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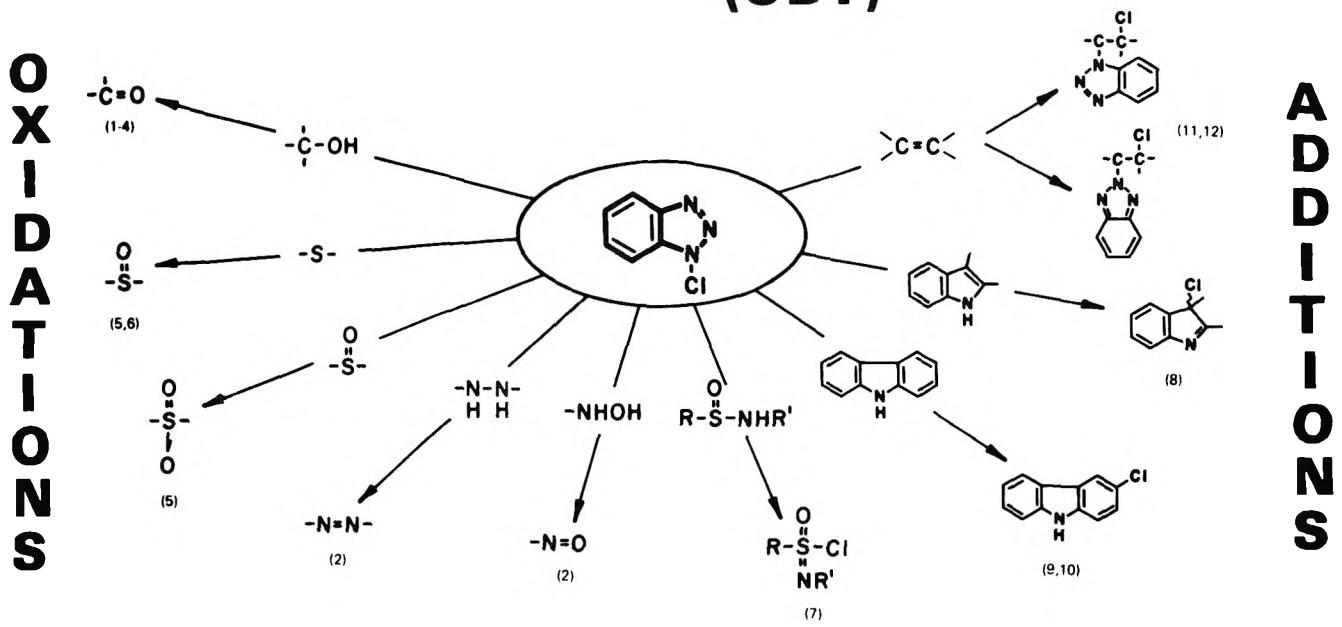
THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 10 MAY 16, 1975

High Yields
Mild Conditions
1 - CHLOROBENZOTRIAZOLE
(CBT)



CHLORINATIONS

1-Chlorobenzotriazole (CBT) is a superior oxidizing agent. Reactions proceed rapidly and selectively under mild conditions to give high yields of pure products. Primary alcohols are oxidized to the corresponding aldehydes without further oxidation to the acid, while secondary alcohols are oxidized to the corresponding ketones.[1-4] **CBT** oxidation of cyclobutanol, for example, gives cyclobutanone in 72% yield with no rearrangement, whereas N-chlorosuccinimide oxidation fails to give any of the desired product.[4] **CBT** oxidation of cetyl alcohol in the presence of pyridine gives palmitaldehyde in 90% yield.[3]

Sulfides are selectively oxidized to sulfoxides with no sulfone contamination.[5,6] For example, methylphenylsulfide is oxidized to the corresponding sulfoxide in nearly quantitative yield in less than 45 minutes. Further oxidation of the isolated methylphenylsulfoxide with **CBT** gives the sulfone in nearly quantitative yield.[5]

Hydroxylamines are oxidized to nitroso compounds without any nitro formation, whereas hydrazo compounds are oxidized to the corresponding azo compounds.[2] For example, ethyl quinoline-2-hydrozocarboxylate is oxidized to the corresponding azo compound in 96% yield.[2]

CBT also serves as a versatile and selective chlorinating agent.[7-10] For example, **CBT** is the preferred reagent in the conversion of sulfinamides to sulfonimidoylchlorides[7] and indoles to chloroindolenines.[8] **CBT** also chlorinates various aromatic rings with or without a Lewis acid present.[9,10]

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(1) C. W. Rees and R. C. Storr, *Chem. Commun.*, 1305 (1968).
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AUTHOR INDEX

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MAY 16, 1975

Decomposition Reactions of Hydroxyalkylphosphorus Compounds. I. Reaction of Benzylbis(α-hydroxybenzyl)phosphine Oxide with Primary Amines[1a]

Armand B. Pepperman, Jr.*

Southern Regional Research Center,[1b] New Orleans, Louisiana 70179

Thomas H. Siddall, III

University of New Orleans,[1c] New Orleans, Louisiana 70122

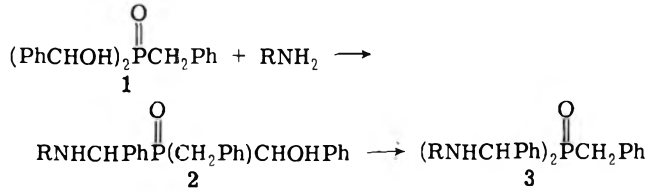
Received November 7, 1974

The reaction of benzylbis(α-hydroxybenzyl)phosphine oxide (1) with primary amines has been shown to produce monomeric, crystalline products in the first example of its kind. Equimolar quantities of 1 and aliphatic primary amines in dilute benzene solutions at reflux afforded the phosphorus amino alcohols, $RNHCHPhP(=O)(CH_2Ph)CHOHPh$ (2). If 2 mol of the amine to 1 mol of 1 were used under these conditions then the diamine, $(RNHCHPh)_2P(=O)CH_2Ph$ (3), resulted. Aromatic amines and 1, when combined in equimolar quantities, afforded mixtures of 2 and 3. Aliphatic amines possessing a tertiary carbon adjacent to the nitrogen did not react with 1 under these conditions. The reaction apparently proceeds through decomposition of 1, by loss of 1 mol of benzaldehyde, before reaction with the amine. The loss of benzaldehyde forms a secondary phosphine oxide $[PhCHOHP(=O)(H)CH_2Ph]$ which can add to the imine (formed by reaction of benzaldehyde and the amine) to produce the amino alcohol.

The reaction of hydroxyalkylphosphorus compounds with primary amines has, until recently, afforded only polymeric products.[2-4] Frank, however, demonstrated that the reaction of aniline with tetrakis(hydroxymethyl)-phosphonium chloride or tris(hydroxymethyl)phosphine yields well-defined crystalline monomers.[5] The reaction of bis- or tris(hydroxyalkyl)phosphine oxides with primary or secondary amines has never been shown to yield monomeric products. The aminomethylphosphine oxides have been produced through oxidation of the aminomethylphosphines[6,7] or through addition of a dialkyl phosphite to an imine.[8] Although both tetrakis(hydroxymethyl)phosphonium chloride and tris(hydroxymethyl)phosphine gave good yields of the corresponding aminomethylphosphines when treated with secondary amines,[6,7] tris(hydroxymethyl)phosphine oxide gave none of the desired aminomethylphosphine oxide when treated with secondary amines under the same conditions.[9] We wish to report the reaction of benzylbis(α-hydroxybenzyl)phosphine oxide (1) with primary amines.

Results and Discussion

The reaction of 1 with primary amines gave 2 or 3 depending on the reaction conditions. This is the first report, to our knowledge, of monomeric products from the reaction of a bis- or trishydroxyalkylphosphine oxide with primary amines. The amino alcohol 2 was produced when equimolar amounts of the primary amine and 1 were heated at reflux in dilute benzene solutions with removal of water by azeotropic distillation into a Dean-Stark trap (method b). By use of very dilute solutions, the reddish color, which often occurs on heating of hydroxyalkylphosphorus compounds, was avoided. Work-up was conducted as described in the Experimental Section and the major product was identified as 2, by NMR, ir, and elemental analysis.



The results of the reaction of 1 with primary amines are summarized in Table I. The NMR spectra of the crude products demonstrated that isomeric mixtures were obtained. Separation of the isomers by fractional recrystallization was not effective in all cases. Only where R = benzyl were two pure isomers isolated. These isomers had visibly different crystalline forms; one formed platelets, 4a, which increased in size on purification by recrystallization (mp 151.5–152.5°), and the other formed needles, 4b (mp 149.5–150.5°). A mixture melting point of 4a and 4b was depressed to 143–148° and the ir and NMR spectra of these stereoisomers were clearly different.

When the carbon adjacent to the amine nitrogen was primary (4, 5, 6, 7, and 8), water evolution was essentially quantitative and the yields of crude product were fair to good. Primary amines bearing secondary alkyl substituents

Table I
Phosphorus Amino Alcohols,
RNHCHPhP(=O)(CH_2Ph)CHOHPh

R	Crude yield, %[a]	Recrystallizing solvent	Compd	Mp, °C
$C_6H_5CH_2$	67	Acetone	4a	151.5–152.5
		Methanol	4b	149.5–150.5
$CH_3(CH_2)_7$	54	Ethyl ether–acetone	5	138
$(CH_3)_2CHCH_2$	41	Acetone	6	150–151
$CH_3CH_2CH_2CH_2$	27	Acetone–pentane	7	143–144
$CH_3OCH_2CH_2$	38	Ethyl acetate	8	141–143
c-C_6H_{11}	61	Methanol	9	157.5–159
$(CH_3)_3CCH(CH_3)$	22	Acetone–methanol	10	151–152
c-C_3H_5	32	Methanol–water	11	165–167

[a] Based on the amino alcohol.

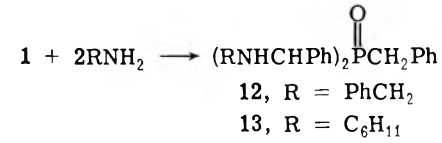
(9, 10, and 11) generally gave lower yields of product than the less hindered counterparts with primary alkyl groups, with the exception of cyclohexylamine. This may be indicative of steric requirements of the reaction, since in cyclohexylamine the two carbons β to the nitrogen are tied back into a ring.

The steric requirements of the reaction were further illustrated by the reaction of 1 with amines possessing a tertiary carbon adjacent to the nitrogen. These reactions were unsuccessful. Both *tert*-butylamine and *tert*-octylamine, when combined with 1, were the only treatments with primary amines in which 1 was recovered in sufficient quantities to be identified. The reactions with *tert*-butylamine were run by methods a, b, and c (see Experimental Section) and 1 was recovered in 75, 88, and 77% yields, respectively. The reaction with *tert*-octylamine was run by method b and 1 was recovered in 31% yield. None of the recovered solids from the *tert*-butylamine and *tert*-octylamine reactions with 1 showed any protons between δ 0 and 2 in their NMR spectra, where the terminal methyl group protons would be expected to appear.

