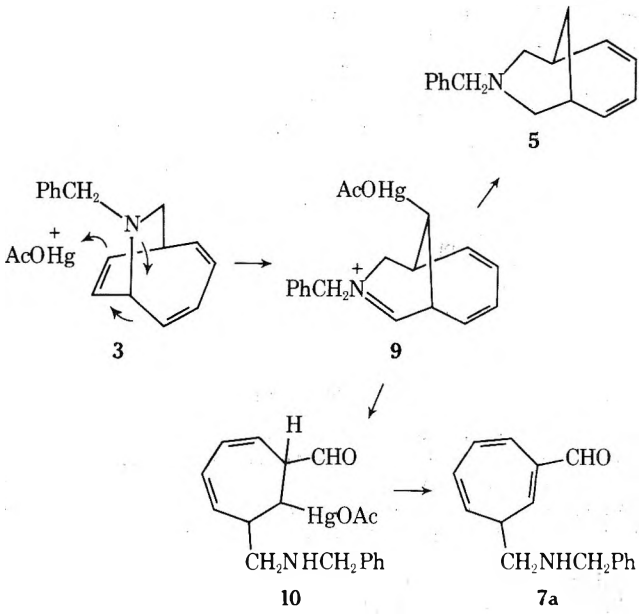
Proton	δ	Appearance, J, Hz	Proton	δ	Appearance, J, Hz
CH_3	2.14	s	CH_3	2.08	s
H_1	2.31	br, $J_{1,2} = 5$	H_1	2.30	m, $J_{1,2} = 4$
H_2	5.30	dd, $J_{2,3} = 9$	H_2	5.65	dd, $J_{2,3} = 10$
H_3	6.22	dd, $J_{3,5} = 6$	H_3	6.22	dd, $J_{3,4} = 6$
H_4	6.11	d, $J_{1,4} = 6$	H_4	7.06	d
H_5	6.70	dd, $J_{5,6} = 11$	H_5	6.69	d, $J_{5,6} = 10$
H_6	6.99	d	H_6	5.46	dd, $J_{1,6} = 5$
CH_2N	3.80	br	CH_2N	3.74	m, $J_{vic} = 5$; $J_{gem} = 14$
CH_2Ph	4.60, 7.09	s, s	CH_2Ph	4.48, 7.26	br, br
CHO	9.53	s	CHO	9.58	s

Treatment of amine **3** with mercuric acetate is anhydrous methanol followed by sodium borohydride demercuration afforded the rearranged amine **5.** Under these conditions amine **4** rearranged to afford amine **6a.** The structures of amines **5** and **6a** were determined on the basis of spectral data including nmr spin decoupling (Table I). Structure **6a** was confirmed by independent synthesis from **6b.**[12] If, however, amine **3** was stirred with mercuric acetate in aqueous tetrahydrofuran, elemental mercury was formed along with the novel rearranged ring cleavage product, cycloheptatriene carboxaldehyde (**7a**). Amine **4** afforded cycloheptatriene carboxaldehyde **8a** under these latter conditions. The rearrangements could also be effected in acetic acid–acetic anhydride solution to afford upon addition of water the aldehydes **7b** and **8b.** The structures of **7b** and **8b** were readily determined from their special data (Table II and Experimental Section).



The most plausible mechanisms for the formation of **5** and **7** from **3** are shown in Scheme I. Coordination of a mercuric ion with the olefinic bridge is followed by bond migration to form the stabilized immonium ion **9.** This ion **9,** or its amino ketal equivalent, is reduced in methanol by sodium borohydride to form bicyclic amine **5,** However, in water ion **9** hydrolyzes to give cycloheptadiene **10,** which upon loss of mercury and acetic acid affords cycloheptatriene carboxaldehyde **7a.**

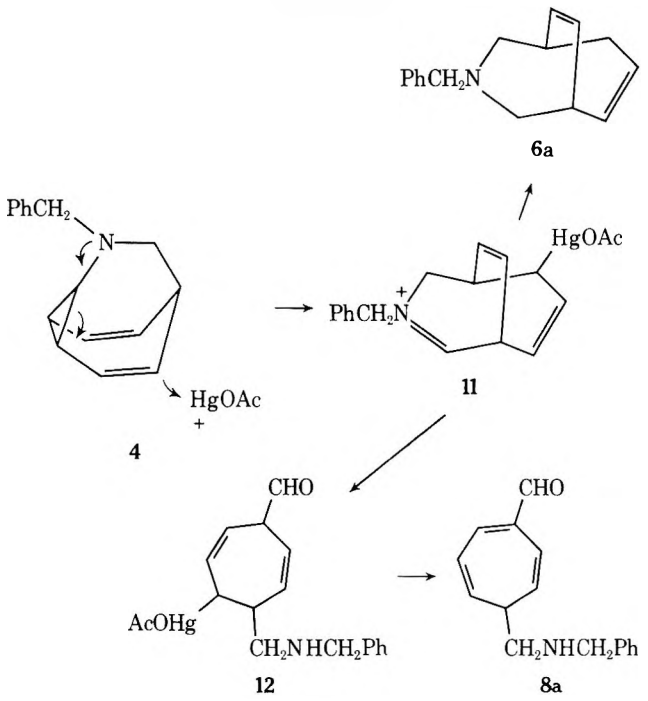
Scheme I



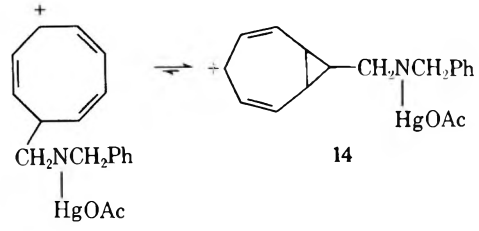
In Scheme II pathways for formation of **6a** and **8** from **4** are depicted. Coordination of a mercuric ion with an olefinic bond of **4** is followed by ring opening with nitrogen participation from the less stable tautomeric form of **4** to afford immonium ion **11.** In methanol ion **11,** or its amino ketal equivalent, is reduced by sodium borohydride to bicyclic amine **6a.** In water ion **11** hydrolyzes to cycloheptadiene **12,** which upon oxidative demercuration yields cycloheptatriene carboxaldehyde **8a.**

Alternatives to Schemes I and II involving coordination of mercuric acetate with nitrogen followed by carbon–ni-

Scheme II



trogen bond cleavage and generation of a homotropylium cation are unlikely. The cation **13** formed from amine **3** should readily convert to its valence tautomer **14** formed from **4**. Thus, product overlap would be expected if a ring cleavage process had occurred.



Experimental Section

The nmr spectra were determined on a Varian Associates XL-100-15 spectrometer using tetramethylsilane as internal standard. Couplings and coupling constants were determined with the aid of spin-decoupling experiments; where necessary several solvents were employed to improve resolution of individual peaks. Uv spectra were recorded on a Cary 14 spectrometer. Melting points and boiling points are uncorrected. Microanalyses were performed by Microanalysis, Wilmington, Del.

***N*-Benzyl-9-azabicyclo[4.2.2]deca-2,4,7-triene (3).** A magnetically stirred solution of lactam **1a**[12] (4.0 g, 27 mmol) in sodium hydride–57% oil dispersion (1.16 g, 28 mmol) in dry dimethylformamide (100 ml) was heated at 65° for 1 hr and cooled to 45°, and benzyl chloride (3.8 g, 30 mmol) was added. After 8 hr at 45°, the reaction mixture was filtered to remove sodium chloride, solvent was removed *in vacuo* and the oily residue was washed with pentane. The oil solidified to give *N*-benzyl lactam **1b** (6 g, 93%): mp 117.5–119° (tetrahydrofuran–pentane); nmr ($CDCl_3$) δ 7.24 (Ph), 6.06 and 5.62 (olefinic), 5.02 (d, J = 15 Hz, CHPh), 4.14 (d, J = 15 Hz, CHPh), 4.00 (CHN), and 3.82 (CHCO); ir ($CHCl_3$) 1640 cm^{-1}; uv (95% ethanol) λ_{max} 268 (ϵ 3900), 259 mμ (3900).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90. Found: C, 80.79, H, 6.39, N, 5.90.

To lactam **1b** (23 g, 97 mmol) in methylene chloride (200 ml) was added trimethyloxonium fluoroborate[13] (19 g, 100 mmol) under nitrogen. After 20 hr at 25°, solvent was removed *in vacuo*, and the residue was dissolved in anhydrous methanol (100 ml). Sodium borohydride (3.8 g) was added in small portions to the solution which was maintained below 5° during addition. After 12 hr at ambient temperature ether (300 ml) was added and the solution was washed with 10% sodium carbonate and dried (magnesium sulfate). Removal of solvent afforded a tan oil. Digestion with cold pentane and filtration removed unreacted amide **1b** (4 g). Removal of solvent gave amine **3** (14.5 g, 67%): bp 97–102° (0.5 mm); nmr ($CDCl_3$) δ 7.72 (Ph), 6.50 and 6.24 (olefinic), 4.14 (s, CH_2Ph), 3.94 (CHN), and 3.34 (CH_2N, $CH(C{=}C)_2$); uv (95% ethanol) λ_{max} (appear as shoulders) 277 mμ (ϵ 900), 265 (1600), 247 (2050); picrate, mp 139–140° (ethanol).

Anal. Calcd for picrate $C_{22}H_{20}N_4O_7$: C, 58.40; H, 4.46; N, 12.38. Found: C, 58.53, H, 4.47, N, 12.29.

***N*-Benzyl-4-azatricyclo[3.3.2.0^{2,8}]deca-6,9-diene (4).** Lactam **2a**[12] (8g) was benzylated as above for **1a** to afford *N*-benzyl lactam **2b** (9.5 g, 74%), mp 260°, unless placed in a bath preheated to 240°: nmr ($CDCl_3$) δ 7.24 (Ph), 6.04 (m), 5.74 (dd, J = 8 Hz), 4.74 (CH_2Ph, s), 3.54 (t, J = 8 Hz), 3.04 (t, J = 9 Hz), 2.44 (m, two protons).

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.99; H, 6.37; N, 5.90. Found: C, 80.72, H, 6.37; N, 6.01.

A 1.5 *M* solution of lithium aluminum hydride in tetrahydrofuran (50 ml) was added to dry ether (100 ml). This solution was cooled to 0° and 100% sulfuric acid (2.1 ml) was added dropwise keeping the temperature below 10°.[14] To this cold solution lactam **2b** (7.4 g) was added. The reaction mixture was stirred for 6 hr at 25° and then excess aluminum hydride was quenched with 10% sodium hydroxide solution until hydrogen evolution ceased. Filtration of solid, drying (magnesium sulfate), and removal of solvent afforded amine **4** (6.0 g, 90%) as an oil which crystallized from petroleum ether to give white crystals, mp 47–48.5°, nmr reported previously,[15] picrate, mp 131.5–133 (ethanol).

Anal. Calcd for picrate $C_{22}H_{20}N_4O_7$: C, 58.40; H, 4.46; N, 12.38. Found: C, 58.20; H, 4.56; N, 12.40.

***N*-Benzyl-8-azabicyclo[4.3.1]deca-2,4-diene (5).** A solution of **3** (530 mg, 2.4 mmol) and mercuric acetate (755 mg, 2.4 mmol) in dry methanol (25 ml) was stirred for 0.5 hr. Sodium borohydride (0.3 g) was then added to the solution cooled in an ice bath. Filtration through Celite removed mercury. Ether (100 ml) was added and the organic phase was washed with water and dried (magnesium carbonate). Removal of solvent afforded amine **5** (340 mg, 50%): purified by gc (1 m, 3% XF1150 Chromosorb W, 180°); uv (95% ethanol) λ_{max} 263 mμ (ϵ 5200), 252 (8600), 243 (8400);[4] nmr ($CDCl_3$, Table I).

Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.43; H, 8.55; N, 6.05.

***N*-Benzyl-3-azabicyclo[3.3.2.]deca-6,9-diene (6a).** A solution of **4** (580 mg, 2.6 mmol) and mercuric acetate (8.15 mg, 2.6 mmol) in dry methanol (25 ml) was reacted as above to afford after work-up amine **6a** (600 mg, 83%), purified by gc (1 m, 3% XF1150 Chromosorb W, 180°), nmr ($CDCl_3$, Table I).

Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.17; H, 8.52; N, 6.26.

Alternate Synthesis of 6a. Amine **6b**[12] (0.9 g) was allowed to react with benzoyl chloride (1 g) in pyridine (10 ml) on a steam bath to afford upon routine work-up benzamide **6c** (1.4 g), mp 78–79.5° (petroleum ether).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.42; H, 7.21; N, 5.88.

Benzamide **6c** (100 mg) in tetrahydrofuran (10 ml) was reduced for 8 hr at 25° with lithium aluminum hydride (25 mg). Usual work-up afforded amine **6a** (85 mg) identical with that obtained above.

Cycloheptatriene 2-Carboxaldehyde 7b. Route A. A solution of **3** (320 mg, 1.4 mmol) in 50% aqueous tetrahydrofuran (20 ml) containing mercuric acetate (460 mg, 1.4 mmol) was stirred for 10 hr at 25°. Free mercury formed in 10–20 min. The reaction mixture was basified and extracted with ether to afford amine **7a** (260 mg, 76%), which could be purified by tlc on alumina (R_f 9.0, 70–30 pentane–ether), or converted in 90% yield with acetic anhydride in methylene chloride to oily acetamide **7b**: uv (ethanol) λ_{max} 231 mμ (ϵ 3000), 204 (5200); ir (CCl_4) 1690 1650 cm^{-1}; nmr (acetone-d_6, Table II). The amine **7a** was analyzed as its methanesulfonamide 2,4-dinitrophenylhydrazone, mp 149–150° (ethanol).