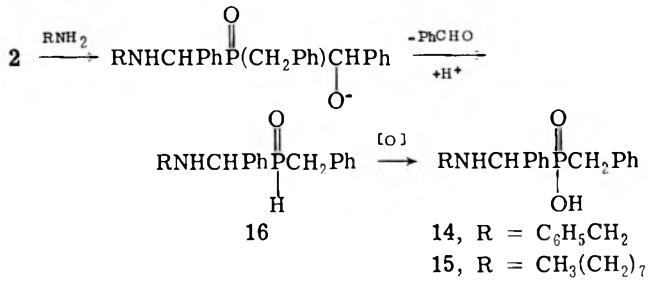
Treatment of 1 with primary aromatic amines gave fair to good yields (40–70% based on the amino alcohol) of solid products. Unfortunately, the products were difficult to purify because they decomposed to highly colored materials during recrystallization. The reaction of 1 with aniline or *N,N*-dimethyl-*p*-phenylenediamine gave about equal quantities of the diamine and the amino alcohol after recrystallization. On the other hand, the only product isolated from the reaction of 1 with *p*-nitroaniline was the diamine and the only product isolated from treatment of 1-naphthylamine with 1 was the amino alcohol. The light and/or air sensitivity of these products precluded an accurate material balance, but it is clear that the formation of the diamines is important in the reaction of primary aromatic amines with 1. It remains to be established why the aromatic amines yield the diamines while no diamine was isolated in the aliphatic amine reactions unless 2 mol of the amine were used per mole of 1.

When 2 mol of the amine were used for 1 mol of 1, the diamines 3 were the predominant product. In this manner the benzylamine derivative, **12**, was prepared in a 72% yield. A similar reaction, with cyclohexylamine in refluxing toluene, gave the appropriate diamine, **13**, in a 39% yield.

In the reactions of benzylamine and octylamine with 1, the last solids collected from the reaction mixture were

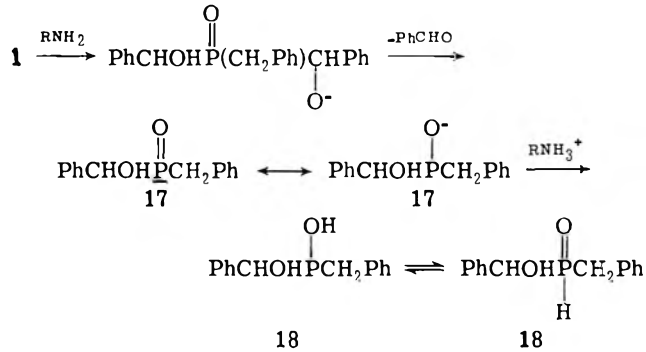


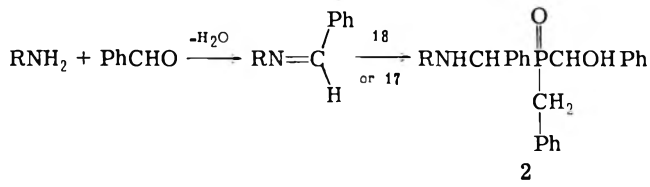
higher melting than the earlier fractions. These late fractions were recovered in about 5% yields and identified as the aminobenzylphosphinic acids. The phosphinic acids would arise from the base-catalyzed (or thermally induced) elimination of benzaldehyde from 2 to form the secondary phosphine oxide **16**, which would oxidize[10] on standing to form 14 and 15. In all cases, part of the reaction mixture remained as a viscous oil from which no more solid product could be obtained.



The reaction of primary amines with 1 could be considered as a nucleophilic displacement of hydroxyl by the amine, which would be unusual. However, since the odor of benzaldehyde was obvious above the reaction mixtures and the aminobenzylphosphinic acids were isolated from the reaction mixture, 1 probably decomposed preceding the reaction with the amine.

A mechanism can be proposed whereby the amine would remove a proton[11,12] from 1 and eliminate benzaldehyde to form **17**, which is resonance stabilized by delocalization of the charge to oxygen. The anion removes a proton from the conjugate acid of the amine to form **18**. No spectroscopic evidence indicates the existence of the trivalent form, but kinetic studies show that this species is normally present in extremely low concentrations.[13] For these reasons 18 will be referred to as the "secondary phosphine oxide" with the realization that if the neutral compound is to show nucleophilic reactivity, then the trivalent tautomer of 18 must be the reactive species. The amine could react with the free benzaldehyde to form the imine to which 18 (or its anion 17) would readily add to form the amino alcohol 2.

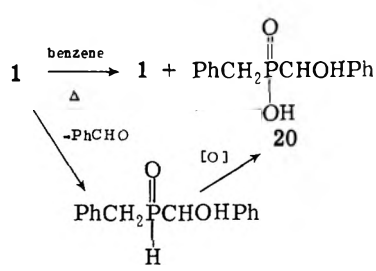




Kreutzkamp and Storck[14] have shown that secondary phosphine oxides will add across the C=N bonds of imines,

isocyanates, etc., to form the tertiary phosphine oxides. Buckler demonstrated that primary phosphine oxides add to the carbonyl group of ketones[15] and that dibenzylphosphine oxide reacts readily with benzaldehyde under acidic conditions[16] to give the tertiary phosphine oxide. Fields has shown that diesters of phosphonic acids react exothermically when mixed with imines.[8] Thus, there is ample precedent for the reaction of a secondary phosphine oxide with an electrophilic center. It is proposed that the reaction occurred through decomposition of 1 to form the secondary phosphine oxide, 18, which then reacts with the imine, formed from the free benzaldehyde and the amine, to produce the amino alcohol 2. If this mechanism is operative, then 1 should react with benzaldehyde imines to give similar products. The reaction of 1 with benzaldehyde imines is the subject of an accompanying publication.[17]

The ready decomposition of 1 was further indicated by heating it in refluxing benzene for 4 hr. After removal of the benzene the viscous oil was dissolved in ether and solid slowly precipitated. Eventually 63% of 1 was recovered while another product, identified as benzyl(α-hydroxybenzyl)phosphinic acid (20), was isolated in a 12% yield. This product must result from oxidation of the secondary phosphine oxide 18, which is formed on the loss of benzaldehyde from 1.



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Isolation of 20 indicates that decomposition of 1 can occur thermally, without added acid or base.

Experimental Section

Reagent grade chemicals and solvents were used without further purification. Other chemicals and solvents were purified as stated. Benzene, toluene, and xylene were dried for 24 hr or more over Linde molecular sieve 4A before use.

The ir spectra were taken on a Perkin-Elmer Model 137 with NaCl optics. Solid samples were run as KBr pellets using about 1% of the sample. The NMR spectra were taken on a Varian Model A-60A or JeOLCO MH-60-II. Elemental analyses and molecular weight determinations were performed by Enviro Analytical Laboratory, Knoxville, Tenn., and Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points are uncorrected.

Benzylbis(α-hydroxybenzyl)phosphine Oxide (1). Buckler's[16] procedure was used to prepare 1; however, the maximum crude yield was 35%. Recrystallization of the crude product from ethanol gave pure 1, mp 151–52°. The diol was assigned as one of the possible *dl* forms based on its NMR spectrum.[18]

Reaction of Benzylbis(α-hydroxybenzyl)phosphine Oxide (1) with Primary Amines. Method a. When the amine had a sufficiently high boiling point to allow reflux in benzene, the following method was used. Equimolar quantities (5–10 mmol) of 1 and the amine were combined in a boiling flask with 50–60 ml of anhydrous benzene. The flask was fitted with a Dean-Stark trap, a water-cooled condenser, and a drying tube. The contents of the flask were magnetically stirred while being refluxed until water evolution ceased. This was often 6–12 hr after most of the water had evolved to ensure completeness of reaction. The solvent was removed in vacuo, the oily residue was triturated with or dissolved in an appropriate solvent (usually ether, occasionally low-boiling petroleum ether or acetone), and the solid which formed slowly was collected in several fractions over several days to months. This solid was then recrystallized from an appropriate solvent.

Method b. A variation of method a, which often gave better yields of the desired product, consisted of simply using a more dilute solution for reaction. Thus equimolar quantities of 1 and the amine (10–30 mmol) were combined in 500–800 ml of benzene. Reflux was carried out until the water evolution ceased and work-up was carried out as in method a. Although this method often required longer reflux times, the solution would remain water white. In method a the presence of hydroxyalkylphosphorus decomposition products was indicated by the distinct yellow color of the solution after several hours of reflux. In a few cases method b was used with only 1–5 mmol of 1 and the amine in 170–200 ml of benzene.

Method c. Equimolar quantities of 1 and the amine (10–20 mmol) were combined with 600 ml of anhydrous benzene and 40 g of Linde molecular sieve 4A in a 1.5-l. erlenmeyer flask. The flask was stoppered and warmed gently at 30–35° with mechanical shaking for 2 weeks. The reaction mixture was filtered and the solvent was removed in vacuo. The oily residue was triturated with ether, collected, and recrystallized from an appropriate solvent.

Method d. Equimolar quantities of 1 and the amine (5 mmol) were combined with 400 ml of anhydrous benzene and 20 g of Linde molecular sieve 4A in the pressure bomb of a Parr Series 4000 pressure reactor. The bomb was sealed, placed in the heating jacket, and heated at 85° for 6 hr with mechanical agitation. The reaction mixture was cooled and filtered. The solvent was removed in vacuo and the oily residue was triturated with ether. This method was used primarily on gaseous or low-boiling amines.

Benzyl(α-benzylaminobenzyl-α′-hydroxybenzyl)phosphine Oxide (4). The use of method b afforded 67% yield of crude product which was recrystallized three times from acetone to yield white platelets, **4a**: mp 151.5–152.5°; ir (KBr) 3.0 (NH), 3.25 (hydrogen-bonded OH), 3.46 (aliphatic CH), 8.75 μ (P=O); NMR ($CDCl_3$) δ 2.4–3.27 (m, AB portion of an ABX pattern, J_{AB} = 15 Hz, 2 H, PCH_2Ph), 3.61 (q, J = 13 Hz, 2 H, NCH_2Ph), 3.67–4.5 (m, 1 H, NH), 4.08 (d, J = 12 Hz, 1 H, PCHN), 5.36 (d, J = 10 Hz, 1 H, PCHO), 6.67–7.73 (m, 21 H, aromatics plus OH); the multiplet at δ 3.67–4.5 and one of the 21 protons in the aromatic multiplet exchanged with D_2O.

Anal. Calcd for $C_{28}H_{28}NO_2P$: C, 76.17; H, 6.39; N, 3.17; P, 7.02; mol wt, 441.5. Found: C, 76.05; H, 6.34; N, 3.28; P, 7.05; mol wt (MeOH), 432.

The filtrates from the recrystallizations of **4a** were combined and evaporated to dryness in vacuo. The residue was recrystallized four times from methanol to yield white needles, **4b**: mp 149.5–150.5°; ir (KBr) 3.0 (NH, not as sharp as in **4a**), 3.15 and 3.25 (hydrogen-bonded OH), 3.5 (aliphatic CH), 8.70 μ (P=O); NMR ($CDCl_3$) δ 2.37–3.24 (m, AB portion of an ABX pattern, J_{AB} = 15 Hz, 2 H, PCH_2Ph), 3.58 (q, J = 13 Hz, 2 H, NCH_2Ph), 3.16–4.33 (m, 1 H, NH), 4.05 (d, J = 8 Hz, 1 H, PCHN), 5.2 (s, J < 1 Hz, 1 H, PCHO), 6.5–7.57 (m, 21 H, aromatics plus OH); the multiplet at δ 3.16–4.33 and one of the 21 protons in the aromatic multiplet exchanged with D_2O.

Anal. Calcd for $C_{28}H_{28}NO_2P$: C, 76.17; H, 6.39; N, 3.17; P, 7.02. Found: C, 76.12; H, 6.29; N, 3.17; P, 7.10.

Benzyl(α-hydroxybenzyl-α′-octylaminobenzyl)phosphine Oxide (5). The crude yield of product (54%) was obtained by method b. Recrystallization from 150 ml of ethyl ether and 20 ml of acetone yielded the analytical sample, **5**: mp 138°; ir (KBr) 3.0 (shoulder, NH), 3.10 and 3.25 (hydrogen-bonded OH), 3.4 (strong, aliphatic CH), 8.75 and 8.9 μ (P=O); NMR ($CDCl_3$) δ 0.6–1.67 [m, 15 H, $(CH_2)_6CH_3$], 2.0–3.34 (m, 5 H, PCH_2Ph, NCH_2, and NH), 4.07 (d, J = 8 Hz, 0.5 H, PCHN), 4.23 (d, J = 13 Hz, 0.5 H, PCHN), 5.02 (d, J = 8 Hz, 0.5 H, PCHO), 5.23 (s, J < 1 Hz, 0.5 H, PCHO), 6.73–7.63 (m, 16 H, aromatics plus OH); one of the protons under the multiplet at δ 2.0–3.34 and one of the protons under the aromatic multiplet were lost on D_2O exchange. The NMR spectrum clearly shows a mixture of isomers in a 1:1 ratio.

Anal. Calcd for $C_{29}H_{38}NO_2P$: C, 75.10; H, 8.26; N, 3.02; P, 6.68. Found: C, 74.96; H, 8.10; N, 3.06; P, 6.58.

Benzyl(α-hydroxybenzyl-α′-isobutylaminobenzyl)phosphine Oxide (6). A crude yield of 41% was obtained by method b. The white solid was recrystallized three times from acetone to yield long, fluffy needles, **6**: mp 150–151°; ir (KBr) 3.0 (shoulder, NH), 3.15 and 3.25 (hydrogen-bonded OH), 3.36 (aliphatic CH), 8.7 μ (P=O); NMR ($CDCl_3$) δ 0.67–1.03 (m, 6 H, CH_3), 1.33–3.5 (m, 6 H, includes PCH_2Ph, 3.5–2.5, NCH_2, 2.5–2.0, and the NH and $HC(CH_3)_2$ spread over the region), 4.0 (d, J = 8 Hz, 0.625 H, PCHN), 4.15 (d, J = 14 Hz, 0.375 H, PCHN), 4.97 (d, J = 7 Hz, 0.375 H, PCHO), 5.18 (s, J < 1 Hz, 0.625 H, PCHO), 6.67–7.67 (m, 16 H, aromatics plus OH); one of the protons under the multiplet at δ 1.33–3.5 and one of the protons under the aromatic multiplet were lost on D_2O exchange. The NMR spectrum clearly shows a

mixture of isomers with the predominant isomer exhibiting a singlet for the proton on the carbon bonded to both phosphorus and oxygen.

Anal. Calcd for $C_{25}H_{30}NO_2P$: C, 73.69; H, 7.42; N, 3.44; P, 7.60. Found: C, 73.89; H, 7.45; N, 3.26; P, 7.43.

Benzyl(α-butylaminobenzyl-α′-hydroxybenzyl)phosphine Oxide (7). Reaction by method a gave a 27% yield of white solid. Recrystallization from acetone–pentane afforded the analytical sample **7:** mp 143–144°; ir (KBr) 3.0 (shoulder, NH) 3.08, 3.15, 3.25 (hydrogen-bonded OH) 3.39 (aliphatic CH), 8.65 μ (P=O); NMR ($CDCl_3$) δ 0.5–1.71 [m, 7 H, $CH_3(CH_2)_2$], 2.1–2.83 (m, 2 H, NCH_2), 2.83–3.67 (m, 2 H, PCH_2), 3.95 (d, J = 17.5 Hz, 1 H, PCHN), 5.0 (d, J = 11 Hz, 1 H, PCHO), 6.84–7.70 (m, 15 H, aromatics); the NH and OH protons appear to be spread along with the base line at δ 2.0–5.0.

Anal. Calcd for $C_{25}H_{30}NO_2P$: C, 73.69; H, 7.42; N, 3.44; P, 7.60. Found: C, 73.57; H, 7.42; N, 3.37; P, 7.72.

Benzyl[α-hydroxybenzyl-α′-[(2-methoxy)ethylaminobenzyl]]phosphine Oxide (8). A 38% yield of white solid resulted from method b. Recrystallization from ethyl acetate afforded the analytical sample, **8:** mp 141–143°; ir (KBr) 3.0 (shoulder, NH), 3.09 and 3.25 (hydrogen-bonded OH), 8.68 and 8.9 μ (P=O); NMR ($CDCl_3$) δ 2.15–3.67 (m, 9 H, contains PCH_2, NCH_2, CH_3OCH_2, and OCH_3 spike at 3.36), 3.95 (d, J = 18 Hz, 1 H, PCHN), 4.98 (d, J = 12 Hz, 1 H, PCHO), 6.90–7.67 (m, 15 H, aromatics); these assignments were made after D_2O exchange, since the NH and OH protons were spread out along the base line at δ 2.4–5.4. Integration was decreased only in this region after exchange with D_2O.

Anal. Calcd for $C_{24}H_{28}NO_3P$: C, 70.40; H, 6.89; N, 3.42; P, 7.56. Found: C, 70.22; H, 6.76; N, 3.37; P, 7.56.

Benzyl(α-cyclohexylaminobenzyl-α′-hydroxybenzyl)phosphine Oxide (9). From method b the white solid which formed in 58% yield was recrystallized twice from methanol to yield white needles, **9:** mp 157.5–159°; ir (KBr) 3.0 (shoulder, NH), 3.12, 3.17, 3.25 (hydrogen-bonded OH), 3.4 (aliphatic CH), 8.74 μ (P=O); solubility of 9 in $CDCl_3$, DMSO-d_6, and others was too low to obtain an interpretable NMR spectrum.

Anal. Calcd for $C_{27}H_{32}NO_2P$: C, 74.8; H, 7.44; N, 3.23; P, 7.15. Found: C, 74.43; H, 7.47; N, 3.23; P, 7.06.

Benzyl[α-[(3,3-dimethyl)-2-butylaminobenzyl]-α′-hydroxybenzyl]phosphine Oxide (10). Method b produced only a 22% yield of white solid. This was recrystallized twice from acetone–methanol to yield the analytical sample **10:** mp 151–152°; ir (KBr) 3.0 (shoulder, NH), 3.2 (hydrogen bonded OH), 3.38 (aliphatic CH), 8.7 μ (P=O); NMR ($CDCl_3$) δ 0.7–1.17 (m, 12 H, CH_3), 2.02–2.4 (m, 1 H, NCH), 2.8–3.6 (m, 2 H, PCH_2Ph), 4.0–4.5 (m, 1 H, PCHN), 4.8–5.27 (m, 1 H, PCHO), 6.5–7.67 (m, 16 H, aromatics plus OH); the NH proton appears to be spread along the base line at δ 2.0–5.0 and added slightly to the integration of the peaks in this area. The NMR spectrum indicated a complex mixture of isomers despite the narrow melting point range.

Anal. Calcd for $C_{27}H_{34}NO_2P$: C, 74.46; H, 7.87; N, 3.22; P, 7.11. Found: C, 74.49; H, 7.87; N, 3.14; P, 7.18.

Benzyl(α-cyclopropylaminobenzyl-α′-hydroxybenzyl)phosphine Oxide (11). Reaction by method d gave a 32% yield of white solid which was recrystallized from methanol–water to provide the analytical sample, **11:** mp 165–167°; ir (KBr) 3.0 (NH), 3.17 and 3.22 (hydrogen-bonded OH), 8.71 and 8.86 μ (P=O); NMR (DMSO-d_6), although **11** was not soluble enough to allow for a readily interpretable spectrum, it was possible to show that the aromatic protons and cyclopropyl ring protons were in the proper ratio, δ 0.15–1.23 (m, 4 H, cyclopropyl ring methylene H), 6.7–7.67 (m, 15 H, aromatics).

Anal. Calcd for $C_{24}H_{26}NO_2P$: C, 73.64; H, 6.70; N, 3.58; P, 7.91. Found: C, 73.15; H, 6.75; N, 3.37; P, 8.09.

Benzylbis(α-anilinobenzyl)phosphine Oxide (21). Reaction by method b produced three distinct crystalline fractions on workup (47% yield). The first two were shown to be similar by ir and were combined and recrystallized from toluene to give the analytical sample, **21:** mp 205–207°; ir (KBr) 2.9 and 3.0 (NH), 3.25 (aromatic CH, weak), 6.2 and 6.65 (C=C, very strong), 8.47 and 8.65 μ (P=O); the most intense absorption in the ir spectrum of **21** is the aromatic double bond stretch, which is a sharp contrast from the aliphatic diamines and amino alcohols, where the phosphoryl band is the most intense absorption; NMR ($CDCl_3$) δ 2.0–3.4 (m, 2 H, PCH_2Ph), 5.0 (d, J = 14 Hz, 2 H, PCHN), 6.1–7.67 (m, 25 H, aromatics), these assignments were made on the D_2O-exchanged spectrum since the NH protons were spread along the base line at δ 5.0–2.3 and caused difficulty in the integration.

Anal. Calcd for $C_{33}H_{31}N_2OP$: C, 78.86; H, 6.22; N, 5.57; P, 6.16. Found: C, 78.77; H, 6.08; N, 5.46; P, 6.19.

Benzyl(α-anilinobenzyl-α′-hydroxybenzyl)phosphine Oxide (22). The third crop of solid (10% yield) obtained from the aniline reaction mixture had an ir spectra that was significantly different than the previous two fractions. Recrystallization from methanol gave the analytical sample which was identified as the amino alcohol **22:** mp 171–175°; ir (KBr) 2.95 (NH), 3.15 and 3.25 (hydrogen-bonded OH), 6.25 and 6.67 (intense C=C), 8.7 and 8.9 μ (P=O), as in the dianilino derivative the most intense absorptions in the ir spectrum were the aromatic double bond stretchings; NMR ($CDCl_3$) δ 2.5–3.5 (m, 2 H, PCH_2), 4.2–5.3 (m, 2 H, PCHN, PCHO), 5.9–7.5 (m, 20 H, aromatics), assignments were made on the D_2O-exchanged spectrum as the NH appeared to be spread along the base line at δ 4.0–5.5 while the OH was under the aromatics.

Anal. Calcd for $C_{27}H_{26}NO_2P$: C, 75.86; H, 6.13; N, 3.28; P, 7.25. Found: C, 75.78; H, 6.11; N, 3.29; P, 7.12.

Benzylbis(α-p-nitroanilinobenzyl)phosphine Oxide (23). The use of method b with *p*-nitroaniline produced only the diamine, **23,** in a 47% yield. Attempts at recrystallization yielded lower melting products, so the original material was used as the analytical sample, **23:** mp 195–196°; ir (KBr) 2.95 and 3.05 (NH), 3.25 (medium, aromatic CH), 6.25 (C=C), 6.67 and 7.55 (NO_2), 8.45 (P=O), 9.0 (?), bands at 6.25, 6.67, 7.55, and 9.0 μ are all stronger absorptions than the phosphoryl; NMR (DMSO-d_6) δ 2.9–3.5 (m, 2 H, PCH_2), 5.21 (d, J = 11 Hz, 1 H, PCHN), 5.53 (d, J = 18 Hz, 1 H, PCHN), 6.25–8.0 (m, 23 H, aromatics), the assignments were made on the D_2O-exchanged spectrum as the water present in the DMSO-d_6 interfered with the integration.

Anal. Calcd for $C_{33}H_{29}N_4O_5P$: C, 66.88; H, 4.93; N, 9.46; P, 5.23. Found: C, 67.19; H, 4.98; N, 9.29; P, 5.15.

Benzylbis(α-p-dimethylaminoanilinobenzyl)phosphine Oxide (24). The use of method b with *N,N*-dimethyl-*p*-phenylenediamine produced a mixture of diamine and amino alcohol in a 71% yield. Recrystallization of this solid from acetone–ethanol and twice more from acetone yielded the analytical sample, **24:** mp 173–175°; ir (KBr) 2.85 and 3.02 (NH), 3.28 (aromatic CH), 3.56 (aliphatic CH), 6.57 (C=C), 8.30, 8.58 μ (P=O), the ir identified **24** as the diamine; however, the analysis was off, probably owing to the instability of the compound.