Anal. Calcd for $C_{23}H_{23}N_5O_6S$: C, 55.53; H, 4.66; N, 14.08. Found: C, 55.67; H, 4.77; N, 13.89.

Route B. A solution of **3** (600 mg, 2.6 mmol) in acetic acid (20 ml) containing acetic anhydride (1 ml) and an excess of mercuric acetate (1.68 g, 5.25 mmol) was stirred at room temperature for 10 hr. During this time a small quantity of elemental mercury precipitated. The reaction mixture was concentrated to 5 ml, neutralized with sodium hydroxide, and extracted with ether to afford after drying ($MgSO_4$) and removal of solvent an oil **7b** (380 mg, 55%).

Cycloheptatriene 3-Carboxaldehyde 8b. Amine **4** (580 mg, 2.5

mmol) and mercuric acetate (820 mg, 2.5 mmol) in acetic acid (10 ml) containing acetic anhydride (1 ml) were stirred for 10 hr. Addition of water and work-up as above for **7b** resulted in formation of acetamide **8b**: uv (95% ethanol) λ_{max} 291 mμ (ε 4100), 226 (7400);[16] ir (CH_2Cl_2) 1690, 1650 cm^{-1}; nmr ($CDCl_3$, Table II). Amine **8a**, prepared as **6a** above, was analyzed as its methanesulfonamide 2,4-dinitrophenylhydrazone, mp 240–241° (ethanol).

Anal. Calcd for $C_{23}H_{23}N_5O_6S$: C, 55.53; H, 4.66; N, 14.08. Found: C, 55.34, H, 4.70, N, 14.04.

Registry No.—**1a**, 17198-06-0; **1b**, 52895-39-3; **2a**, 17303-53-6; **2b**, 52895-40-6; **3**, 52895-42-8; **3** picrate, 52928-64-0; **4**, 49542-98-5; **4** picrate, 52895-41-7; **5**, 52928-65-1; **6a**, 52895-43-9; **6b**, 52895-44-0; **6c**, 52895-45-1; **7a** methanesulfonamide 2,4-dinitrophenylhydrazone, 52895-46-2; **7b**, 52895-47-3; **8a** methanesulfonamide 2,4-dinitrophenylhydrazone, 52895-48-4; **8b**, 52895-49-5.

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Model Studies of Terpene Biosynthesis. Synthesis of (+)-2-[*trans*-2′-(2″-Methylpropenyl)cyclopropyl]-propan-2-ol[1]

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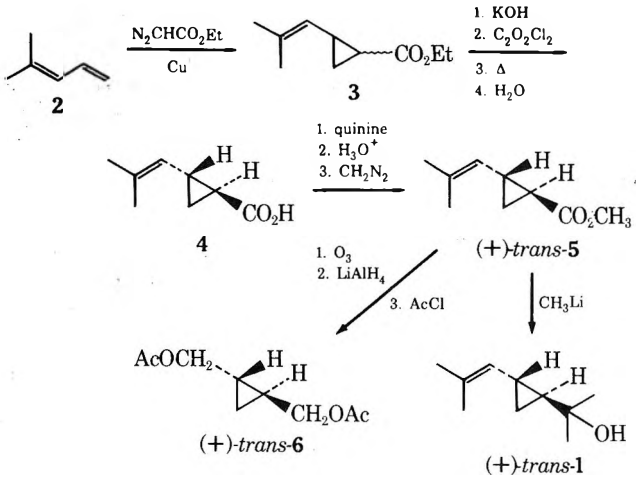
Tertiary cyclopropylcarbinyl cations have been proposed as intermediates in the rearrangements of C_{30} and C_{40} cyclopropylcarbinyl pyrophosphates to squalene and phytoene, respectively.[2] In this note we describe the synthesis of a C_{10} alcohol, (+)-2-[*trans*-2′-(2″-methylpropenyl)cyclopropyl]propan-2-ol, of known absolute configuration and optical purity, which serves as a precursor of the tertiary cation in model studies.[2e]

The synthesis of and optical correlations for (+)-*trans*-**1** are outlined in Scheme I. A 57:43 trans:cis mixture of ethyl ester **3** was obtained by copper-catalyzed addition of ethyl diazoacetate to 4-methyl-1,3-pentadiene (**2**).[3] The reaction was regiospecific (>98%) for the monosubstituted double bond.

The trans:cis ratio was increased from 57:43 in **3** to 95:5 in carboxylic acid **4** by the method of Smejkal and Farkas.[4] Saponification of **3** followed by treatment with oxalyl chloride gave a mixture of acid chlorides which were heated at

Scheme I



145° for 45 min. The acid obtained by hydrolysis of equilibrated acid chlorides was mostly (95%) trans.

Acid **4** was partially resolved by multiple recrystallization of its quinine salt. Although recrystallization was complicated by a small amount of salt from *cis*-**4**, quinine salts of *trans*-**4** were obtained free of cis contamination. The carboxylic acid was liberated from its quinine salt with hydrochloric acid and treated with diazomethane. The resulting ester, (+)-*trans*-**5**, was a single isomer, as judged by glpc and nmr.

The absolute configuration and optical purity of (+)-*trans*-**5**, $[\alpha]^{25}D$ +103° (c 2.3, $CHCl_3$), was determined by converting a portion of the ester to (+)-*trans*-1,2-diacetoxymethylcyclopropane (*trans*-**6**), $[\alpha]^{25}D$ +9.60° (c 1.6, EtOH). Since the maximum rotation of (1*R*,2*R*)-**6** is $[\alpha]^{25}D$ −17.75° (c 2.0, EtOH),[5] our sample of (+)-*trans*-**5** was 54% optically pure and predominately the 1*S*,2*R* enantiomer. Addition of methyllithium to (+)-*trans*-**5** gave (+)-*trans*-**1**.[3] Based on correlations with (1*R*,2*R*)-**6**, (1*S*,2*R*)-**5** and (1*S*,2*R*)-**1** should have maximum rotations of $[\alpha]^{25}D$ +191 and +33.5°, respectively, in chloroform.

Experimental Section

General. Boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer using tms as an internal standard. Analytical gas chromatography was carried out on a Varian Model 1200 gas chromatograph with a flame ionization detector, using a 500 ft × 0.03 in. open tubular column coated with Carbowax 20M. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Microanalyses were performed by M-H-W Laboratories, Garden City, Mich.

Ethyl *cis*- and *trans*-2-(2′-Methylpropenyl)cyclopropanecarboxylate, *cis*- and *trans*-3. Ethyl diazoacetate was prepared by the method of Moser.[6] In a typical run, 20.0 g (0.244 mol) of 4-methyl-1,3-pentadiene and 2.3 g of copper dust, which had been dried overnight under aspirator vacuum in a drying pistol heated by refluxing toluene, were placed in a dry 100-ml three-necked flask. To this was added, dropwise with stirring under a nitrogen atmosphere, 27.9 g (0.244 mol) of ethyl diazoacetate. Addition was as slow as possible, consistent with maintaining a gentle reflux of the reaction mixture. Complete addition took approximately 3 hr, after which the mixture was heated to reflux for an additional 15 min.

Unreacted diene was removed by distillation and the residue was filtered. Distillation of the filtrate at aspirator pressure gave 13.9 g (36%) of a colorless oil, bp 89–92°. An nmr spectrum of the distillate was similar to that reported by Robinson.[3]

(+)-*trans*-2-(2′-Methylpropenyl)cyclopropanecarboxylic acid, (+)-*trans*-4. A methanol solution of 12.8 g (76.2 mmol) of *cis*- and *trans*-**3** and 6.3 g of sodium hydroxide was heated at reflux for 3 hr. After cooling, the solution was added to 400 ml of water, acidified with hydrochloric acid, and extracted with three 150-ml portions of ether. The combined ether fractions were washed with brine, filtered through anhydrous sodium sulfate, and

dried over molecular sieves. Rotary evaporation of solvent gave 10.3 g (96%) of a syrupy residue which was dissolved in 45 ml of dry benzene. To the resulting solution was added 11.2 g (88.5 mmol) of oxalyl chloride. Gas evolution continued for 45 min and stirring was maintained for an additional hour. Solvent was removed at reduced pressure and the residue was heated at 145° for 45 min. The reaction was followed by quenching samples in methanol and determining the cis:trans ratio of methyl esters by glpc. At the end of the isomerization the mixture was 95% trans and 5% cis. The acid chloride was allowed to cool before water was added. The trans acid was isolated as described above; yield 6.3 g (61%).

Samples of *trans*-**4** from several isomerizations, 9.6 g (68 mmol), were allowed to react with 22.0 g (68 mmol) of quinine, and the resulting salt was partially resolved by recrystallization from 40:60 ethyl acetate–diethyl ether. After four recrystallizations, treatment of a less soluble fraction with dilute hydrochloric acid followed by extraction with diethyl ether yielded 1.54 g of optically active carboxylic acid, $[\alpha]^{25}D$ +72.5° (*c* 4.95, CH_3OH). From a more soluble fraction of the quinine salt, (−)-*trans*-**4**, $[\alpha]^{25}D$ −90.7° (*c* 4.84, CH_3OH), was obtained: nmr δ ($CDCl_3$) 0.7–2.3 (4, m, H at C_1, C_2, and C_3), 1.67 and 1.74 (6, two d, methyls at $C_{2'}$, $J \simeq$ 1.5 Hz), and 4.63 ppm (1, d of septets, H at $C_{1'}$, $J_{2,1'}$ = 9 Hz).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.80; H, 8.75.

(+)-Methyl *trans*-2-(2′-Methylpropenyl)cyclopropanecarboxylate, (+)-*trans*-5. *N*-Methyl-*N*-nitrosourea, 3.0 g (29 mmol), was stirred with 9 ml of 50% aqueous KOH and 36 ml of diethyl ether in an acetone–ice bath for 7 min, before the resulting yellow ether layer was decanted into a flask containing 1.54 g (11.0 mmol) of (+)-*trans*-**4**, $[\alpha]^{25}D$ + 72.5°. The reaction mixture was allowed to stand in the hood until the ether had evaporated, fresh ether was added, and the resulting organic fraction washed successively with saturated sodium bicarbonate and brine solutions. The organic layer was dried, and the ether evaporated, yielding 1.46 g (87%) of a colorless oil. Samples for spectra and analysis were purified by glpc (Carbowax 20M): $[\alpha]^{25}D$ +103° (*c* 2.33, $CHCl_3$); nmr δ 0.6–2.2 (4, m, cyclopropyl H), 1.63 and 1.70 (6, two d, methyls at $C_{2'}$, $J \simeq$ 1.5 Hz), 3.57 (3, s, carbomethoxy), and 4.52 ppm (1, d of septets, H at $C_{1'}$, $J_{2,1'}$ = 9 Hz); ir (CCl_4) 2950, 2900, 1725, 1660, 1450, 1180, and 1040 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.13; H, 9.28.

(+)-*trans*-1,2-Diacetoxymethylcyclopropane, (+)-*trans*-6. Ozone was passed through a solution of 107 mg (6.7 mmol) of (+)-*trans*-**5** in 15 ml of dry methylene chloride at −78° until a pale blue color persisted. Excess ozone was removed at −78° with a stream of dry nitrogen, and solvent was removed at reduced pressure. The residue was dissolved in 30 ml of dry ether to which was added 150 mg of $LiAlH_4$, and the mixture was allowed to stir overnight. Excess hydride was decomposed by addition of a saturated solution of NH_4Cl, and addition continued until the inorganic salts precipitated. The clear ether layer was decanted, and the precipitate was washed repeatedly with ether. The combined ether fractions were dried over anhydrous $MgSO_4$ and solvent was removed at reduced pressure, leaving 73 mg (100%) of a colorless oil:[5] nmr ($CDCl_3$) δ 0.1–1.4 (4, m, H at C_1, C_2, and C_3) 3.0–4.0 (4, m, hydroxymethyls at C_1 and C_2), and 4.25 ppm (2, br s, OH).

To a solution of 73 mg (0.70 mmol) of the trans diol and 500 mg (6.5 mmol) of pyridine in 10 ml of dry benzene was added 256 mg (3.26 mmol) of acetyl chloride. Heat was evolved and a white precipitate formed. After 30 min the reaction was diluted with 30 ml of ether and extracted with successive 10-ml portions of water, 3 *N* HCl, water, and saturated $NaHCO_3$. The ether layer was dried, and solvent removed at reduced pressure, yielding 101 mg (79%) of (+)-*trans*-**6**.[5] Analytical samples were purified by glpc (Carbowax 20M): $[\alpha]^{25}D$ +9.60° (*c* 1.57, EtOH); nmr ($CDCl_3$) δ 0.47–0.75 (2, m, H at C_3), 0.97–1.35 (2, m, H at C_1 and C_2), 2.13 (6, s, acetate methyls), and 4.08 ppm (4, d, acetoxymethyl at C_1 and C_3, J = 7 Hz).