Benzyl(α-p-dimethylaminoanilinobenzyl-α′-hydroxybenzyl)phosphine Oxide (25). The filtrates from above were reduced in volume and recrystallized from methanol–benzene twice to give the analytical sample, **25:** mp 177–179°; ir (KBr) 2.98 (NH), 3.27 (hydrogen-bonded OH), 3.56 (aliphatic CH), 6.57 (C=C), 8.70 μ (P=O). The ir and analysis indicate the amino alcohol.

Anal. Calcd for $C_{29}H_{31}N_2O_2P$: C, 74.0; H, 6.64; N, 5.96; P, 6.58. Found: C, 73.95; H, 6.57; N, 5.93; P, 6.42.

Reaction of 1 with 1-Naphthylamine. Method b produced 3.1 g (73% crude yield) of white to light green solid. Recrystallization of this solid from methanol–benzene mixtures yielded a light beige solid which turned green on standing, **26:** mp 178–180°; ir (KBr) 2.99 (NH), 3.27 (hydrogen-bonded OH), 3.57 (aliphatic CH), 6.60 (aromatic C=C), 8.32 and 8.7 μ (P=O), the ir identified **26** as the amino alcohol, benzyl(α-hydroxybenzyl-α′-1-naphthylaminobenzyl)phosphine oxide, but the analysis was off, probably owing to the instability of **26.**

Reactions of 1 with Methylamine, Ammonia, *tert*-Butylamine, and *tert*-Octylamine. The reactions of **1** with methylamine and ammonia were carried out by method d and both gave highly colored oils from which only very small amounts (0.1–0.25 g) of wide melting point range solids could be isolated. The ir spectra of these solids indicated that they were neither the amino alcohols nor the diamines. The reaction of **1** with *tert*-butylamine was performed by methods a, b, and c. However, the only isolable solid from these reactions was the starting material **1,** which was recovered in 75, 88, and 77% yields, respectively. The reaction of **1** with *tert*-octylamine was carried out by method b but only the starting material (31%) was recovered while the rest of the reaction mixture remained as an intractable oil.

Benzyl(α-benzylaminobenzyl)phosphinic Acid (14). The later fractions collected in the equimolar benzylamine reactions had higher melting points. The ir and NMR spectra of these fractions identified the product as the phosphinic acid **14** (9% yield). Recrystallization from methanol–water yielded the analytical sample, **14:** mp 206–208°; ir (KBr) 2.9 (NH), 3.3 (aromatic CH), 3.4 (aliphatic CH), 3.65–4.5 (hydrogen-bonded POH), 8.33 μ (P=O); NMR ($CDCl_3$) δ 2.64 (d, J = 17 Hz, 2 H, PCH_2), 3.3–4.3 (m, 3 H, includes NCH_2 and PCHN), 6.9–7.7 (m, 15 H, aromatics); assign-

ments were made after D_2O exchange as the NH and POH protons were spread under the spectral region of interest.

Anal. Calcd for $C_{21}H_{22}NO_2P$: C, 71.78; H, 6.31; N, 3.99; P, 8.82. Found: C, 71.95; H, 6.47; N, 3.91; P, 9.08.

Benzyl(α-octylaminobenzyl)phosphinic Acid (15). Similar to the benzylamine reactions, the later solid fractions collected had high melting points. In particular the fourth fraction collected, from the reaction of *n*-octylamine with 1 described above, had mp 182–188° and was recovered in a 4.3% yield. This was recrystallized once from methanol to yield the analytical sample, **15:** mp 193°; ir (KBr) 2.9 (NH), 3.3 (aromatic CH) 3.4 and 3.48 (aliphatic CH), 3.62–4.4 (broad peak, POH), 8.28 μ (P=O).

Anal. Calcd for $C_{22}H_{32}NO_2P$: C, 70.8; H, 8.65; N, 3.76; P, 8.30. Found: C, 70.64; H, 8.53; N, 3.68; P, 8.31.

Benzylbis(α-benzylaminobenzyl)phosphine Oxide (12). A mixture of 3.52 g (0.01 mol) of **1**, 2.14 g (0.02 mol) of benzylamine, and 170 ml of dry benzene was refluxed for 46 hr. Most of the water (0.30 ml, 0.36 ml theoretical) had evolved after 24 hr. The benzene was removed in vacuo and solid formed as the solvent was removed. The oily solid was mixed with ethyl ether and filtered, and 3.8 g (72% yield) of white solid was recovered, mp 135–138°. Two recrystallizations from acetone and one from cyclohexane–$CHCl_3$ gave no improvement in the melting point. However, recrystallization twice from a methanol–water mixture afforded the analytical sample, **12:** mp 144–145°; ir 3.05 (NH), 3.3 (aromatic CH), 3.4 and 3.52 (aliphatic CH), 8.67 μ (P=O); NMR ($CDCl_3$) δ 2.58 (s, 2 H, NH, exchanged with D_2O), 2.68 (d, J = 12 Hz, 2 H, PCH_2Ph), 3.61 (q, J = 13 Hz, 4 H, NCH_2), 4.22 (d, J = 12 Hz, 2 H, PCHN), the simplicity of the NMR spectrum demonstrated that the isomer isolated was the meso form while the NMR of the crude product indicated a mixture of isomers.

Anal. Calcd for $C_{35}H_{35}N_2OP$: C, 79.22; H, 6.65; N, 5.28; P, 5.84. Found: C, 79.32; H, 6.77; N, 5.46; P, 6.01.

Benzylbis(α-cyclohexylaminobenzyl)phosphine Oxide (13). A mixture of 0.99 g (0.01 mol) of cyclohexylamine, 1.76 g (0.005 mol) of **1**, and 50 ml of dry toluene was refluxed for 15 hr. All of the water (0.2 ml, 0.18 ml theoretical) had collected after 4 hr. The solvent was removed in vacuo and the oily residue was dissolved in ether. The solid which precipitated (1.01 g, 39% yield) had mp 133–139°. Recrystallization from methanol–water gave the analytical sample, **13:** mp 139–140°; ir (KBr) 3.0 (NH), 3.25 (aromatic CH), 3.39 and 3.48 (aliphatic CH), 8.55 μ (P=O); NMR ($CDCl_3$) δ 0.6–2.6 (m, 24 H, cyclohexyl ring H, NH), 2.88 (m, 2 H, PCH_2Ph), 4.02 (d, J = 11 Hz, 1 H, PCHN), 4.43 (d, J = 16 Hz, 1 H, PCHN), 6.85–7.5 (m, 15 H, aromatics); after D_2O exchange two protons were lost in the δ 0.6–2.6 region. The complexity of the NMR spectrum demonstrated that the isomer obtained was the *dl* form.

Anal. Calcd for $C_{33}H_{43}N_2OP$: C, 77.01; H, 8.42; N, 5.44; P, 6.02. Found: C, 76.86; H, 8.36; N, 5.21; P, 6.30.

Benzyl(α-hydroxybenzyl)phosphinic Acid (20). A mixture of 10 mmol of **1** and 300 ml of benzene was heated at reflux for 4.5 hr. On cooling, the solution precipitated no solid; so the benzene was removed in vacuo to yield a yellow oil. The oil was triturated with ether overnight to yield 1.26 g (36% recovery) of **1**. Four days later another 0.7 g (20% recovery) of **1** was obtained. Two weeks later another 0.24 g (7%) of **1** was collected while 2 weeks after that a solid was collected which had a ir spectrum markedly different from that of **1**. This solid was identified as benzyl(α-hydroxybenzyl)phosphinic acid (**20**) by NMR and ir spectra and was obtained in an 11.8% yield (0.31 g). The analytical sample was obtained by recrystallization from water–ethanol, **20:** mp 176–177.5°; ir (KBr) 3.0 (OH), 3.25 (aromatic CH), 3.5–5.0 (low broad absorption, POH), 6.7 and 6.9 μ (aromatic C=C); NMR (DMSO-d_6) δ 2.9–3.5 (m, 2 H, PCH_2Ph), 4.89 (d, J = 9 Hz, 1 H, PCHO), 7.03 (broad s, contains COH, POH, and H_2O in DMSO-d_6), 7.1–7.9 (m, 10 H, aromatics).

Anal. Calcd for $C_{14}H_{15}O_3P$: C, 64.12; H, 5.77; P, 11.81. Found: C, 64.10; H, 5.81; P, 11.64.

Registry No.—**1**, 36871-68-8; **4**, 54617-83-3; **5**, 54617-84-4; **6**, 54617-85-5; **7**, 54617-86-6; **8**, 54617-87-7; **9**, 54617-88-8; **10**, 54617-89-9; **11**, 54617-90-2; **12**, 54617-91-3; **13**, 54617-92-4; **14**, 54617-93-5; **15**, 54617-94-6; **20**, 54617-95-7; **21**, 54617-96-8; **22**, 54617-97-9; **23**, 54617-98-0; **24**, 54617-99-1; **25**, 54618-00-7; **26**, 54618-01-8; benzylamine, 100-46-9; octylamine, 111-86-4; isobutylamine, 78-81-9; butylamine, 109-73-9; 2-methoxyethanamine, 109-85-3; cyclohexylamine, 108-91-8; 3,3-dimethyl-2-butanamine, 3850-30-4; cyclopropylamine, 765-30-0; benzenamine, 62-53-3; *p*-nitrobenzenamine, 100-01-6; *N,N*-dimethyl-*p*-phenylenediamine, 99-98-9; 1-naphthylamine, 134-32-7.

References and Notes

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Synthesis of 5′-*C*-Acylaminomethyl Derivatives of Adenosine 5′-Phosphate and Adenosine 5′-Triphosphate

Francis Kappler and Alexander Hampton*

The Institute for Cancer Research, Philadelphia, Pennsylvania 19111

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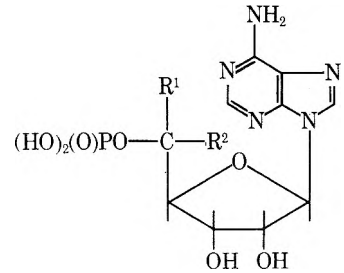
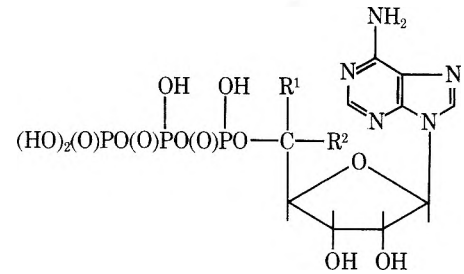
Novel nucleotides have been synthesized in which the phosphoester ($POCH_2$) grouping of adenosine 5′-phosphate (AMP) is replaced by $POCH(CH_2NHR)$ where R = H, C(O)Me, C(O)Et, C(O)Ph, or CH_2CH_2CN. Reaction of 2′,3′-*O*-isopropylideneadenosine-5′-aldehyde (produced in situ from 2′,3′-*O*-isopropylideneadenosine) with nitromethane in dimethyl sulfoxide in the presence of triethylamine gave 19% overall yield of the allo epimer **8a** and 6% overall yield of the talo epimer **8b** of 5′-C-nitromethyl-2′,3′-*O*-isopropylideneadenosine. Catalytic reduction of these gave the corresponding 5′-*C*-aminomethyl nucleosides (**6a** and **6b**) in high yield; **6a** was also obtained, but in low yield, by reduction with diborane of the previously synthesized allo epimer of 5′-C-carbamoyl-2′,3′-*O*-isopropylideneadenosine. The configuration of **6a** and **6b** was determined by treating them with nitrous acid followed by an acidic hydrolysis which produced D-allose and L-talose, respectively. Treatment of **6a** or **6b** with acetic, propionic, benzoic, or *p*-nitrobenzoic acids in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline gave the respective 5′-acylaminomethyl derivatives of 2′,3′-*O*-isopropylideneadenosine. Phosphorylation of these with 2-cyanoethyl phosphate–dicyclohexylcarbodiimide and removal of blocking groups gave the allo and talo 5′-*C*-acetamidomethyl and 5′-*C*-propionamidomethyl derivatives **14a, 14b, 15a,** and **15b,** respectively, of AMP and the allo 5′-*C*-benzamidomethyl derivative **16** of AMP. A more efficient route to these nucleotides comprised protection of the aliphatic amino group of **6a** and **6b** with a phenoxycarbonyl group, phosphorylation of the 5′ hydroxyl, and removal of blocking groups, which gave the pure epimeric 5′-C-aminomethyl derivatives **18a** and **18b** of AMP in 10% overall yield from **8a** and **8b,** respectively. Treatment of **18a** and **18b** in methanol with acetic or propionic acids together with *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline gave high yields of **14a, 14b,** and **15a,** and treatment of **18a** with benzoyl chloride in aqueous sodium carbonate gave **16** in high yield. The AMP derivatives **14a** and **14b** were converted to the corresponding ATP derivatives by a known anion-exchange procedure by which nucleoside 5′-phosphates can be converted to phosphoanhydrides. The allo and talo epimers of 5′-*C*-cyanoethylaminomethyl AMP were identified as by-products formed in the synthesis of **18a** and **18b** and were shown to arise from reaction of **18a** and **18b** with cyanoethylene released during one of the deblocking operations. The synthetic routes developed appear to be general for the introduction of acyl- and aroylaminomethyl substituents at C-5′ of AMP and ATP.

Adenosine 5′-phosphate (AMP) and more especially adenosine 5′-triphosphate (ATP) are substrates of a large proportion of known enzymes and in addition are utilized frequently in metabolism as allosteric regulators of enzyme activity.[1] This laboratory has synthesized a number of derivatives of AMP and ATP with mono-C substituents on the sugar moiety and has found them to be valuable agents with which to delineate electronic and steric features of enzymes in and around their binding sites for AMP or ATP.[2,3,4] One phase of those studies[4] revealed that the complexes of AMP with several AMP-utilizing enzymes have sufficient room to accommodate a methyl group substituted on C-5′ of AMP. In order to assess the extent of bulk tolerance at C-5′ of AMP and ATP in their complexes with enzymes it became necessary to extend these studies to AMP and ATP derivatives with larger and more varied substituents at C-5′. The only 5′-C-substituted adenine nucleotides yet synthesized appear to be 5′-*C*-methyl AMP,[4,5] 5′-*C*-carbamyl AMP,[4] 5′-di-*C*-methyl AMP,[5] and 8,5′-cyclo-AMP.[6,7] This report describes the synthesis of 5′-*C*-acylaminomethyl derivatives of AMP and ATP which were obtained in the two possible 5′ epimeric configurations, i.e., as derivatives of β-D-allose (**1** and **3**) or of α-L-talose (**2** and **4**). Evidence summarized previously[2,6] shows that binding of AMP and ATP to enzymes usually involves interactions of enzymic groups with both the phosphate and the ribose segments of the nucleotides and that rotation about the 4′,5′ bond in the enzyme–substrate complexes is thereby considerably restricted. As a consequence, a group attached to C-5′ will, in such a complex, bear a spatial relationship to nearby groups of the enzyme which is determined by the stereochemical configuration at C-5′. The 5′-C-substituted adenine nucleotides made accessible by the present work thus constitute two distinct groups of molecular probes with which to study the numerous enzymes for which adenine nucleotides are substrates or effectors. An account of the interactions of these analogs with enzymes for which AMP and ATP are substrates will be presented elsewhere.

The required 5′-*C*-acylaminomethyl AMP derivatives **1** and **2,** which served as precursors of the ATP derivatives **3** and **4,** were prepared by two routes. In the first of these,



1, $R^1 = CH_2NHCOR$; $R^2 = H$
2, $R^1 = H$; $R^2 = CH_2NHCOR$

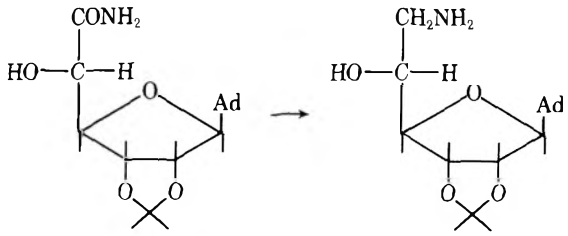


3, $R^1 = CH_2NHCOCH_3$; $R^2 = H$
4, $R^1 = H$; $R^2 = CH_2NHCOCH_3$

the hitherto undescribed nucleosides 9-(6-amino-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (**6a**) and

9-(6-amino-6-deoxy-2,3-O-isopropylidene-α-L-talofuranosyl)adenine (**6b**) were prepared and selectively N-acylated on the sugar moiety, after which the 5′ hydroxyl group was phosphorylated; the second approach differed in that phosphorylation of **6a** and **6b** was performed prior to the N-acylation.

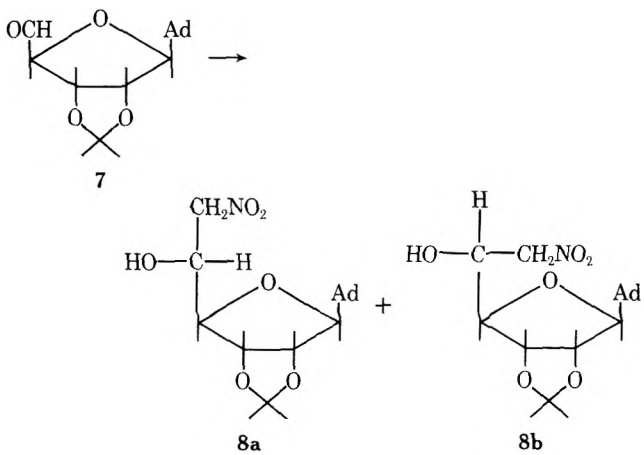
We initially attempted to secure the 5′-C-aminomethyl nucleosides **6a** and **6b** by reduction of the corresponding 5′-C-carbamoyl nucleosides, since we had previously found[4] that these epimers can be synthesized readily from 2′,3′-O-isopropylideneadenosine-5′-aldehyde and easily separated from each other. Both epimers proved resistant to reduction by aluminum hydride or lithium aluminum hydride, but when treated with an excess of diborane the allo epimer (**5**) did yield a small amount of the 5′-C-aminomethyl nucleoside **6a** whereas the talo epimer gave no



5 **6a**

Ad = adenine

6b. The reduction of **5** produced complex mixtures and the yield of **6a** was less than 5%. In another approach to the 5′-C-aminomethyl nucleosides, the crude 5′-C-cyano nucleosides, which were unisolated intermediates in the synthesis of the epimeric 5′-C-carbamoyl derivatives of 2′,3′-O-isopropylideneadenosine,[4] were treated with lithium aluminum hydride, but the principal product was 2′,3′-O-isopropylideneadenosine, presumably produced by a retro cyanohydrin reaction and reduction of the resultant nucleoside 5′-aldehyde **7**. Synthesis of the 5′-C-nitromethyl nucleosides **8a** and **8b** was next investigated. For this purpose, 2′,3′-O-isopropylideneadenosine was oxidized in dimethyl sulfoxide solution by the carbodiimide procedure of Pfitzner and Moffatt[8] to give a mixture containing 80–85% of 2′,3′-O-isopropylideneadenosine-5′-aldehyde (**7**) and 15–20% starting material. When 2 equiv of nitromethane and of triethylamine were added directly to this mixture, **7** was converted within several hours at room temperature to 9-(6-deoxy-6-nitro-2,3-O-isopropylidene-α,L-talofuranosyl)adenine (**8b**) and 9-(6-deoxy-6-nitro-2,3-O-isopropylidene-β-D-allofuranosyl)adenine (**8a**). The two epimers were

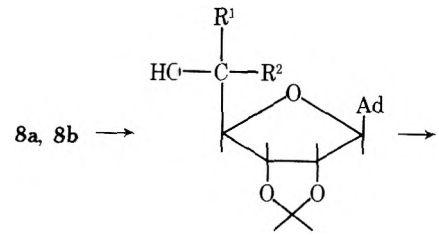


7

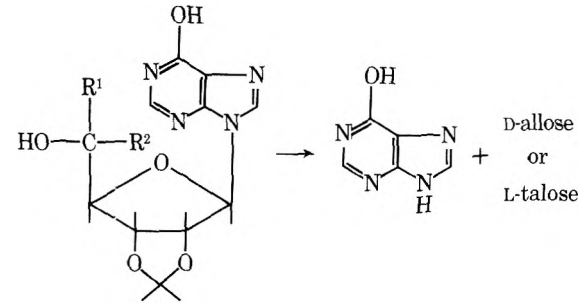
8a **8b**

readily separated from each other and from 2′,3′-O-isopropylideneadenosine by means of column chromatography on silica gel in two different solvent systems and isolated in 6 and 19% yields respectively. The ^{1}H NMR, ir, and uv spectral characteristics of the crystalline epimers **8a** and **8b** accorded with their assigned structures, which, as described below, were further supported by subsequent reduction of the nitro group, N-acylation of the resulting amine, and 5′-O-phosphorylation of the 5′ hydroxyl group. An unusual feature of the uv spectra of **8a** and **8b** is a 35% hyperchromic effect observed at pH 11 but not at pH 2–7 which is apparently due to interaction of the acinitro anion with the purine ring. A similar hyperchromic effect is given by the epimeric 5′-C-nitromethyl derivatives of nonblocked adenosine, the synthesis of which was reported by Hogenkamp and coworkers[9] after this phase of our work had been completed. These workers isolated the allo and talo epimers in 17 and 5% yields, respectively, following treatment of preisolated adenosine-5′-aldehyde with nitromethane and sodium hydroxide in aqueous dioxane.

The absolute configuration at C-5′ of **8a** and **8b** was established in a sequence of three operations. Firstly, the nitro group was reduced catalytically with platinum to furnish the respective 5′-C-aminomethyl nucleosides **6a** and **6b**. The yield in this conversion was high provided that rel-



6a, $R^1 = CH_2NH_2$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_2NH_2$



9a, $R^1 = CH_2OH$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_2OH$

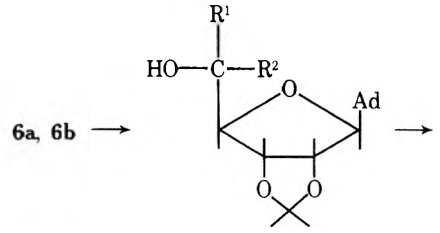
atively large amounts of platinum were employed; two uv-absorbing by-products were also detected, but in trace amounts. As expected, **6a** and **6b** migrated as monocations on paper electrophoretograms run at pH 4.5. Treatment of **6a** and **6b** with nitrous acid yielded the 5′-hydroxymethyl-2′,3′-O-isopropylideneinosines **9a** and **9b**, which were directly treated with an aqueous suspension of Dowex-50 (H^+) ion-exchange resin under conditions which removed the isopropylidene group and cleaved the glycosidic bond to produce hypoxanthine and a single sugar corresponding to allose and talose respectively. These sugars were identified by paper chromatographic comparison with authentic samples in several solvent systems. The chromatograms also established that neither **9a** nor **9b** had given rise to L-mannose, thus showing that the reaction of 2′,3′-O-isopropylideneadenosine-5′-aldehyde with nitromethane was not accompanied by inversion at C-4′, a possibility suggested by the tendency of nucleoside 5′-aldehydes to invert at C-4′ under mild conditions.[10] In addition, Walker et al.[9] have established that reaction of adenosine-5′-aldehyde with nitromethane produced nucleosides derived from allose and

talose but not from mannose or gulose. The 5′-*C*-aminomethyl nucleosides (**6a, 6b**) could be distinguished from each other on paper chromatograms, thus enabling us to determine the absolute configuration of the 5′-*C*-carbamoyl nucleoside **5,** from which a small amount of **6a** was obtained by the action of diborane, as described above. The allo configuration thus indicated for **5** is in agreement with that previously suggested[4] on the basis of its specific rotation. In further confirmation of this assignment, the aminomethyl nucleoside obtained by reduction of **5** with diborane was treated successively with nitrous acid and with Dowex-50 (H^+), when it produced a sugar which was chromatographically identical with allose.