(+)-2-[*trans*-2′-(2″-Methylpropenyl)cyclopropyl]propan-2-ol, (+)-*trans*-1. In a 100-ml three-necked flask with condenser, addition funnel, and N_2 inlet was placed 1.08 g (7.0 mmol) of (+)-*trans*-**5**, $[\alpha]^{25}D$ +103°, in 25 ml of anhydrous ether, and 10 ml of 1.5 *M* MeLi (15 mmol) was added dropwise. After stirring for an hour, 2 ml of saturated NH_4Cl was carefully added, and the clear ether layer was decanted and washed with brine. The ether solution was filtered through sodium sulfate and dried over molecular sieves. The solvent was evaporated at reduced pressure, leaving 0.97 g (90%) of a colorless, fragrant oil. Samples for analysis were collected by glpc: $[\alpha]^{25}D$ +18.1° (*c* 2.28, $CHCl_3$); nmr ($CDCl_3$) δ 0.6–2.2 (4, m, cyclopropyl H), 1.18 (6, s, H at C_1 and C_3), 1.63 and 1.70 (6, pair of d, CH_3's at $C_{2''}$, $J \simeq$ 1 Hz), and 4.58 ppm (1, d of septets, H at $C_{1''}$, $J_{2',1''}$ = 8 Hz); ir (CCl_4) 3500, 2900, 1660, 1440, 1370, 1160, and 910 cm^{-1}. Our spectra are similar to those reported by Robinson for racemic trans-**1**.[3]

Registry No.—(+)-*trans*-**1**, 52152-29-1; **2**, 926-56-7; *cis*-**3**, 53166-49-7; *trans*-**3**, 53166-50-0; *trans*-**4**, 53166-51-1; (+)-*trans*-**4**, 53187-84-1; (−)-*trans*-**4**, 53187-85-2; (+)-*trans*-**5**, 53187-86-3; (+)-*trans*-**6**, 53166-30-6; (+)-*trans*-**6** free diol, 53187-82-9; ethyl diazoacetate, 623-73-4.

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(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, Research Corporation, and the National Institutes of Health (Grant GM 19557) for support of this research.

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Homolysis of Methyl Phenylazo Sulfones

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Kice and Gabrielsen studied the thermolysis of methyl phenylazo sulfone (Ia) and concluded that the decomposition is homolytic on the basis of the product studies.[1] However, thermolysis of azo sulfones tends to contain some acid-catalyzed ionic decomposition because of the production of sulfinic or sulfonic acids.

When Ia was decomposed in nitrobenzene, the nitrobiphenyls formed were rich in its meta isomer, as shown in Table I. The isomer distribution suggests that both homol-

Table I
Products of Decomposition of Azo Sulfones in Nitrobenzene

Azo sulfone	Pyridine, mol/mol I	Temp, °C	Nitrobiphenyls: Yield, %	Orientation, % Ortho	Meta	Para	Nitrogen, %
I_a	0	80.5	*a*	33	41	26	38
I_a	2/1 I_a	80.2	77.1	67.0	10.0	23.0	86
I_a	3/1 I_a	80.1	75.3	68.3	9.4	22.3	95
II[b]	2/1 II	60.0	54.4	64.5	7.7	27.8	*a*

[a] Not determined. [b] In ref 2.

ysis and heterolysis are taking place. In the decompositions of phenylazo *p*-tolyl sulfone (II), acid-catalyzed heterolysis was effectively prevented by the addition of a base.[2a] Therefore, I was decomposed in the presence of pyridine. When 2 mol of pyridine per mol of I was present, the isomer distribution found indicated that the decomposition is

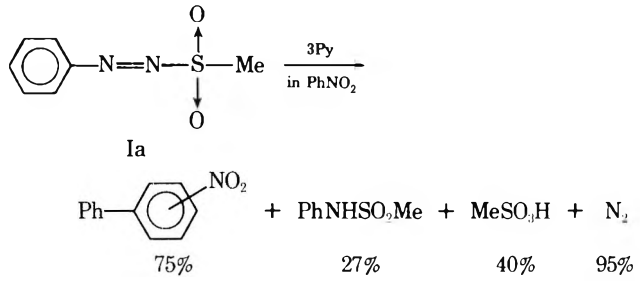
Table II
Coupling Constants of Nitroxide Radicals

	Nitroxide radical										
	V		VI		VII			VIII			
	A_N	g	A_N	g	A_N	A_H	g	A_N	$A_{o,pH}$	A_{mH}	g
Found											
Ether	15.1	2.0060	12.9	2.0059	13.6	2.8	2.0061				
C_6H_6	15.3	2.0060	12.9	2.0060				12.4	1.9	0.9	2.0060
Lit.[6]											
C_6H_6	15.2							12.3	2.0	0.9	

homolytic.[2] The presence of a greater amount of the base did not affect the isomer distribution greatly.

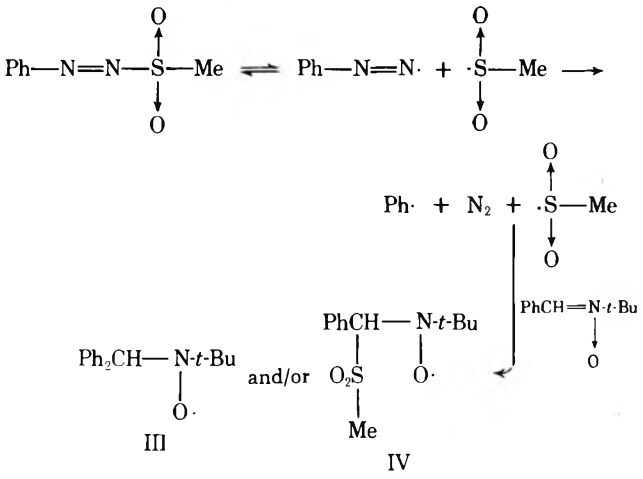
The rates of homolysis of Ia were determined in nitrobenzene in the presence of 3 mol of pyridine per mol of Ia, and were of first order in Ia; the first-order rate constants were 2.53 (80.1°), 4.25 (84.8°), 6.43 (89.5°), and 18.4 × 10^{-5} sec^{-1} (95.0°). The activation parameters obtained (ΔH^* = 33.5 kcal/mol, ΔS^* = 19.3 eu) are similar to those reported for azo sulfone II.[2]

The products of decomposition of Ia are summarized below.



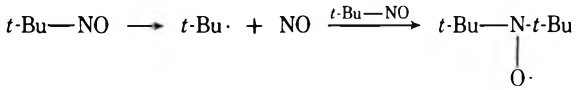
Formation of methanesulfonanilide is of interest. Since the yield of nitrogen gas is almost quantitative, the anilide moiety must come from nitrobenzene. When methyl *p*-tolylazo sulfone (Ib) was decomposed under similar conditions, methanesulfonanilide was found in a 24% yield. This finding ascertains that the anilide moiety comes from nitrobenzene. When a reaction mixture was concentrated under reduced pressure, a yellowish-green liquid was distilled, which was identified as nitrosobenzene. This suggests that nitrobenzene is reduced during the decomposition of I.

Spin Trapping. When Ia was decomposed in the presence of α-phenyl-*N*-*tert*-butylnitrone (PBN) in benzene, esr signals observed were a triplet of doublets with A_N = 14.5, A_H = 2.3 G, and g = 2.0061. These signals must be ascribable to either the adduct III or IV. As for the coupling

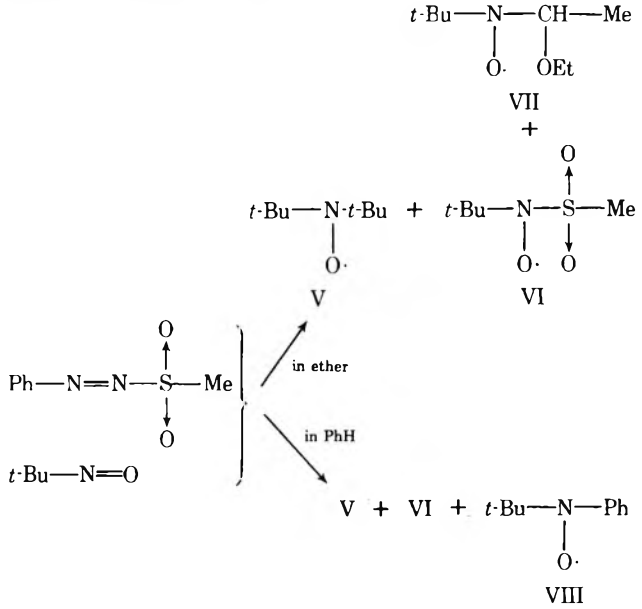


constants of III, Janzen and Blackburn[4] reported that A_N = 13.8 G and A_H = 2.1 G, while Bluhm and Weinstein[5] reported that under deoxygenated conditions A_N = 14.7 G and A_H = 2.18 G. In our reaction conditions nitrogen gas is continuously evolved and the system is virtually deoxygenated; our coupling constants are similar to those reported by Bluhm and Weinstein. Thus PBN effectively traps phenyl radical, but not methanesulfonyl radical.

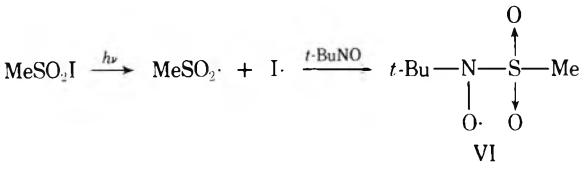
In an attempt to trap the methanesulfonyl radical, Ia was decomposed in the presence of 2-nitroso-2-methylpropane in diethyl ether. The ether was used as the solvent because phenyl radical will abstract the α hydrogens and the trapping of only methanesulfonyl radical is expected. The esr spectrum observed showed a stable triplet, a very unstable triplet, and a triplet–doublet. The stable triplet was ascribed to di-*tert*-butyl nitroxide radical (V), which could be formed by the addition of *tert*-butyl radical to 2-nitroso-2-methylpropane.



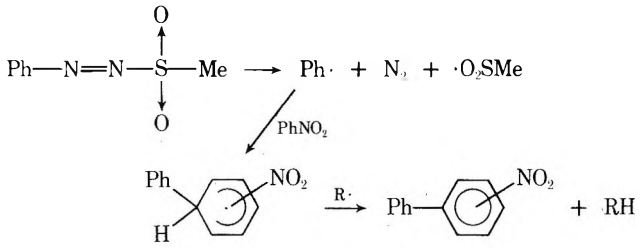
When benzene was used as the solvent, the triplet–doublet was not observed. Therefore, it must be due to radical VII, the adduct of the ether radical to the spin trap. The coupling constants and assignments of these nitroxide radicals are summarized in Table II. In order to check the assign-



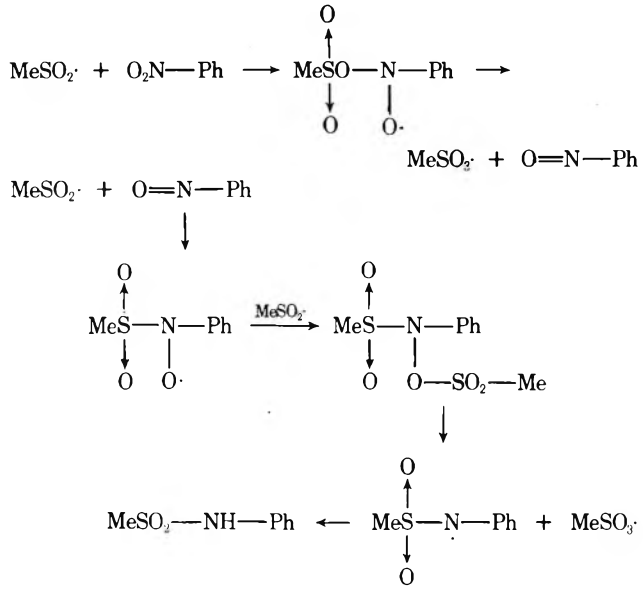
ment of the unstable triplet to VI, methanesulfonyl iodide was photolyzed in the presence of 2-nitroso-2-methylpropane; an unstable triplet ($\tau_{1/2}$ = about 50 sec) with A_N = 12.9 G and g = 2.0060 was observed. Thus the identity of the radical VI was established.



All the data obtained show that Ia decomposes homolytically, yielding phenyl radical and methanesulfonyl radical.



Phenyl radical attacks nitrobenzene, yielding nitrobiphenyls. Methanesulfonyl radical also attacks nitrobenzene and reduces it. Details of the reaction mechanism are not clear, but the following reaction steps are possible.



It is known that sulfonyl radicals do not attack arene nuclei,[7] and it appears reasonable that methanesulfonyl radical reacts with the nitro group, forming a nitroxide radical.

Experimental Section

Materials. Nitrobenzene and pyridine were purified according to conventional procedures. Methyl phenylazo sulfone (Ia) was prepared from sodium methanesulfinate[8] (2.62 g, 2 mmol) according to the method of Kice and Gabrielsen:[1] yield, 2.29 g (65%); mp 69.5–70.3° (lit.[1] 73–74.5°).

Methyl *p*-tolylazo sulfone (Ib) was prepared from sodium methanesulfinate (2.8 g, 2 mmol) by the method of Dutt:[9] yield, 1.5 g (37%); mp 109.3–111.5° dec (lit.[9] 112–113°).

α-Phenyl-*N*-*tert*-butylnitrone,[10] 2-nitroso-2-methylpropane,[11] and methanesulfonyl iodide[13] were synthesized according to the methods described in the literature.