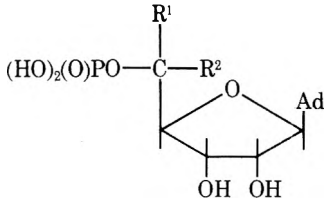
Phosphorylation of the 5′ hydroxyl group of **8a** or **8b** was briefly investigated with several of the agents known to be useful phosphorylating agents for nucleosides. Phosphorus oxychloride in trimethyl phosphate,[11] which phosphorylates the 5′ hydroxyl group of the epimeric 5′-*C*-methyl-2′,3′-*O*-isopropylideneadenosines,[4] did not phosphorylate the 5′ hydroxyl of **8a** or **8b.** Dibenzyl phosphorochloridate in pyridine[12] also failed to phosphorylate **8a** or **8b.** A 2-cyanoethylphosphoryl group could be attached to the 5′ oxygen of **8a** or **8b** by means of the 2-cyanoethyl phosphate–dicyclohexylcarbodiimide procedure,[13] but attempted base-promoted release of cyanoethylene from this intermediate, while furnishing a small yield of material with the properties of the desired 5′-*C*-nitromethyl-2′,3′-*O*-isopropylideneadenosine 5′-phosphate, gave predominantly a phosphorus-free nucleoside which had less polar properties than **8a** or **8b** as judged from paper partition chromatography and which was tentatively concluded to be the 5′,6′-dehydro derivative of **8a** or **8b** resulting from more rapid β-elimination of the 2-cyanoethyl phosphate dianion than of the nucleoside 5′-phosphate dianion.

Difficulties were also encountered when direct phosphorylation of the 5′-*C*-aminomethyl nucleosides **6a** and **6b** was attempted. These compounds remained largely unchanged after prolonged treatment (72 hr) with excess (4 equiv) of 2-cyanoethyl phosphate in the presence of dicyclohexylcarbodiimide. The principal product had the same ultraviolet absorption properties as **6a** or **6b** but did not undergo the ninhydrin reaction and behaved as a monoanion upon paper electrophoresis at pH 7.6; it was acid labile, being decomposed within 30 min at pH 2 and 25°. This limited evidence suggests that this nucleoside may possess a (2-cyanoethyl)phosphorylaminomethyl group at C-5′. By phosphorylation of both the aminomethyl and the hydroxyl groups of **6a** or **6b** with polyfunctional phosphorylating agents it was then hoped to obtain a cyclic phosphoramidate which might undergo P–N bond cleavage under acidic conditions to give the required 5′-phosphate. However, *p*-nitrophenyl phosphorodichloridate[14] or phosphorus oxychloride in pyridine as well as phosphorus oxychloride in trimethyl phosphate upon reaction with **6a** or **6b** gave complex mixtures which after mild acidic treatment gave no 5′-*C*-aminomethyl nucleoside 5′-phosphates.

Selective acetylation of the amino group of the 5′-*C*-aminomethyl nucleosides **6a** and **6b** could be achieved by the action of acetic anhydride in boiling pyridine. Analytically pure 9-(6-acetylaminomethyl-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (**10a**) and 9-(6-acetylaminomethyl-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranosyl)adenine (**10b**) were obtained in this way in 24–45% yields. The corresponding 5′-*C*-propionylaminomethyl nucleosides **11a** and **11b** were similarly obtained. Slightly higher yields of these 5′-*C*-acylaminomethyl nucleosides were obtained by the action of acetic or propionic acids on **6a** or **6b** in methanolic solution in the presence of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.[15,16] By the latter procedure we obtained also 9-(6-benzamidomethyl-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (**12**) and its *p*-nitrobenzamidomethyl analog **13.** The foregoing four 5′-*C*-acylaminomethyl nucleosides as well as the 5′-*C*-benzamidomethyl nucleoside were converted in 25–50% overall yields to chromatographically homogeneous 5′-*C*-acylaminomethyl derivatives of AMP (**14a** to **16**) by application of the β-cyanoethyl phosphate–dicyclohexylcarbodiimide (DCC) method[13] for the phosphorylation of nucleosides followed by stepwise removal of the cyanoethyl and isopropylidene protecting groups by successive basic and acidic treatments.

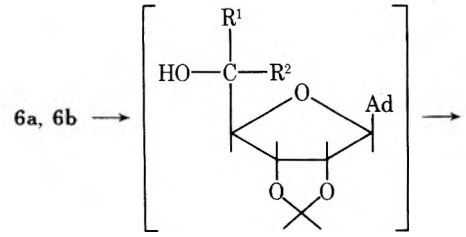


10a, $R^1 = CH_2NHCOCH_3$; $R^2 = H$
10b, $R^1 = H$; $R^2 = CH_2NHCOCH_3$
11a, $R^1 = CH_2NHCOC_2H_5$; $R^2 = H$
11b, $R^1 = H$; $R^2 = CH_2NHCOC_2H_5$
12, $R^1 = CH_2NHCOC_6H_5$; $R^2 = H$
13, $R^1 = CH_2NHCO(p\text{-}NO_2)C_6H_4$; $R^2 = H$

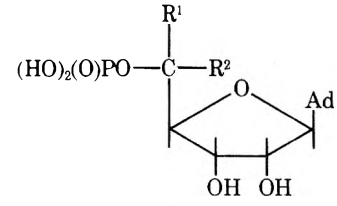


14a, $R^1 = CH_2NHCOCH_3$; $R^2 = H$
14b, $R^1 = H$; $R^2 = CH_2NHCOCH_3$
15a, $R^1 = CH_2NHCOC_2H_5$; $R^2 = H$
15b, $R^1 = H$; $R^2 = CH_2NHCOC_2H_5$
16, $R^1 = CH_2NHCOC_6H_5$; $R^2 = H$

Subsequent studies disclosed a suitable method for synthesis of the unprotected epimeric 5′-*C*-aminomethyl derivatives of AMP (**18a** and **18b**), and these compounds proved to be more valuable than the 5′-*C*-methylamino nu-



17a, $R^1 = CH_2NHCOOC_6H_5$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_2NHCOOC_6H_5$

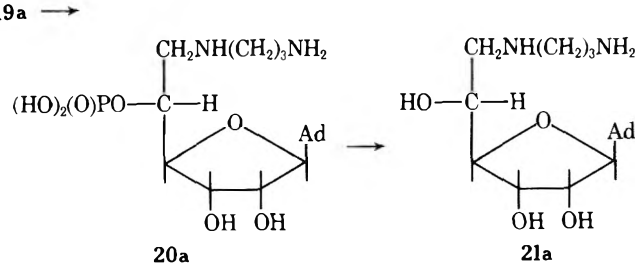


18a, $R^1 = CH_2NH_2$; $R^2 = H$
18b, $R^1 = H$; $R^2 = CH_2NH_2$
19a, $R^1 = CH_2NHCH_2CH_2CN$; $R^2 = H$
19b, $R^1 = H$; $R^2 = CH_2NHCH_2CH_2CN$

cleosides **6a** and **6b** as intermediates for the required 5′-acylaminomethyl derivatives of AMP. For the preparation of **18a** or **18b**, the appropriate 5′-*C*-nitromethyl-2′,3′-*O*-isopropylideneadenosine (**8a** or **8b**) was reduced as previously described and the crude aminomethyl nucleoside was treated in tetrahydrofuran with 1 equiv of phenyl chloroformate. Chromatography on silica gel showed conversion of the aminomethyl nucleoside to a less polar compound, presumed to be the phenylurethane **17a** or **17b**. The crude mixture was treated with β-cyanoethyl phosphate–DCC, after which the phenoxycarbonyl and 2-cyanoethyl groups were removed with aqueous sodium hydroxide, and finally the isopropylidene group was removed with aqueous acid. The 5′-*C*-aminomethyl nucleotides **18a** and **18b** were then obtained in homogenous form in 10% overall yield (from **8a** or **8b**) following their elution from a column of Dowex 1 bicarbonate with aqueous triethylammonium bicarbonate. In accord with the presence of the aminomethyl function, **18a** and **18b** underwent the ninhydrin reaction and migrated as monoanions when subjected to paper electrophoresis at pH 7.6.

The above sequence of reactions provided also an approximately equal amount of a second nucleotide which eluted from a column of Dowex 1 bicarbonate more slowly than the 5′-aminomethyl AMP derivatives **18a** and **18b**. Its NMR spectrum showed an adenosine moiety and a 5′ substituent which contained six nonexchangeable protons made up of a two-proton triplet at δ 3.58 and a four-proton broad multiplet at δ 3.85.[17] The CH_2NH grouping in the starting material suggested CH_2NHCH_2 for the broad resonance at δ 3.85. The addition to this of a methylene group responsible for the δ 3.58 resonance was indicated by the coupling constant of 6 Hz, and suggested a partial structure in which $CH_2NHCH_2CH_2X$ was substituted at C-5′ of adenosine. The elemental analysis indicated that the compound could be a 5′-*C*-(2-cyanoethyl)aminomethyl derivative of AMP (**19a** or **19b**). This was supported by paper electrophoresis, which showed that the compound, like the aminomethyl nucleotides **18a** and **18b**, had a net ionic charge of zero at pH 4.5 (AMP had one negative charge), whereas at pH 7.6 it had 1.6 negative charges compared to 1.0 negative charges in the case of **18a** and **18b** and 2.0 negative charges for AMP. This suggests that the cyanoethyl group lowers the pK_a of the aliphatic amino group of **18a** or **18b** from a value in excess of 9.0 to a value less than 7.6. An ir absorption peak assignable to the cyano group of **19a** or **19b** proved difficult to detect, and to confirm the presence of this group, **19a** was hydrogenated in 15% aqueous ammonium hydroxide in the presence of rhodium–alumina, when rapid and quantitative reduction occurred to give a single compound which at pH 4.5 migrated on electrophoretograms as a monocation and which was concluded to be the 5′-*C*-(3-aminopropyl)aminomethyl nucleotide **20a**. That

19a →



20a **21a**

the ionic charge was due to the net effect of two positive charges on the two aliphatic amino groups and one negative charge on the phosphoryl group was confirmed by treating **20a** with alkaline phosphatase to produce a single uv-absorbing component (presumably the nucleoside **21a**) which migrated as a dication at pH 4.5.

The 5′-*C*-aminomethyl nucleotide **18a** produced significant amounts of **19a** when treated with cyanoethylene under the basic conditions employed to remove the cyanoethyl and phenoxycarbonyl groups in the foregoing synthesis of **18a**. The amount of cyanoethylene employed in the reaction was the same as that which would have been generated from the 2-cyanoethyl phosphate employed in the phosphorylation of **17a**. This indicates that the nucleotide **19a** is produced primarily by intermolecular reaction of the 5′-*C*-aminomethyl group with cyanoethylene liberated during the alkaline deblocking procedure and that an intramolecular reaction between adjacent 5′-*C*-aminomethyl and 2-cyanoethylphosphate groups is probably not involved in the formation of **19a**. It should be noted that the AMP derivatives **19a** and **19b** have the same potential value as steric probes of enzyme–AMP complexes as do the 5′-*C*-acylaminomethyl derivatives of AMP. Studies of their interactions with enzymes will be described in a subsequent publication.

Selective acetylation or propionylation of the aliphatic amino group of the 5′-*C*-aminomethyl AMP epimers **18a** and **18b** was readily accomplished in methanolic solution by acetic or propionic acids which had been converted in situ to mixed carbonic anhydrides by the action of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.[18] The only products detected were the starting material, which was quantitatively recovered by paper chromatography, and the required *N*-acyl derivatives **14a**, **14b**, and **15a** which were isolated in 84–91% yield as their disodium salts. The D-allofuranosyl epimer **18a** was employed as its methanol-soluble triethylammonium salt, whereas it was necessary to employ the less soluble L-talofuranosyl epimer **18b** as a trioctylammonium salt. When N-benzoylation of **18a** was attempted by means of this procedure, the yield of **16** was reduced as a result of the formation of appreciable amounts of an unidentified nucleotide.[19] However, treatment of **18a** in aqueous sodium carbonate solution with an excess of benzoyl chloride rapidly produced solely the desired 5′-*C*-benzamidomethyl AMP derivative **16**, which was obtained in high yield as its disodium salt following paper chromatographic purification. That the position of acylation of all these nucleotides was the aliphatic amino group was shown by their inability to undergo the ninhydrin reaction, and by their migration as dianions on electrophoretograms run at pH 7.6.

Conversion of the epimeric 5′-*C*-acetylaminomethyl derivatives of AMP (**14a** and **14b**) to the corresponding derivatives (**3** and **4**) of ATP was accomplished by the anion-exchange reaction of Michelson,[20] which is of general utility for the conversion of naturally occurring 5′ nucleotides to a variety of phosphoanhydride derivatives. In the present case, this comprised conversion of **14a** and **14b** with diphenyl phosphorochloridate to P^1,P^1-diphenyl-P^2-nucleoside 5′-pyrophosphates and reaction of these in situ with tributylammonium pyrophosphate. Paper chromatography satisfactorily separated unchanged **14a** and **14b** and traces of the corresponding nucleoside 5′-diphosphates from the nucleoside 5′-triphosphates **3** and **4**, which were obtained in 35% yield and isolated as their tetrasodium salts. As expected, **3** and **4** possessed the same ultraviolet extinction coefficients as ATP and their paper chromatographic and electrophoretic properties also resembled those of ATP. Further confirmation of the structure of **3** and **4** was provided by the action of alkaline phosphatase, which liberated 3.0 mol of inorganic phosphate per mole of each nucleotide.

Experimental Section[21]

9-(6-Deoxy-6-nitro-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (8a) and 9-(6-Deoxy-6-nitro-2,3-*O*-isopropylidene-α-L-talofuranosyl)adenine (8b). To a solution of 2′,3′-*O*-isopropylideneadenosine (8 g, 26 mmol) in dry dimethyl sulfoxide (50 ml) was added pyridine (2 ml), trifluoroacetic acid (1 ml), and dicyclohexylcarbodiimide (16 g). The mixture was stirred at room temperature for 18 hr and dicyclohexylurea was filtered off and washed with dimethyl sulfoxide (3 × 25 ml). The combined filtrate and washings were extracted with cyclohexane (3 × 25 ml). To the dimethyl sulfoxide solution was added nitromethane (3 g, 50 mmol) and triethylamine (6.6 g, 65 mmol), and the red solution was stirred at room temperature for 18 hr. Volatile materials were removed at 35° (1 mm) during which additional dicyclohexylurea precipitated. This was filtered off, the dimethyl sulfoxide was diluted with ethyl acetate (100 ml), and the mixture was extracted with water (3 × 30 ml). The aqueous solutions were extracted with ethyl acetate (30 ml). The combined ethyl acetate extracts were dried ($MgSO_4$) and then concentrated to small volume and chromatographed over silica gel (2.7 × 120 cm) using a linear gradient of ethyl acetate to 5% ethanol in ethyl acetate (4 l.). Evaporation of fractions containing **8a** and **8b** gave a yellow foam (4.5 g). This was dissolved in chloroform and chromatographed over silica gel (2.7 × 120 cm) using a linear gradient of chloroform to 5% methanol in chloroform (5 l.); 15-ml fractions were collected. Compound **8b** was eluted in fractions 203–219 and **8a** in fractions 228–270. Fractions 220–227 contained small amounts of both **8a** and **8b**. Compound **8b** was obtained as a lustrous white solid (0.50 g, 5.6% yield) which crystallized from ethanol as fine needles (0.42 g): mp 216–218° dec, $[\alpha]^{23}D$ −79.4° (*c* 1.1, DMSO); ir 1555, 1375 cm^{-1} ($-NO_2$); uv max (pH 2) 257 nm (ε 15,500), (pH 11) 254 nm (ε 21,700); NMR (DMSO-d_6) 8.73 (s, 1, H-8), 8.51 (s, 1, H-2), 7.71 (s, 2, $-NH_2$), 6.89 (d, 1, *J* = 4Hz, –OH), 6.50 (d, 1, *J* = 4 Hz, H-1′), 5.59 (dd, 1, *J* = 4, 6 Hz, H-2′), 5.42 (dd, 1 *J* = 6, 2 Hz, H-3′), 5.20 (m, 1, H-4′), 4.77 (m, 3, H-5′, H-6′, 6″), 1.92 (s, 3) and 1.68 ppm (s, 3, isopropylidene).

Anal. Calcd for $C_{14}H_{18}N_6O_6$: C, 45.89; H, 4.92; N, 22.95. Found [dried at 78° (0.01 mm)]: C, 45.79; H, 5.09; N, 22.54.

From the foregoing column chromatography, compound **8a** was obtained as a yellow glass (1.8 g, 19% yield) free of uv-absorbing impurities. It was dissolved in ethyl acetate and chromatographed on a silica gel column (3.7 × 30 cm) using ethyl acetate as eluent. This gave **8a** as an off-white solid which separated from ethanol as microcrystalline aggregates (0.94 g): mp 179–182° dec; $[\alpha]^{21}D$ −60.8° (*c* 1.0, DMSO); ir 1560, 1375 cm^{-1} ($-NO_2$); uv max (pH 2) 257 nm (ε 15,000), (pH 11) 254 nm (ε 20,400); NMR (DMSO-d_6) 8.68 (s, 1, H-8), 8.55 (s, 1, H-2), 7.66 (s, 2, $-NH_2$), 6.55 (d, 1, *J* = 2.7 Hz, H-1′), 6.50 (1, –OH , 5.84 (dd, 1, *J* = 2.7, 6 Hz, H-2′), 5.56 (dd, 1, *J* = 2.6, 6 Hz, H-3′), 4.85 (m, 3, H-4′, H-6′, 6″), 4.58 (m, 1, H-5′), 1.93 (s, 3), and 1.69 ppm (s, 3, isopropylidene).

Anal. Calcd for $C_{14}H_{18}N_6O_6$: C, 45.89; H, 4.92; N, 22.95. Found [dried at 100° (0.01 mm)]: C, 45.67; H, 5.05; N, 22.97.

Diborane Reduction of 9-(2,3-*O*-Isopropylidene-β-D-allofuranuronamide)adenine (5). To a stirred solution of **5** (47 mg, 150 μmol) in dry tetrahydrofuran (2 ml) at ca. 22° was added an excess of borane in tetrahydrofuran (1 ml of a 1 *M* solution). After stirring for 1 hr, water–tetrahydrofuran (1:1) (1 ml) was added followed by 2 *N* KOH (0.25 ml) and 30% H_2O_2 (0.25 ml). The solution was stirred for an additional 15 min and then evaporated. The residue was dissolved in water and applied to a column (2 × 20 cm) of Dowex-50 (pyridinium form). The column was washed with water and compound **6a** was then eluted with 2 *N* NH_4OH. Evaporation of this eluate gave a pale yellow powder (2 mg, 4.4%) which was homogenous in solvent G (R_f 0.43) and solvent B (R_f 0.76) and indistinguishable from **6a**, but different from **6b** which had R_f 0.46 and 0.78 in the respective solvents. The product, like **6a** and **6b**, reacted positively to the ninhydrin spray test on chromatograms, migrated as a monocation on electrophoretograms at pH 4.5, and after elution from the electrophoretogram had the same uv absorption maxima at pH 2 and 7 as adenosine.

Establishment of the Configurations of 8a and 8b. Compound **8a** or **8b** (50 mg) was added to a suspension of prereduced PtO_2 (50 mg) in methanol (25 ml). This was shaken at 50° and 50 psi of hydrogen for 18 hr, when TLC (silica gel, EtOAc) showed no starting material (R_f 0.44) and a single ninhydrin-positive spot of zero R_f. The catalyst was filtered off and the filtrate was evaporated. A solution of the residue in water was applied to a Dowex-50 (pyridinium form) column. The column was washed with water to remove nonbasic material and compound **6a** or **6b** was eluted with 1 *N* NH_4OH. The chromatographically homogeneous residue obtained upon evaporation was dissolved in water (1 ml) and acetic acid (0.45 ml). Sodium nitrite (0.25 g) was added and the solution was stirred at ca. 22° for 4 hr. An additional 0.07 g of sodium nitrite and 0.25 ml of acetic acid was added and stirring was continued for 18 hr. The mixture was then adsorbed onto charcoal. The charcoal was washed with water, and the nucleoside **9a** or **9b** [uv max (pH 12) 254 and 252 nm, respectively] was then eluted with 1:1 ethanol–0.05 *M* NH_4OH and the eluate evaporated. The residue was dissolved in water (5 ml), Dowex-50 (H^+) (10 ml wet resin) was added, and the mixture was heated at 100° for 1.5 hr to yield from **8b** hypoxanthine as the only uv-absorbing component and talose (R_f 0.36 in system G, 0.30 in system H, 0.63 in system J) as the only sugar component. Compound **8a** gave allose (R_f 0.27 in G, 0.21 in H, and 0.52 in J) and hypoxanthine. The sugars were detected by spraying the papers with 3% *p*-anisidine in butanol and heating them for 10 min at 105°. Mannose had R_f 0.31 in G, 0.23 in H, and 0.55 in J.

General Syntheses of Nucleosides 10a–13. Method A. Compound **8a** or **8b** (1.4 mmol) was added to a suspension of prereduced PtO_2 (0.5 g) in methanol (100 ml) and hydrogenation was carried out as described above. The catalyst was filtered off and the filtrate was evaporated. To the residue was added pyridine (2 ml) and the required anhydride (1.9 mmol). This was heated at reflux for 2 hr. After cooling, the solvents were removed in vacuo and the residue was dissolved in chloroform and subjected to preparative layer chromatography on silica gel with solvent A.

Method B. Compound **8a** or **8b** (1.4 mmol) was reduced as above. The catalyst was removed by filtration and the filtrate was concentrated to about 50 ml. The required carboxylic acid (2.5 mmol) was added followed by *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ, 0.5 g, 2 mmol). The solution was stirred at 30–35° for 15 hr. The solvent was evaporated and the residue was dissolved in chloroform (10 ml) and added dropwise to rapidly stirred cold petroleum ether (250 ml). The precipitate was collected and chromatographed on thick layer silica gel plates with solvent A. This showed that all preparations contained minor amounts of at least four by-products.