Rates of Decomposition of Ia. A reaction vessel containing nitrobenzene (40 ml) and pyridine (0.451 g, 6.0 mmol) was placed in a constant-temperature bath under a nitrogen atmosphere and then Ia (0.362 g, 2.0 mmol) was mixed. The amount of nitrogen gas evolved was determined with a gas buret. The reaction vessel was covered with aluminum foil in order to prevent photolysis.

Products of Decomposition of Ia. After the decomposition was complete, the pyridinium sulfonate which precipitated was removed, and the solution was washed with water. When the aqueous extracts were made alkaline with Na_2CO_3 and evaporated, sodium methanesulfonate was obtained. The pyridinium salt and sodium salts were dissolved in D_2O, and their amounts were determined by nmr spectroscopy.

The nitrobenzene solution was concentrated under reduced pressure. Nitrobiphenyls were determined by glc, and methanesulfonanilide was determined by nmr spectroscopy.

Spin Trapping. With PBN. When a mixture of Ia, PBN, and pyridine in benzene was placed in an esr spectrometer (a JES-ME-3X), weak signals were observed. When the sample tube was irradiated with a 500-W mercury lamp, the signals became very strong. When the esr spectra were determined under a nitrogen atmosphere, the same results were obtained.

With 2-Nitroso-2-methylpropane. When a mixture of Ia, the dimer of 2-nitroso-2-methylpropane,[11] pyridine, and benzene (or ether) was placed in an esr tube in a JES-ME-3X, weak signals were observed, which were ascribable to VI. The mixture was irradiated with a 500-W mercury lamp using a Toshiba Filter UV-D2 (in order to decrease the formation of V). 2-Nitroso-2-methylpropane absorbs at 680 nm,[12] and the UV-D2 has maximum transparency at 360 nm, absorbing at a longer wavelength region.

Registry No.—Ia, 23265-32-9; Ib, 53188-52-6; II, 26788-89-6; V, 2406-25-9; VI, 53188-53-7; VII, 52704-27-5; VIII, 3229-61-6.

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One-Step Preparation of Tetrakis(bromomethyl)ethylene from Pinacolyl Alcohol

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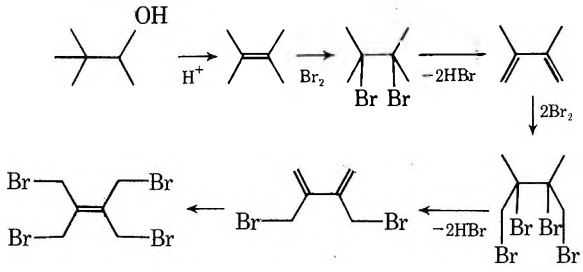
Tetrakis(bromomethyl)ethylene, $(BrCH_2)_2C{=}C(CH_2Br)_2$, has been used as a means of synthetic entry into the bicyclo[3.3.0]oct-1-ene[2a] and other[2b] alicyclic systems. During other work we have found that it can be prepared conveniently and inexpensively by treating the readily available pinacolyl alcohol with a large excess of neat bromine at 40–50°.

The bromination of pinacolyl alcohol has been investigated over many years; in 1907 Delacre reported the preparation of a compound, mp 132–133°, whose bromine analysis (no CH analysis was given) corresponded to the formula $C_6H_{11}Br_3$.[3] He further alluded to a dibromide, $C_6H_{12}Br_2$, prepared earlier by Friedel. In repeating this reaction we obtained instead products of widely varying melting point, which by recrystallization or sublimation gave samples identical in and homogeneous by tlc, but having melting

points varying between 145 and 163°. The nmr spectrum showed only one sharp singlet at δ 2.0, ruling out a $C_6H_{11}Br_3$ formula. However, these data serve to identify the compound as 2,3-dibromo-2,3-dimethylbutane, which has the same nmr spectrum,[4] and whose melting point has been variously reported (*e.g.*, 159°,[5] 170–175°,[6] 177–177.5°,[7] 180–182°[8]). No other compounds were detected in significant amounts in our repetitions of Delacre's reaction.

Increasing the amount of bromine and prolonging the reaction gave a new compound, mp 156–157°, which had a singlet at δ 4.10 as the only nmr signal. These data are in agreement with those for tetrakis(bromomethyl)ethylene, which Stetter and Tresper[9] have recently prepared by treating 2,3-dimethyl-2-butene, 2,3-dimethyl-1-butene, 2,3-dimethyl-1,3-butadiene, 1,2,3,4-tetrabromo-2,3-dimethylbutane, or 2,3-dimethyl-2-butanol with liquid bromine containing a little hydrogen bromide. We consider that these brominations of pinacolyl alcohol first involve the acid-catalyzed (hydrogen bromide added or generated *in situ*) conversion of the alcohol into tetramethylethylene,[10] which may then be transformed as shown in Scheme I. This scheme accounts also for Stetter and Tresper's results.[9] We believe that Delacre's compound may have been a mixture of 2,3-dibromo-2,3-dimethylbutane with either or both the tetrabromides shown in the scheme.

Scheme I
Suggested Reaction of Pinacolyl Alcohol with Bromine



The above synthesis of tetrakis(bromomethyl)ethylene represents an exceptionally easy and inexpensive preparation of this compound.

Experimental Section

Reaction of Pinacolyl Alcohol with Bromine (Cf. Ref 3). Bromine (5 ml) was added gradually to pinacolyl alcohol (10 ml) in a 50-ml flask. Considerable heat was generated and much HBr was evolved. After the reaction was complete, the colorless mixture was cooled to room temperature, which caused partial solidification. The mixture was partitioned between light petroleum and water. The pale yellow organic layer was decolorized (Norit) and concentrated to a partly solid mass, which was triturated with methanol. The methanol-insoluble portion (mp ~130°) was recrystallized repeatedly from cyclohexane or sublimed below the melting point (water aspirator) to give 2,3-dibromo-2,3-dimethylbutane as colorless crystals with a camphor-like odor: mp (different samples) 145°, 157–158°, 162–163°; homogeneous in tlc with silica gel–light petroleum; nmr ($CDCl_3$) δ 2.0 (s); ref 4 quotes δ 2.0.

Tetrakis(bromomethyl)ethylene from Pinacolyl Alcohol (Cf. Ref 9). To pinacolyl alcohol (0.1 mol, 12.6 ml) and concentrated hydrobromic acid (1 ml) in a flask fitted with a reflux condenser and set up in a hood was added, dropwise at first, neat bromine (40 ml), so that reaction was as gentle as possible. The temperature was maintained at 40–50° during 8 hr, at 20° overnight, and again at 50° for 2 hr. The red solid product was broken up in the presence of a little light petroleum, and excess bromine neutralized by adding solid sodium bisulfite and cracked ice under ice cooling. Water was finally added, and the crude tetrakis(bromomethyl)ethylene filtered off as pale yellow crystals, mp 133–136° (17.1 g, 43%). This material is substantially pure, but may be efficiently recrystallized once or twice from ethyl acetate to give colorless crystals, mp 156–157°; nmr δ 4.12 (s) in $CDCl_3$ [ref 9 cites light yellow crystals, mp 158.5°, δ 4.25 (s) in liquid bromine].

Registry No.—Pinacolyl alcohol, 464-07-3; bromine, 7726-95-6; 2,3-dibromo-2,3-dimethylbutane, 594-81-0; tetrakis(bromomethyl)ethylene, 30432-16-7.

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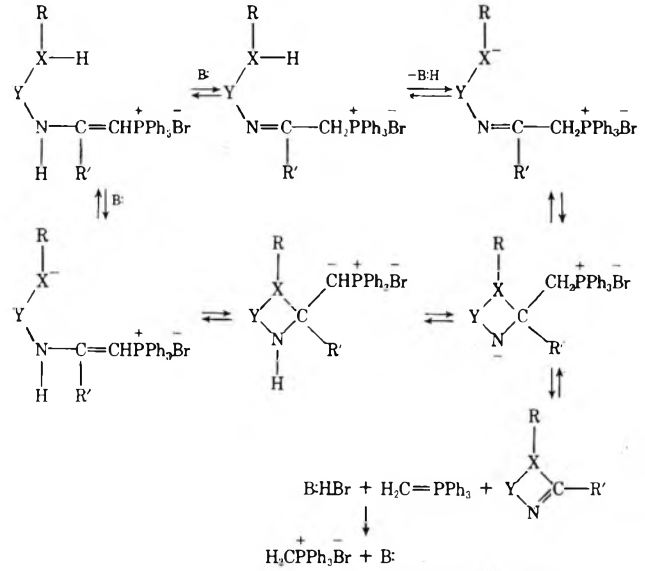
Reactions of Phosphorus Compounds. 36. Heterocyclic Synthesis *via* Methylenetriphenylphosphorane Extrusion

Summary: A synthetically useful ylide elimination reaction has been shown to be generally useful for the preparation of a variety of heterocyclic species.

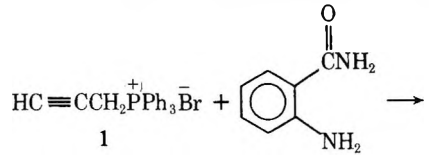
Sir: A number of reactions have been observed which involve the elimination of a phosphorane.[1-4] To date we know of no generally useful synthetic process where the loss of a phosphorane is envisaged.

We wish to propose a general base catalyzed heterocyclic synthesis involving the extrusion of methylenetriphenylphosphorane. The overall reaction pathway may be depicted in the following manner.

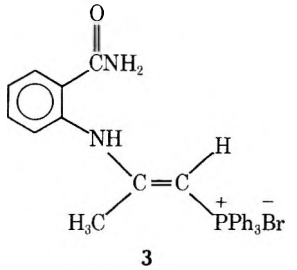


It has been shown that triphenyl(prop-2-ynyl)phosphonium bromide (**1**) undergoes nucleophillic addition with primary amines yielding β-aminopropenyltriphenylphosphonium bromides of synthetic utility for the preparation of substituted quinolines.[5] The β-phosphoniopropenylation reaction is used to prepare the intermediates employed to demonstrate the utility of the current reaction.

The salt **1** was allowed to react with *o*-aminobenzamide (**2**) and 2-hydroxy-5-methylaniline (**4**) in acetonitrile to give the corresponding salts in 96 and 87% yields, respectively.[6]



1 **2**



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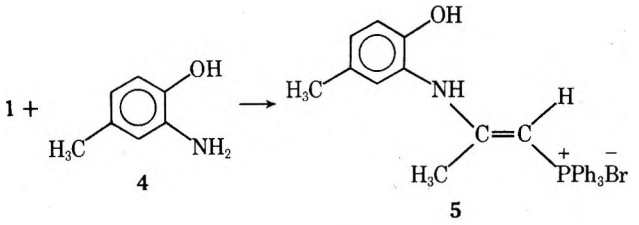
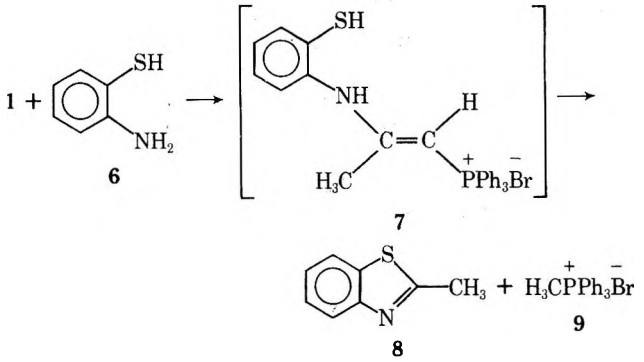


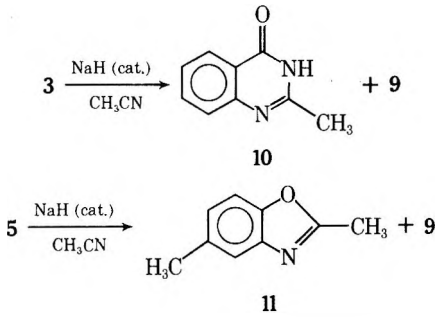
4 **5**

Treatment of *o*-mercaptoaniline (**6**) in acetonitrile with **1** gave the 2-methylbenzothiazole (**8**)[7] in 62% yield and methyltriphenylphosphonium bromide (**9**) directly, presumably *via* the intermediacy of **7**.



6 **7** **8** **9**

The heating of salts **3** and **5** in acetonitrile under reflux with a catalytic amount of sodium hydride gave the corresponding heterocycles, 2-methylquinazol-4-one (**10**)[8] and 2,5-dimethylbenzoxazole (**11**)[9] and the salt **9**.



10

11

The salt **9**[10] was isolated in essentially quantitative yield by adding ethyl acetate to the solutions of all three of the final reaction mixtures and filtering; the desired heterocycles[11] **10** and **11** were isolated from the filtrate in 75 and 80% yields, respectively.[12]

A careful evaluation of the full scope and utility of this procedure for the preparation of heterocyclic species is underway and will be reported at a later data.

Supplementary Material Available. Procedures for the preparation of compounds **3, 5, 8, 10,** and **11** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-75-144.

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(12) See paragraph regarding supplementary material.

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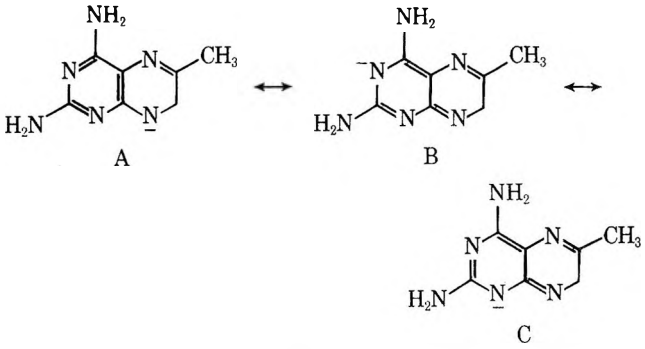
Direct N^8-Alkylation of 2,4-Diamino-7,8-dihydropteridines. Preparation of 7,8-Dihydro-8-methylmethotrexate[1]

Summary: A method is described for the N^8-alkylation of 2,4-diamino-7,8-dihydropteridines by reaction of these compounds with *n*-butyllithium in DMSO followed by treatment with an alkyl halide.

Sir: Dihydro and tetrahydropteridines in which the pyrazine ring is the reduced site are intermediates in many biological reactions in diverse living organisms.[2] The study of the chemical and biological properties of reduced pteridines is complicated by the fact that they are readily oxidized to the parent aromatic compounds, even upon standing in air. Substitution of methyl groups for hydrogen at N^8 in 7,8-dihydropteridines[3] and at N^5 and/or N^8 in 5,6,7,8-tetrahydropteridines[4] results in derivatives which resist facile oxidative degradation at the 5,6 and/or 7,8 positions. Although direct substitution at N^5 in 5,6,7,8-tetrahydropteridines can be accomplished rather easily under mild conditions,[4-7] N^8 is resistant to alkylation[6] and can be acylated only under drastic conditions.[5] In this communication we describe a method by which 2,4-diamino-7,8-dihydropteridines can be directly monoalkylated at N^8 without substitution either in the pyrimidine ring or on the 2- or 4-amino groups. The resulting products can then be hydrogenated catalytically to tetrahydropteridines.

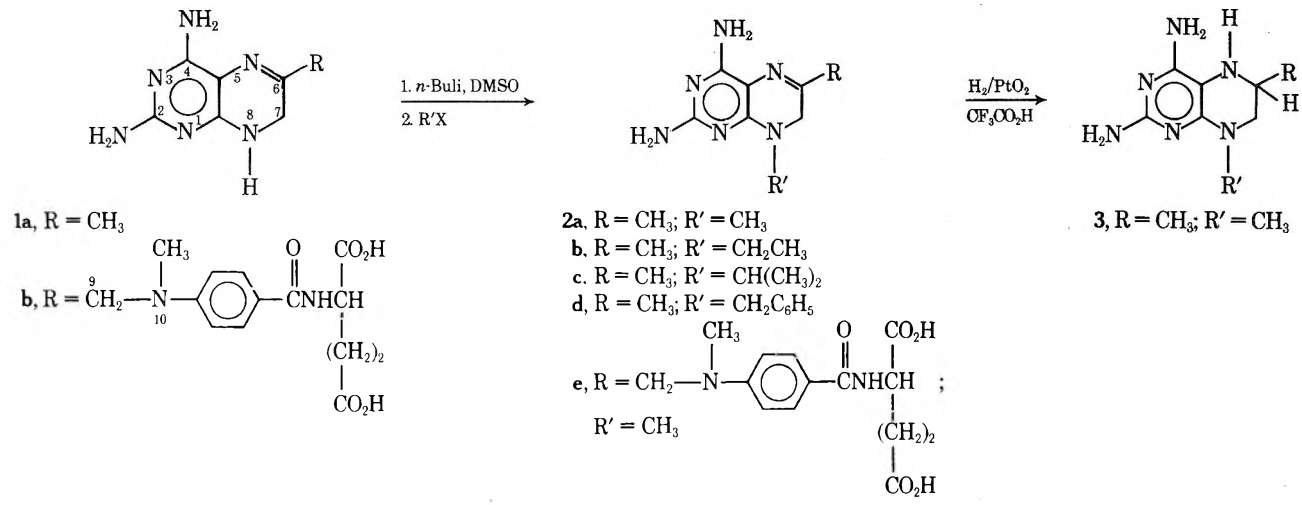
Since most of the biologically important pteridines are substituted at the 6 position, we chose to experiment with 2,4-diamino-7,8-dihydro-6-methylpteridine (**1a**)[8] as a model compound. The nmr spectrum of this compound in DMSO-d_6 (TMS internal standard) shows the C^6 CH_3 at δ 1.86 (s), the 7-CH_2 at 3.96 (s), the amino groups at 5.53 and 5.65 (overlapping singlets), and the N^8 H at 6.27 (s). This spectrum indicates that the N^8 H is deshielded with respect to the hydrogens on the amino groups. It was expected that if **1a** were treated with a powerful base, nucleophilic attack with proton abstraction would occur at N^8 H rather than at either of the amino groups. What is more important is that the resulting anion could be stabilized by resonance forms such as B and C in which the charge is accommodated on the nitrogens of the pyrimidine ring. Treatment of this anion with an alkylating agent should result in attack preferentially at the least hindered N^8 position.



A solution of **1a** in DMSO, under nitrogen at room temperature, was treated with 1.1 equiv of *n*-butyllithium in hexane,[9] followed after a few minutes by the addition of 1.2 equiv of methyl iodide. Addition of water after 15 min precipitated a white solid (71%, mp 260–280° dec) which appeared as a single new compound on tlc (silica gel, 8% MeOH–$CHCl_3$). The product was stable in air and was unchanged upon treatment with hydrogen peroxide in DMF for 30 min, conditions which rapidly oxidized **1a** to the fully aromatic pteridine. Elemental analysis gave the formula $C_8H_{12}N_6$ for this compound, in accordance with the introduction of a single CH_3 group into the starting material, and the uv spectrum [$\lambda_{max}^{0.1\,N\,HCl}$ 236 nm (ϵ 26,700), 263 (sh, 8130), 292 (13,600)] showed little change from that of **1a**.[8] The nmr spectrum in DMSO-d_6 was similar to that of **1a** except that the N^8 H peak was absent and a new singlet appeared at δ 2.78 (3 H). In CF_3CO_2H, the nmr spectrum consisted of singlets at δ 2.61 (C^6 CH_3), 3.24 (N^8 CH_3), and 4.86 (7-CH_2), almost identical with the reported spectrum of 2-amino-4-hydroxy-6,8-dimethyl-7,8-dihydropteridine, prepared by Wahlefeld, *et al.*,[3] by an unambiguous synthesis. These data are consistent with the assignment of structure **2a** for the new product. Hydrogenation of **2a** with PtO_2 in CF_3CO_2H gave the tetrahydropteridine **3**: nmr (CF_3CO_2H) δ 1.67 (d, J = 6 Hz, C^6 CH_3), 3.36 (s, N^8 CH_3), 3.67–4.20 (m, C^6 H and 7-CH_2). This product was isolated as a fairly stable white solid as its dihydrochloride monohydrate.

Compounds **2b**, **2c**, and **2d** were prepared in the same manner as **2a** in yields of 60, 24, and 80%, respectively, by the use of ethyl bromide, isopropyl bromide, and benzyl chloride as the alkylating agents. The relatively low yield for **2c** may be the result of extensive dehydrohalogenation of the sterically hindered isopropyl bromide during the reaction. Elemental and spectral analyses of these compounds substantiated the proposed structures.

We next attempted the alkylation of the more complicated folate derivative 7,8-dihydromethotrexate **1b**.[10,11] A solution of **1b** (as the diacid monohydrate), in DMSO at room temperature under nitrogen, was treated with 4.5 equiv of *n*-butyllithium in hexane followed by 3 equiv of methyl iodide. After 5 min the mixture was diluted with water and the pH adjusted to 3.5 with HCl. The precipitated solid was collected and then reprecipitated from dilute alkali in the same manner to give **2e** as a light tan solid, 50%, mp 185–195° dec. *Anal.* Calcd for $C_{21}H_{26}N_8O_5 \cdot H_2O$: C, 51.63; H, 5.78; N, 22.94. Found: C, 51.84; H, 5.35; N, 22.25. Thin layer chromatography (Eastman 13254 cellulose; 5% aqueous $NaHCO_3$) showed the presence of one major compound (R_f 0.68) with only a trace of unreacted **1b** (R_f 0.55): uv $\lambda_{max}^{0.1\,N\,HCl}$ 295 nm (ϵ 23,700); nmr (CF_3CO_2H) δ 2.3–2.9 (m, side chain CH_2CH_2), 3.24 (s, N^8 CH_3), 3.64 (s, N^{10} CH_3), 4.46 (s, 9-CH_2), 4.72 (s, 7-CH_2), 5.10 (m, side-chain CH), 8.0



(m, 4 H, phenyl CH's). The nmr spectrum was essentially identical with that of **1b** except for the N^8 CH_3 singlet at δ 3.24, which also appears at this δ value in **2a**. To confirm alkylation at N^8, **2e** was treated with excess sodium dithionite in water at reflux for 45 min—conditions which lead to reductive cleavage at the 9,10 bond.[11] The reaction mixture was then made basic and extracted with $CHCl_3$ to give **2a** (46%).

These reactions make available some 7,8-dihydro- and 5,6,7,8-tetrahydropteridine derivatives which would otherwise require lengthier synthetic procedures. The biological properties of these and similar compounds are under investigation.

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(11) 7,8-Dihydromethotrexate has been prepared[12,13] by reduction of MTX with excess sodium dithionite at room temperature, in the presence of sodium ascorbate, according to the method used by S. Futterman [*J. Biol. Chem.*, **228**, 1031 (1957)] for the preparation of 7,8-dihydrofolic acid. In our hands, this procedure led to very low yields of 7,8-dihydro MTX, contaminated with unreacted MTX. We were able to prepare fairly pure 7,8-dihydro MTX in 80% yield by reduction of commercial disodium MTX (Ben Venue Laboratories, Inc., Bedford, Ohio) with 10 molar equiv of sodium dithionite in water at reflux for 15 min, in the presence of 5 equiv of sodium hydroxide. If less sodium hydroxide is used, the pH of the reaction mixture falls below 7 during the reaction and extensive reductive cleavage occurs at the 9,10 bond. The product is precipitated from solution by adjusting the pH to 3.5 with HCl and is obtained as a white solid, mp 180–185° dec, uv $\lambda_{max}^{0.1\ N HCl}$ 292 nm (ϵ 23,400). *Anal.* Calcd for $C_{20}H_{24}N_8O_5 \cdot H_2O$: C, 50.62; H, 5.52; N, 23.62. Found: C, 50.61; H, 5.06; N, 23.49.
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Conjugate Reduction and Reductive Alkylation of α,β-Unsaturated Cyclohexenones Using Potassium Tri-*sec*-butylborohydride

Summary: β-Unsubstituted cyclohexenones undergo 1,4 reduction and reductive alkylation to afford saturated ketones in high yield through the agency of potassium tri-*sec*-butylborohydride.

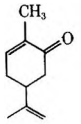
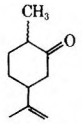
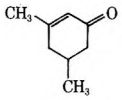
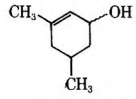
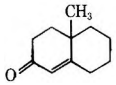
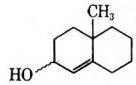
Sir: The reduction of cyclic ketones using hindered borohydrides, especially lithium and potassium tri-*sec*-butylborohydride,[1,2] has been shown to occur with a high degree of stereoselectivity for the less stable isomer. Similar selectivity has been reported in the preparation of allylic alcohols by reduction of acyclic α,β-unsaturated ketones.[3] In view of these facts we were encouraged to study the reaction of these borohydride reagents with cyclic enones. The potentially useful results we encountered prompts this preliminary communication.

We have observed that conjugated cyclohexenone systems which are unsubstituted at the β-vinylic carbon undergo exclusive 1,4-reduction in the presence of potassium tri-*sec*-butylborohydride (K-Selectride™, Aldrich Chemical Co.) to produce the corresponding saturated ketones in nearly quantitative yield.[4] No traces of allylic or saturated alcohol can be detected when 1 equiv of reducing agent is employed. If, however, an excess of 2 equiv of borohydride is present and the reaction is quenched at −78° with water, only saturated alcohols are obtained. Table I summarizes our results.

The reduction seems to occur equally well in pure tetrahydrofuran (THF) or in ether–THF mixtures and is quite rapid at −78°. 3,5-Dimethyl-2-cyclohexenone (**7**) cleanly affords a mixture of allylic alcohols and no saturated ketone or dimethylcyclohexanol whatsoever, thus demonstrating that the 1,4 addition of hydride is extremely sensitive to steric factors.[6] Not surprisingly, reduction of 10-methyl-$\Delta^{1,9}$-2-octalone (**9**) followed a similar course. Numerous attempts to effect the reduction of 2-cyclopentenone by direct or inverse admixture with Selectride™ led to a complex mixture which included cyclopentanol as a major product.

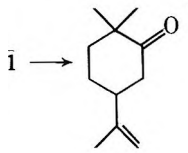
A survey of other conjugated functional groups seems to support the remarkable substrate specificity of this reagent. Ethyl crotonate, for instance, was recovered unchanged after exposure for 1 hr at −78° to an equimolar amount of K-Selectride™. This observation suggests that selective reductions may be feasible in complex polyfunctional structures containing a variety of electron-deficient olefins.

Table I

Enone	No.	Product[5]	No.	Yield,[b] %
	1		2	98
	3		4	99
	5		6	95
	7		8	83
	9		10	95

[a] This product was identical with an authentic sample. [b] Isolated yields of glc pure materials.

In those cases where conjugate enone reduction is successful, we have also been able to use the intermediate enolate in a second, alkylation, step.[7,8] For example, when carvone is treated with 1 mol equiv of K-Selectride™ followed by 1.3 equiv of methyl iodide, a 98% yield of 1-methyl-1,6-dihydrocarvone (11) can be realized.[5] A similar



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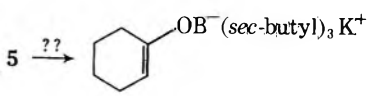
experiment using cyclohexenone and 1.5 equiv of allyl bromide leads to a mixture of 2-allylcyclohexanone (55%), cyclohexanone (15%), and some dialkylated ketone (30%) in high yield.[9] The nature of the intermediate species, whether a simple potassium enolate or a borate such as 12, remains uncertain. If shown to be the former, this method



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would afford a facile and convenient access to reactive potassium enolates in unhindered systems. Work is being continued in an effort to learn whether other unsaturated moieties, particularly esters and nitriles, can also experience 1,4 reduction, reductive alkylation, and perhaps even intramolecular reductive cyclization. A typical experimental procedure follows.

To a dry THF solution (5 ml) of carvone (0.366 g, 2.44 mmol) under nitrogen at −78° was added 1 equiv of K-Selectride™ (0.5 *M* solution, 4.9 ml). After the mixture was stirred for 1 hr at −78°, methyl iodide (1.3 equiv, .20 ml) was injected and the low temperature bath removed. The contents of the flask were brought to 0° for 10 min, by which time a white precipitate had appeared. Addition of 10% NaOH solution (7 ml) and 30% H_2O_2 (5 ml) sufficed to oxidize the trialkylborane by-product after stirring for 3 hr at room temperature. Excess peroxide was destroyed with sodium bisulfite and three hexane extractions afforded 0.400 g (98%) of 11 as a water-white liquid.[10]

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(5) All products exhibited ir and nmr data completely in accord with the assigned structures.
(6) This sensitivity may account for the apparently exclusive formation of allylic alcohol from the β-cyclopentyl-α,β-unsaturated ketone reported in reference 3.
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(10) The author thanks the Department of Chemistry at Cornell University for generous financial support.

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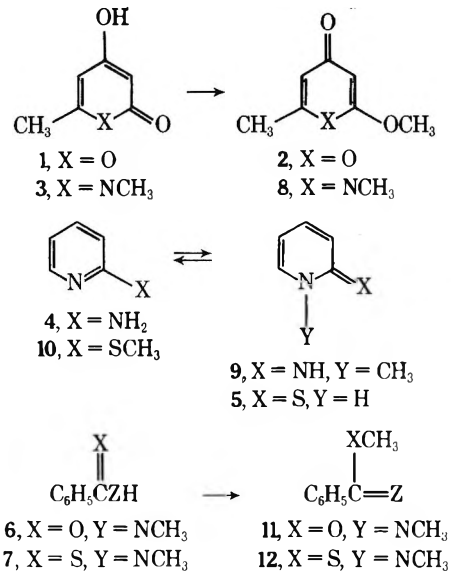
Methylation of Prototropic Ambident Nucleophiles. The Proton as a Formal Directing Group

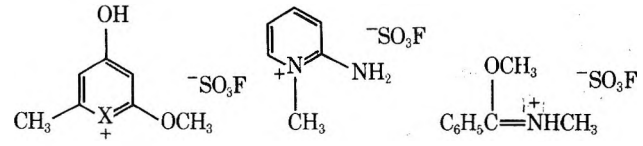
Summary: The fact that six different prototropic ambident nucleophiles react with methylfluorosulfonate and aqueous base to give, in high yields, the product resulting from methylation at the heteroatom which does not bear the proton in the major tautomer is taken to suggest a general regiospecific synthesis of potential synthetic value.

Sir: The mobility of an active hydrogen generally precludes its actually functioning as a blocking or directing group in the traditional sense. Nonetheless, the efficient alkylative conversion of monosubstituted amides to imidates[1] provides one of a number of precedents[2] which suggest, that under some conditions, the proton of a prototropic ambident nucleophile can formally direct alkylation away from its bonding site in the major tautomer. We wish to draw attention to the synthetic value of this prospect with the report that it applied to the reactions of at least six such nucleophiles with methylfluorosulfonate. Comment is also made on the mechanistic considerations which underlie such specificity.

The formation of 2-methoxy-6-methyl-4-pyrone (2) from 4-hydroxy-6-methyl-2-pyrone (1) has been reported after separation of isomers produced by reaction of 1 with diazomethane[3] or by multiple steps involving the trimethylsilyl blocking group[4] in <20% yields. Treatment of 1 with methylfluorosulfonate[5] followed by removal of excess methylating agent under reduced pressure and treatment of the resulting solid with 10% aqueous sodium hydroxide gives 2 in 90% yield. Similar reactions of 3–7 give 8–12,[1a,f,2a,b] in quantitative yields. In each case these products are the formal result of methylation at the heteroatom which does not bear the proton in the major tautomer. This sequence appears to be superior to alternative methods of preparation of these compounds.[1-5]



A scheme which accounts for these results has fast equilibration of the protomers with the ratio of products being determined by kinetically controlled methylation[6] in accord with the Curtin–Hammett principle.[8] Since the transition state energy differences are in the same direction as the ground-state energy differences[3,9,10] and the initial kinetic products are stable and can be deprotonated in the second step, a regiospecific synthesis results in which the proton appears to have acted as a directing group. Support for this interpretation is provided by the fact that the intermediate salts **13–16** can be isolated and identified by



nmr and ir spectroscopy after reaction of **1**, **3**, **4**, and **6** with methylfluorosulfonate.

Although cases can be anticipated in which the alkylating agent might not exhibit the requisite selectivity,[11] the synthetic potential of the regioselective synthesis suggested by these results appears to be significant. The fact that the less stable,[1,3,5b,12] and therefore often more reactive, alkyl substituted isomer may be produced easily and in high yield may prove of particular value.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for support of this work.

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(11) See, for example, M. G. Ahmed and R. W. Alder, *Chem. Commun.*, 1389 (1969).

(12) The less stable isomer will be produced under this hypothesis if the relative stabilities of structually similar methylthropic and prototropic isomers are in the same order.

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Applications of Sulfenylations of Ester Enolates. Synthesis of Pheromones of the Honey Bee

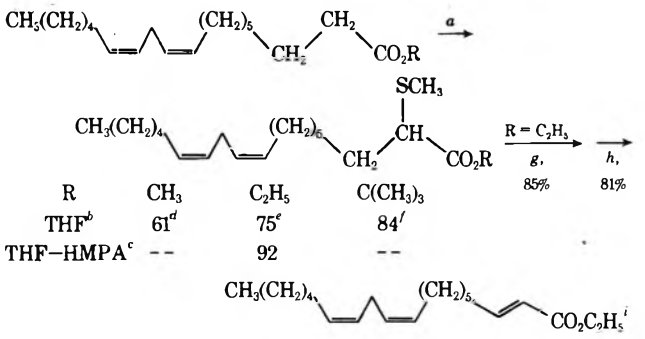
Summary: By the sulfenylation–dehydrosulfenylation method, the queen substance and the pollen attractant of honey bees have been synthesized and a new approach to α-keto esters by direct bissulfenylation has been demonstrated.

Sir: In conjunction with our continuing interest in the application of new synthetic methods to the chemistry of insect pheromones, we have developed short syntheses of the esters of the queen substance[1,2] and the pollen attractant of honey bees.[3,4] In the course of this study we have developed a new synthesis of α-keto esters and have determined the dependence of the sulfenylation reaction on the choice of carboxylic ester.

Sulfenylation[5] of the esters of linoleic acid in THF at 0° (generation of the enolate at −78°) led to the α-methylthiolinoleates in yields that paralleled enolate stability (see Scheme I). Since enolates of methyl and ethyl esters are frequently unstable at this temperature,[6a] decomposition competes with sulfenylation. On the other hand, the enolate of the *tert*-butyl ester[6b] is thermally stable and sulfenylation proceeds smoothly. Enhancing the rate of sulfeny-

lation by utilizing a THF–HMPA mixture overcomes the enolate instability and raises the yield of sulfenylation of ethyl linoleate to 92%. Long reaction times (>1 hr) after quenching of the enolate with the disulfide are also detrimental and effect desulfenylation back to starting ester.

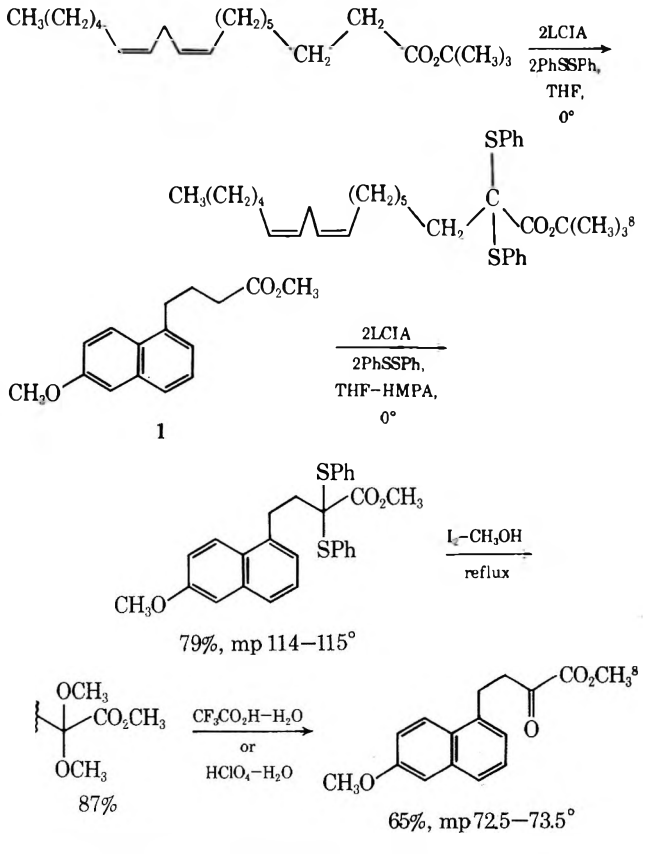
Scheme I
Synthesis of Ethyl
Octadeca-(*E*)-2-(*Z,Z*)-9,12-trienoate



R	CH_3	C_2H_5	$C(CH_3)_3$
THF[b]	61[d]	75[e]	84[f]
THF–HMPA[c]	--	92	--

[a] LCIA (see ref 7), THF, −78°. [b] CH_3SSCH_3, THF. [c] CH_3SSCH_3, THF–HMPA. [d] Inverse quench with disulfide at 0°. [e] Inverse quench with disulfide at 25°. [f] Direct addition of disulfide at 0°. [g] 1 equiv of *m*-chloroperbenzoic acid, CH_2Cl_2, −40°. [h] $PhCH_3$, $CaCO_3$, 110°. [i] See ref 8.

Using 2 equiv of amide base and 2 equiv of diphenyl disulfide led to the α,α-bissulfenylated ester in 90% yield.[9,10] Since this represented the direct introduction of a carbonyl group α to an ester, application to a second system, *i.e.*, **1**,



1

79%, mp 114–115°

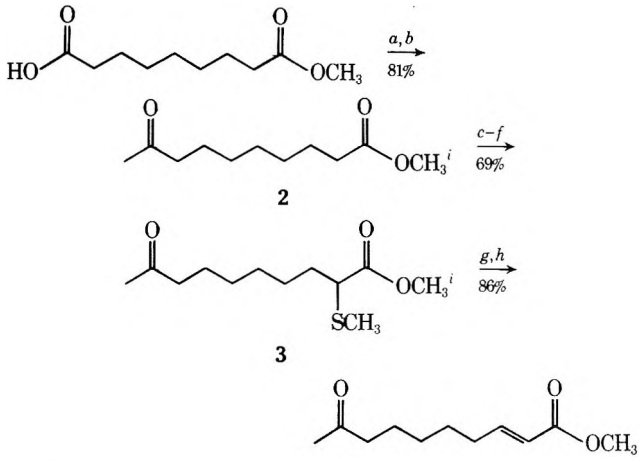
87%

65%, mp 72.5–73.5°

was investigated. Indeed, bissulfenylation occurs smoothly. Hydrolysis to the α-keto ester was effected first by transketalization using a methanolic solution of iodine followed by acid treatment.

Oxidation of ethyl 2-methylthiolinoleate was sluggish with sodium metaperiodate, but could be accomplished with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate or best with *m*-chloroperbenzoic acid. Elimination of the sulfoxide required 16 hr in hot toluene.

Sulfenylation–dehydrosulfenylation offers an especially attractive approach to queen's substance (9-oxo-2-decenoic acid), an important pheromone of queen bees[1] and one which has been implicated as a pheromone of termites.[11] Methyl 9-oxodecanoate (**2**) is available in 81% overall yield



[a] $SOCl_2$, neat, 25°. [b] $Li(CH_3)_2Cu$, ether, −78°. [c] $HOCH_2CH_2OH$, TsOH, PhH, reflux. [d] LCIA, THF, −78°. [e] CH_3SSCH_3, HMPA, 25°. [f] Oxalic acid, H_2O, 25°. [g] $NaIO_4$, C_2H_5OH, H_2O, 25°. [h] $PhCH_3$, $CaCO_3$, 110°. [i] See ref 8.

from commercially available azelaic acid monomethyl ester.[12] Chemospecific sulfenylation of **2** with dimethyl disulfide led to a maximum of 30% of the desired product **3** contaminated with decomposed starting material. The instability of the dienolate is apparently responsible for the low yield. On the other hand, protection of the ketone as the ethylene ketal and sulfenylation by siphoning the enolate solution in THF (generated at −78°) into a room temperature solution of dimethyl disulfide in HMPA, followed by hydrolysis, gave the desired **3** in 69% overall yield. Oxidation with sodium metaperiodate and elimination in hot toluene in the presence of calcium carbonate (16 hr) gave the methyl ester of the queen substance in 86% yield and in 47% overall yield from azelaic acid monomethyl ester.

The spectral data for our synthetic materials agreed with the published spectral data. Note that in both cases the desired *trans* isomer is the exclusive product of elimination.

Acknowledgments. We wish to thank the National Science Foundation and the National Institutes of Health for their generous support of our programs.

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(7) LCIA, lithium cyclohexylisopropylamide.
(8) This compound has been fully characterized by spectral properties and elemental composition.
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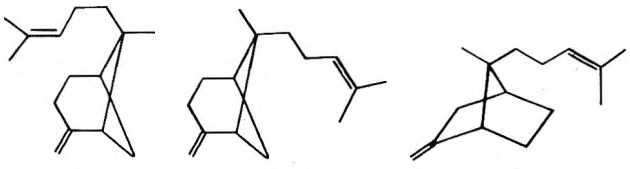
Synthesis of the *Valeriana Waalichi* Hydrocarbon Sesquifenchene. A Route to Specifically Functionalized 7,7-Disubstituted Bicyclo[2.2.1]heptane Derivatives

Summary: A highly stereoselective route to C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives from norbornadiene is reported which has been employed in a total synthesis of sesquifenchene.

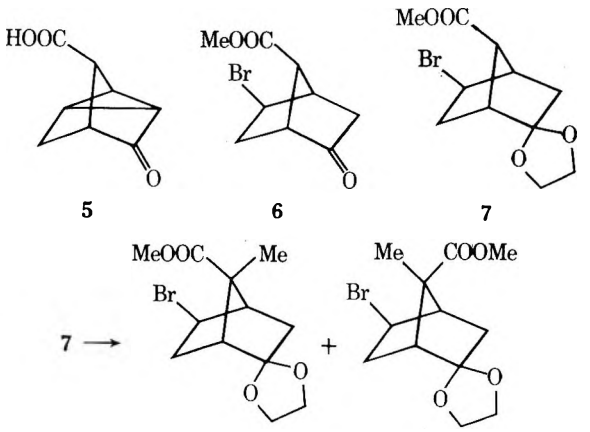
Sir: Bhattacharyya[1] reported some time ago the isolation of a new bicyclic sesquiterpene hydrocarbon from Indian Valerian root oil and proposed the β-*cis*-bergamotene structure **1** on the basis of chemical and spectroscopic studies.[1] Erman[2] demonstrated structure **1** to be untenable by synthesis and revised the structure to the trans isomer **2.** A recent report[3] on an unambiguous synthesis of **2** clearly ruled out structure **2** for Bhattacharyya's sesquiterpene which appeared not even to be a member of the bergamotene class.

Based on the close resemblance of the ir and nmr spectra of Bhattacharyya's compound and those of β- and epi-β-santalene, it has been suggested[3,4] that this compound [sesquifenchene (**3**)][4] is a substitution product of α-fenchene with a γ,γ-dimethyllallyl grouping present. Two recent syntheses have confirmed the structure **3.**[5] We wish to report the details of our synthesis of sesquifenchene which contains a highly stereoselective route to C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives.



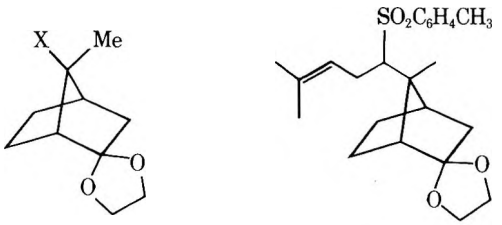
1 **2** **3**

The starting point of our synthesis was the cyclopropyl keto acid **5,** mp 143–144°, obtained in 55–60% overall yield from norbornadiene (**4**).[6] Reaction of acid **5** with refluxing 48% HBr–acetic acid (1:1) for 1.5 hr produced cleanly a bromo acid,[6b] mp 92° (90%).[7] Ketalization (2-methyl-2-ethyl-1,3-dioxalane–benzene–TsOH, 18 hr) of **6** resulted in a 90% yield of pure crystalline bromo ketal **7,** mp 74–75°. Alkylation of the ester enolate derived from **7** (lithium diisopropylamide–THF, −78°) with methyl iodide (−78° → 0°, 1.5 hr) resulted in a 75% isolated yield after chromatography on silica gel of the bicyclo[2.2.1]heptane derivative **8.**



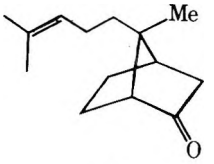
5 **6** **7**

8 **9**



10, X = COOMe
11, X = CH_2I
12, X = $CH_2SO_2C_6H_4CH_3$
14, X = $CH_2CH_2C{=}C(CH_3)_2$

13



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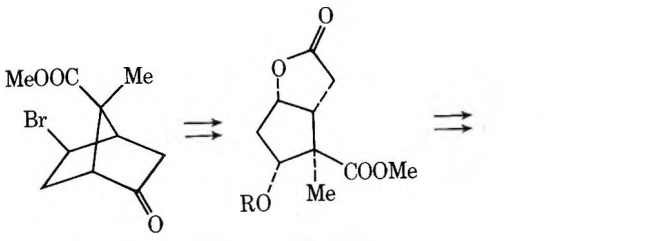
The nmr spectrum of **8** (mp 77–78°) included methyl resonances at δ 1.28 (s, 3 H) and 3.62 (s, 3 H). The corresponding isomer **9** (nmr indicated methyl resonances at δ 1.58 and 3.58) could be isolated in ~5% yield. Initial evidence for structure **8** was obtained in the following manner. Deketalization of **8** afforded a bromo ketone (**16**) whose methyl resonance moved upfield to δ 1.30 owing to shielding by the carbonyl. The bromo ketone derived from **9** exhibited no difference in the chemical shift of the methyl group. The conversion of **8** to sesquifenchene corroborates the stereochemical assignment.

The conversion of **8** to sesquifenchene requires (a) reductive cleavage of the carbon–bromine bond, (b) side-chain elaboration of the γ,γ-dimethylallyl grouping, and (c) methylenation of the protected keto function. Treatment of **8** with tributyltin hydride (1.5 equiv) in benzene containing azobisisobutyronitrile at 50–55° for 1.5 hr resulted in a 94% isolated pure yield of ester **10.** Reduction ($LiAlH_4$–ether, 4.5 hr) of ester **10** followed by tosylation [*p*-toluenesulfonyl chloride (1 equiv)/pyridine, 0°] and exchange with iodide [sodium iodide (3 equiv)–acetone, reflux] produced a 78% overall yield of iodide **11** from **10.** Sulfone formation was carried out in 77% yield (pure) with 2 equiv of sodium *p*-toluenesulfinate in anhydrous DMF at 135–140° (15 hr). The nmr spectrum of **12,** mp 117–118°, exhibited peaks at δ 1.46 (s, 3 H, CCH_3), 2.45 (s, 3 H, $ArCH_3$), 3.02 (s, 2 H, CH_2S), 3.82 (m, 4 H, OCH_2CH_2O), and an AB quartet (aromatic protons, J = 8 Hz) centered at 7.45. Metalation of sulfone **12** at −20° with *n*-butyllithium (1.3 equiv) in THF followed by cooling to −78°, addition of 1-bromo-3-methyl-2-butene (1.6 equiv), and gradual warming to 0° over 1.5 hr resulted in formation of sulfone **13** in near-

quantitative yield.[8] Nmr analysis of the coupled sulfone revealed lack of aliphatic methyl resonance, a consequence of coupling at the γ position and no terminal vinyl resonance. The new sulfone was reduced (Li–$EtNH_2$, −78°, 30 min) and the product chromatographed (hexane–ether, 10:1) on silica gel to yield pure ketal **14** in 82% overall yield from sulfone **12**. Nmr analysis of **14** revealed an olefinic proton at δ 5.00 (t, J = 6.5 Hz), ketal absorption at 3.78 (m, 4 H), two olefinic methyl resonances (1.58 and 1.65), and a saturated methyl resonance at 1.18 (5, 3 H). Deketalization [acetic acid–water (3:7), 85°, 1.5 hr] produced a 97% yield of ketone **15** which was methylenated with methylene triphenylphosphorane in DMSO[9] affording sesquifenchene identical by nmr, ir, glc, and tlc with a sample kindly provided by Professor Bessière-Chrétien and Dr. C. Grison. The nmr spectrum of synthetic **3** displayed a sharp singlet due to the C-8 methyl at δ 0.96, two broadened peaks due to $C{=}C(CH_3)_2$ at 1.60 and 1.67, two methylene protons ($=CH_2$) at 4.58 and 4.77, and one olefinic proton at 5.05 (broadened triplet), in addition to a complex series of peaks in the region 1–2.5 due to remaining protons.

A particularly interesting feature of this synthesis of *dl*-sesquifenchene is the efficiency and high stereoselectivity of the alkylation of ester **7** to provide C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives. In this connection, mention should be made of the possible utilization of **8** and derivatives thereof for construction of 12α-methylprostaglandins (*e.g.*, **17**) *via* a Corey-like intermediate (see Scheme I).

Scheme I



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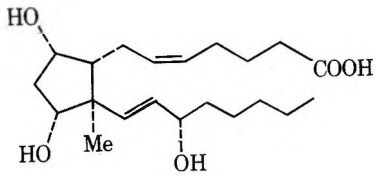

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(8) For the use of sulfones in organic synthesis, see P. A. Grieco and Y. Masaki, *J. Org. Chem.*, **39**, 2135 (1974); M. Julia and J. M. Paris, *Tetrahedron Lett.*, 4833 (1973); M. Julia and P. Ward, *Bull. Soc. Chim. Fr.*, 3065 (1973).
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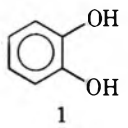
Benzocrown Amino Ethers[1]

Summary: Sixteen new multiheteromacrocycles are reported whose major rings contain O, NH, NTs, CH_2CH_2, and *o*-C_6H_4 units.

Sir: In the design of host molecules for particular complexing tasks, the placement of specific heteroatoms and rigid hydrocarbon groups in desired places in multiheteromacrocycles of different ring sizes provides an interesting synthetic challenge. Good synthetic methods for preparing benzocrown ethers,[2] crown ethers,[3] and crown amino ethers[4] without high dilution have been reported. Certain crown amino ethers have been synthesized with high dilution[5a] or flow cell techniques,[5b] and several benzo-15-crown-5 and benzo-12-crown-4 amino ethers have been prepared from *o*-hydroxyaniline or *o*-phenylenediamine and appropriate dichloro polyethers.[6] We report here simple syntheses of the listed benzocrown amino ethers and their derivatives.[7]

Preparation of **5**, **6**, and **9** from **1**–**4** involved potassium carbonate in dimethylformamide (DMF) at reflux for 5–16 hr.[8] Reductions of **6** and **9** with hydrazine–palladium–carbon in ethanol gave **7** and **10**, respectively. Tosyl or mesyl



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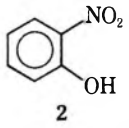
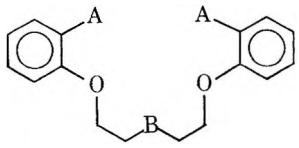


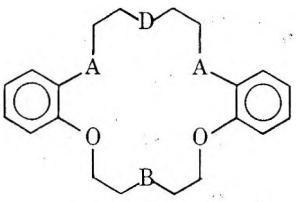
2

$O(CH_2CH_2OTs)_2$
3

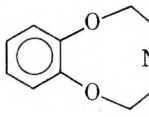
$TsN(CH_2CH_2OTs)_2$
4



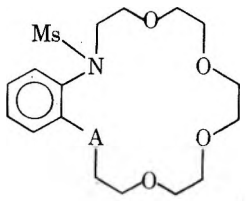
	A	B	Mp, °C	Yield, %	From
5	OH	O	84–86	40	1+3
6	NO_2	O	68–69	77	2+3
7	NH_2	O	63–65	91	6
8	NHMs	O	131–132	71	7
9	NO_2	NTs	123–124	86	2+4
10	NH_2	NTs	147–148	92	9
11	NHTs	NTs	172–173	96	10



	A	B	D	Mp, °C	Yield, %	From
12	O	O	NTs	158-160	34	4 + 5
13	O	O	NH	150-152	35	12
14	NMs	O	O	200-202	40	3 + 8
15	NH	O	O	203-204	71	14
16	O	NTs	NTs	215-216	10	1 + 4
17	O	NH	NH	175-177	45	16
18	NTs	NTs	O	150-153	54	3 + 11
19	NH	NH	O	198-200	82	18
20	NTs	NTs	NTs	glass	20	4 + 11
21	NH	NH	NH	182-183	30	20

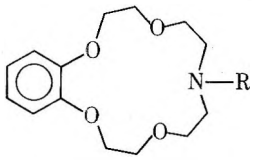


	R	Mp, °C	Yield, %	From
22	Ts	174-175	35	1 + 4
23	H	39-40	50	22



24, A = O

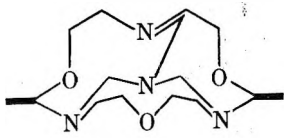
25, A = NMs



	R	Mp, °C	Yield, %	From
26	Ts	136-137	36	Text
27	H	142-143	5	26

chloride in pyridine sulfonated the amines. The important ring-closing steps involved either phenoxides[2] or sulfonylanilides[4,9] with a variety of base–solvent combinations, such as K_2CO_3–DMF at 80° for 12 hr (for **12, 16, 18,** or **20**) or $KOC(CH_3)_3$–$(CH_3)_3COH$ at 82° for 24 hr (for **14**). The yield of **16** was reduced by production of **22** as a competing product, and by the need for chromatographic separation. In these and other ring closures, guanidine in *tert*-amyl alcohol at 100° gave poorer yields of monomers mixed with significant amounts of cyclic oligomers. Yields of 18-membered rings decreased sharply with *o*-disulfonamidobenzene units in starting materials. For example, with pentaethylene glycol ditosylate (NaOH–BuOH at 118°, 24 hr), *o*-hydroxy-*N*-mesylanilide gave 32% **24** (mp 91–92°), but the dimesyl derivative of *o*-phenylenediamine gave after 64 hr only 5% **25** (mp 191–192°). Attempts to make dibenzo-18-crown-6 compounds containing five or six sulfonamide groups failed. In DMF–NaH (80°, 24 hr.), tosylamide and the appropriate ditosylate gave **26.** This ditosylate was prepared from catechol and the tetrahydropyranyl ether of monochlorodiethylene glycol as the primary starting materials. Mesylamides that led to crowded cycles gave higher yields than the corresponding tosylamides, but mesyl protecting groups were harder to remove. The best method[7d] of removing these sulfonamide groups from nitrogen (*e.g.*, from **14** or **18**) involved glacial acetic acid saturated with HBr, 5 *M* in phenol at 80° for 2.5 hr. The small amounts of bromine introduced into the benzene rings of the crowns during this reaction were removed by reduction with hydrazine–palladium–carbon.

These cyclic amines serve as starting materials for syntheses of unusual polycyclic ligands. The conversion of **19** to **28** would be an example. Corey–Pauling–Koltun molecular models of **28** are assemblable only with all CH_2 groups



28

on one side, and all heteroatoms on the other, with their electron pairs "focused" on a single point. Attempts to make this and other host compounds from these multiheteromacrocycles are in progress.

References and Notes

(1) This work was supported by a grant from the National Science Foundation, GP33533X.
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(7) (a) Carbon and hydrogen analyses of new compounds were within 0.30% of theory; (b) mass spectra gave molecular ions; (c) pmr spectra in $CDCl_3$ (60 MHz) were consistent with assigned structures; (d) yields were not maximized.
(8) Compound **6** also was prepared from o-nitrochlorobenzene, diethylene glycol as reactant and solvent, and potassium carbonate as base.
(9) K. Ziegler, Houben-Weyl, "Methoden der Organischen Chemie," Georg Thieme Verlag, Stuttgart, 4th ed, Band IV/2, 1955, p 781.

(10) Fellowships from the Sweden-America Foundation, The Swedish National Science Research Council and the Carl-Bertel Nathhorsts Scientific and Utilitarian Foundations are gratefully acknowledged.

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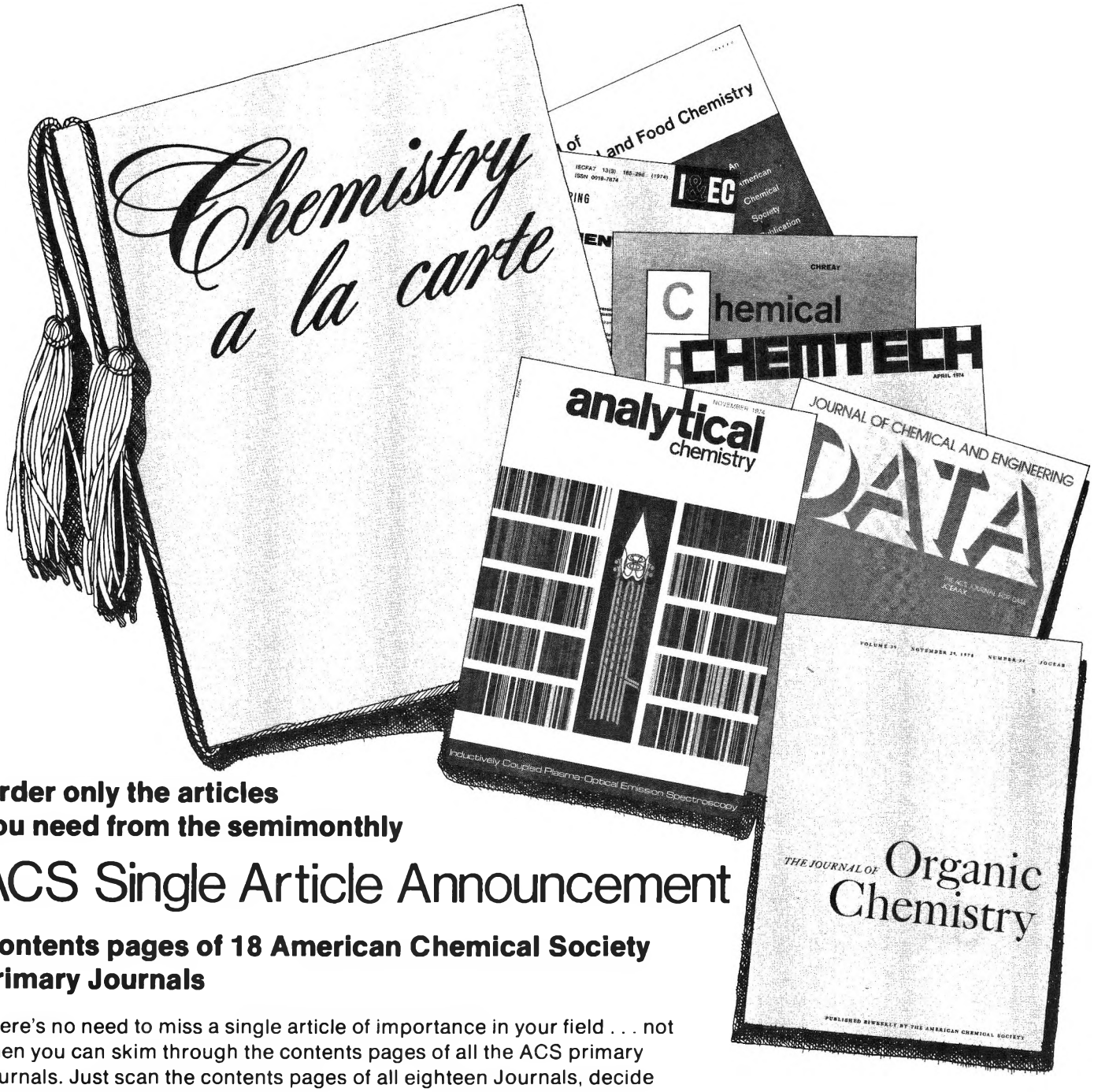

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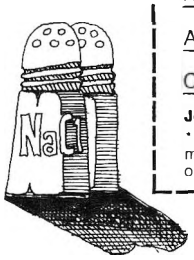
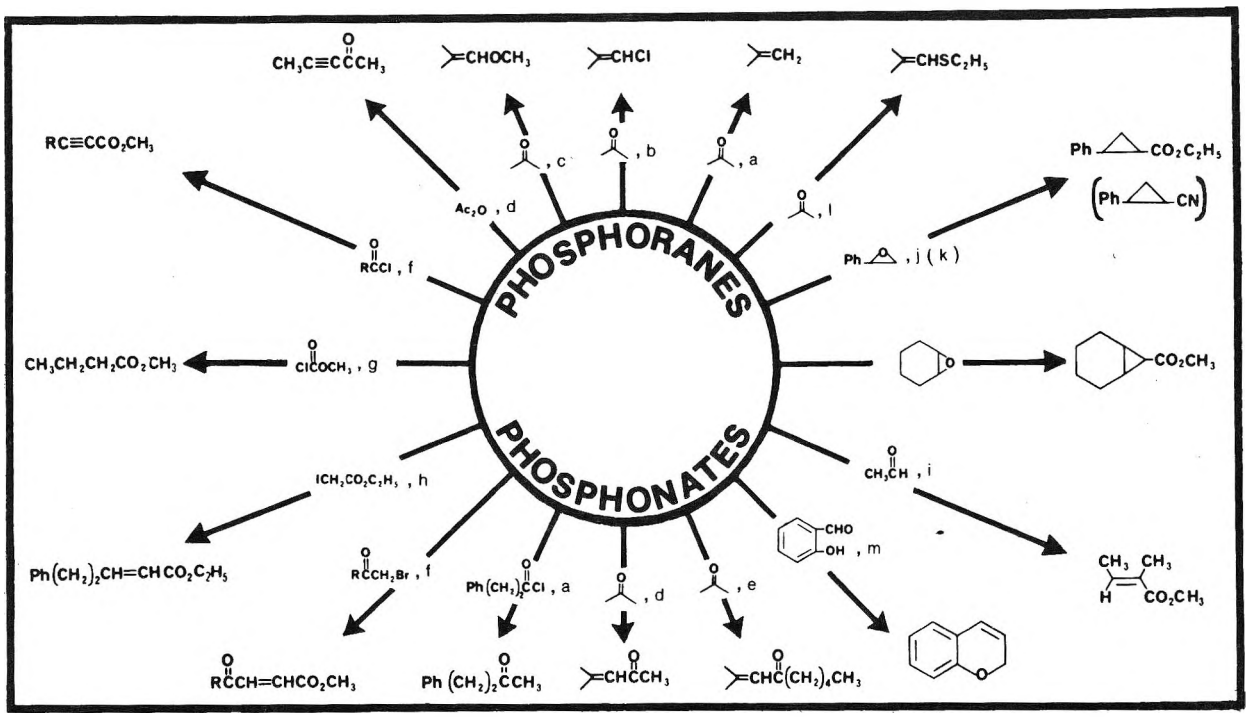


WITTIG REACTIONS AT A GLANCE



Reagents: **a**, $Ph_3P{=}CH_2$; **b**, $Ph_3P{=}CHCl$; **c**, $Ph_3P{=}CHOCH_3$; **d**, $Ph_3P{=}CHC(O)CH_3$; **e**, $(CH_3O)_2P(O)CH_2C(O)(CH_2)_4CH_3$, NaH; **f**, $Ph_3P{=}CHCO_2CH_3$; **g**, $Ph_3P{=}CHC_2H_5$; **h**, $Ph_3P{=}CH(CH_2)_2Ph$; **i**, $Ph_3P{=}C(CH_3)CO_2CH_3$; **j**, $(EtO)_2P(O)CH_2CO_2Et$, NaH; **k**, $(EtO)_2P(O)CH_2CN$, NaH; **l**, $(EtO)_2P(O)CH_2SEt$,[6,7] BuLi; **m**, $Ph_3P{\cdot}CH{=}CH_2Br$, NaH.

Wittig reagents[1-7] through carbonyl olefination lead to olefins, vinyl halides, vinyl ethers (hence, aldehydes), ketones, α,β-unsaturated ketones and esters, acetylenic ketones and esters, etc. A host of heterocyclic compounds such as chromenes, dihydroquinolines, dihydrofurans, etc., are possible using Schweizer's reagent (15,019-3). Since the reaction of phosphoranes and phosphonates is not limited to the carbonyl, the chemist has a variety of choices for his particular needs in synthesis. A partial list of our phosphonium salts, phosphoranes, and phosphonates is shown below.

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15,807-0	Acetonyltriphenylphosphonium chloride	25g $8.80; 100g $23.20
C510-6	(Carbethoxymethylene)triphenylphosphorane	25g $13.50; 34.8g† $18.00; 100g $36.00
C5762-6	(Chloromethyl)triphenylphosphonium chloride	25g $18.10
D9170-5	Diethyl cyanomethylphosphonate	17.7g† $26.00; 50g $53.00
15,653-1	Diethyl (ethylthiomethyl)phosphonate	5g $14.75; 25g $49.50
11,613-0	Diethyl vinylphosphonate	10g $16.20; 16.4g† $22.26; 25g $27.10
15,793-7	Dimethyl (2-oxoheptyl)phosphonate	10g $18.00; 22.2g† $40.00; 50g $59.00
10,000-5	(Methoxymethyl)triphenylphosphonium chloride	34.3g† $11.00; 100g $19.50
13,007-9	Methyltriphenylphosphonium bromide	25g $5.00; 35.7g† $8.15; 100g $13.40
15,792-9	Methyl (triphenylphosphoranylidene)acetate	25g $15.60; 100g $42.00
13,156-3	*n*-Propyltriphenylphosphonium bromide	100g $13.15
T6130-1	Triethyl phosphonoacetate	22.4g† $4.70; 100g $16.60
T7975-8	Trimethyl phosphonoacetate	18.2g† $6.35; 100g $19.95
T8440-9	Triphenylphosphine	100g $7.60; 262.3g† $17.15; 100g $50.25
15,019-3	Vinyltriphenylphosphonium bromide	25g $12.00; 36.9g† $18.00; 100g $40.00

†Designates molar units