9-(6-Acetamido-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (10a). The crude product obtained from 2 g (5.4 mmol) of **8a** by method A was chromatographed over silica gel (46.5 × 2 cm). The column was washed with chloroform (500 ml) followed by chloroform–methanol (19:1) (2 l.). Compound **10a** was thereby obtained as a white, chromatographically homogeneous glass (0.96 g). This material was sufficiently pure for use in the phosphorylation described under method C. A solution of the product in chloroform (15 ml) was added to petroleum ether (200 ml). The resulting powder was precipitated twice more from chloroform using diethyl ether in place of petroleum ether to give 0.75 g (37% yield): mp 123–128°; R_f 0.34 (solvent A); $[\alpha]^{22}D$ −61° (*c* 1.0, $CHCl_3$); ir 1625 cm^{-1} (C=O); uv max (pH 2) 256 nm (ε 15,100), (pH 11) 259 nm (ε 15,300); NMR (DMSO-d_6) 8.75 (s, 1, H-8), 8.55 (s, 1, H-2), 8.22 (s, 1, –CONH), 7.88 (s, 2, $-NH_2$), 6.46 (d, 1, *J* = 4 Hz, H-1′), 5.55 (m, 3, H-2′, H-3′, –OH), 4.42 (s, 1, H-4′), 4.0 (m, 1, H-5′), 3.37 (m, 2, H-6′, H-6″), 2.15 (s, 3, $-CH_3$), 1.90 and 2.0 ppm (s, 3, CMe_2).

Anal. Calcd for $C_{16}H_{22}N_6O_5$: C, 50.79; H, 5.82; N, 22.22. Found [dried at 78° (0.01 mm)]: C, 50.98; H, 5.91; N, 22.42.

9-(6-Acetamido-6-deoxy-2,3-*O*-isopropylidene-α-L-talofuranosyl)adenine (10b). Method B was applied to 0.35 g of **8b**, and **10b** was extracted from the silica gel chromatogram with ethyl acetate. The solvent was volatilized and the residue was dissolved in chloroform and precipitated from petroleum ether to give 205 mg (54% overall yield) of a white powder: mp 125–132°; R_f 0.35 (solvent A); $[\alpha]^{24.5}D$ −112° (*c* 1.0, $CHCl_3$); ir 1620 cm^{-1} (C=O); uv max (pH 2) 257 nm (ε 15,100), (pH 12) 259 nm (ε 15,300); NMR (DMSO-d_6) 8.70 (s, 1, H-8), 8.45 (s, 1, H-2), 8.15 (d, 1, *J* = 5 Hz, –CONH), 7.60 (s, 2, $-NH_2$), 6.40 (d, 1, *J* = 4 Hz, H-1′), 5.97 (d, 1, *J* = 5 Hz, –OH), 5.35 (m, 2, H-2′, H-3′), 4.57 (m, 1, H-4′), 4.05 (m, 1, H-5′), 3.47 (m, 2, H-6′, H-6″), 2.05 (s, 3, $-CH_3$), 1.82 and 1.57 ppm (s, 3, CMe_2).

Anal. Calcd for $C_{16}H_{22}N_6O_5$: C, 50.79; H, 5.82; N, 22.22. Found [dried at 78° (0.01 mm)]: C, 50.93; H, 5.99; N, 21.99.

9-(6-Deoxy-6-propionamido-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (11a). Method A was applied to 0.5 g (1.4 mmol) of **8a** and **11a** was eluted with chloroform from its zone of the thick layer silica gel chromatogram and purified by three precipitations from chloroform by addition of diethyl ether. This gave 139 mg of material (25% yield): mp 124–129°; R_f 0.40 (solvent A); $[\alpha]^{23}D$ −62° (*c* 1.1, $CHCl_3$); ir 1615 cm^{-1} (C=O); uv max (pH 2)

Table I
Paper Chromatography and Electrophoresis

Compd	R_f values system				Electrophoretic mobility relative to AMP		
	B	C	E	F	pH 7.5	pH 4.5	pH 3.5
AMP	0.10	0.26	0.43	0.56	1.00	1.00	1.00
14a	0.15	0.31	0.52	0.69	0.94	0.98	
14b	0.17	0.33	0.54	0.71	0.94	0.98	
15a	0.24	0.39	0.62	0.79	0.93	1.08	
15b	0.24	0.41	0.62	0.80	0.94	1.08	
16	0.26	0.51	0.64	0.87	0.87	0.91	
18a	0.06	0.19	0.39	0.76	0.51	0.00	
18b	0.07	0.18	0.40	0.74	0.53	0.00	
19a	0.17	0.24		0.52	0.81	0.00	
ATP	0.03	0.09	0.44	0.42			2.34
4	0.06	0.10	0.45	0.43			2.13
3	0.05	0.10	0.44	0.42			2.17

258 nm (ε 15,000), (pH 12) 259 nm (ε 15,200); NMR (DMSO-d_6) 8.78 (s, 1, H-8), 8.60 (s, 1, H-2), 7.95 (s, 1, –CONH–), 7.60 (s, 2, $-NH_2$), 6.54 (d, 1, J = 4 Hz, H-1′), 5.52 (m, 3, H-2′, H-3′, –OH), 4.73 (m, 1, H-4′), 4.35 (m, 1, H-5′), 3.75 (m, 2, H-6′, H-6″), 2.60 (q, 2, J = 7 Hz, $-COCH_2-$), 1.95 and 1.72 (s, 3, CMe_2), 1.45 ppm (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_{17}H_{24}N_6O_5$: C, 52.04; H, 6.14; N, 21.43. Found [dried at 78° (0.01 mm)]: C, 51.89; H, 6.33; N, 21.21.

9-(6-Deoxy-6-propionamido-2,3-*O*-isopropylidene-α-L-talofuranosyl)adenine (11b). This was prepared in the same manner as its 5′ epimer **11a**, except that it was eluted from the silica gel with ethyl acetate and crystallized from the same solvent to give 100 mg of **11b** (13% overall yield): R_f 0.40 (solvent A); mp 117–120°; $[\alpha]^{23}D$ −100° (c 1.2, $CHCl_3$); ir 1620 cm^{-1} (C=O); uv max (pH 2) 258 nm (ε 15,100), (pH 12) 259 nm (ε 15,300); NMR (DMSO-d_6) 8.80 (s, 1, H-8), 8.55 (s, 1, H-2), 8.15 (s, 1, –CONH–), 7.70 (s, 2, $-NH_2$), 6.48 (d, 1, J = 4 Hz, H-1′), 6.10 (d, 1, J = 5 Hz, –OH), 5.38 (m, 2, H-2′, H-3′), 4.56 (s, 1, H-4′), 4.10 (m, 1, H-5′), 3.30 (m, 2, H-6′, H-6″), 2.45 (q, 2, J = 7 Hz, $-COCH_2-$), 1.85 and 1.60 (s, 3, CMe_2), 1.35 ppm (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_{17}H_{24}N_6O_5$: C, 52.04; H, 6.14; N, 21.43. Found [dried at 78° (0.01 mm)]: C, 51.90, H, 6.14; N, 21.52.

9-(6-Benzamido-6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (12). Method B was applied to 0.5 g of **8a**, and **12** was extracted from the silica gel chromatogram with ethyl acetate. The solvent was volatilized and the residue was dissolved in chloroform and precipitated from petroleum ether to give 206 mg (34% overall yield) of **12** as a white powder: R_f 0.60 (solvent A); mp 105–110°; $[\alpha]^{25.5}D$ −120° (c 1.3, $CHCl_3$); ir 1630 cm^{-1} (C=O); uv max (pH 2) 256 nm (ε 15,200), (pH 12) 257 nm (ε 15,600); NMR (DMSO-d_6) 8.72 (s, 1, H-8), 8.62 (d, 1, J = 6 Hz, –CONH–), 8.53 (s, 1, H-2), 7.77–8.23 (m, 5, aromatic), 7.65 (s, 2, $-NH_2$), 6.51 (d, 1, J = 4 Hz, H-1′), 5.67 (m, 1, H-2′), 5.49 (m, 1, H-3′), 4.54 (m, 1, H-4′), 4.30 (m, 2, –OH, H-5′), 3.77 (m, 2, H-6′, H-6″), 1.91 and 1.69 ppm (s, 3 each, CMe_2).

Anal. Calcd for $C_{21}H_{24}N_6O_5 \cdot {}^1/_{20}\ CHCl_3$: C, 56.50; H, 5.38; N, 18.83; Cl, 1.35. Found [dried at 78° (0.01 mm)]: C, 56.32; H, 5.72; N, 18.35; Cl, 1.23.

9-(6-Deoxy-6-*p*-nitrobenzamido-2,3-*O*-isopropylidene-β-D-allofuranosyl)adenine (13). Method B was applied to 0.25 g of **8a**, and **13** was extracted from the silica gel chromatogram with ethyl acetate. The solvent was volatilized and the residue was dissolved in chloroform and precipitated from petroleum ether to give 85 mg (25% overall yield) of **13** as a pale yellow powder (R_f 0.58, solvent A): mp 123–127° $[\alpha]^{25.5}D$ −117° (c 1.0, $CHCl_3$); ir 1635 cm^{-1} (C=O); NMR (DMSO-d_6) 8.07–8.75 (m, 7, H-8, H-2, –CONH–, aromatic), 7.60 (s, 2, $-NH_2$), 6.50 (d, 1, J = 4 Hz, H-1′), 5.50 (m, 1, H-3′), 4.50 (m, 1, H-4′), 4.28 (m, 2, –OH, H-5′), 3.75 (m, 2, H-6′, H-6″), 1.90 and 1.70 ppm (s, 3 each, CMe_2).

Anal. Calcd for $C_{21}H_{23}N_7O_7$: C, 51.96; H, 4.76; N, 20.21. Found [dried at 78° (0.01 mm)]: C, 51.40; H, 5.15; N, 20.36.

Syntheses of Nucleoside 5′-Monophosphates. Method C. The 5′-C-substituted 2′,3′-O-isopropylidene nucleoside (0.4 mmol) was dissolved in pyridine (10 ml) and a pyridine solution of 2-cyanoethyl phosphate (1 mmol) was added. The solution was evaporated to dryness and twice again after addition of 10 ml of dry pyridine. The residue was dissolved in anhydrous pyridine (5 ml) and dicyclohexylcarbodiimide (1 g) was added. The mixture was stirred at room temperature for 15 hr. Water (5 ml) was added and stirring was continued for 30 min. Concentrated NH_4OH (10 ml) was added and the mixture was heated at 70° for 60 min and then evaporated to dryness. Water (20 ml) was added and the filtered solution was adjusted to pH 1.5 with concentrated HCl and heated at 70° (bath temperature) for 2 hr. The pH was adjusted to 3.5, Darco G-60 charcoal (1 g) and Celite filter aid (1 g) were added, and the mixture was stirred for 2 hr. The charcoal was collected by filtration and washed with water (500 ml). The nucleotide was desorbed from the charcoal with 200 ml of aqueous 50% ethanol containing 0.6 ml of concentrated NH_4OH. The extract was concentrated and subjected to downward chromatography for 3 days in solvent D on four sheets (width 20 cm) of Whatman 3MM paper. The aqueous eluate of the nucleotide was lyophilized, giving the ammonium salt of the nucleotide as a white powder which was homogeneous in all the solvent systems listed in Table I. This was dissolved in methanol (5 ml) containing Et_3N (2 drops). Volatiles were removed, and a solution of the residue in MeOH (5 ml) was clarified by filtration and treated with 1 *M* NaI (0.6 ml) followed by acetone (25 ml). The precipitated disodium salt of the nucleotide was collected by centrifugation, washed with acetone (3 × 10 ml), and dried at 0.01 mm (18 hr, P_2O_5).

Method D. Compound **8a** or **8b** (2.0 g, 5.3 mmol) was reduced in the normal manner. The residue of **6a** or **6b** obtained on work-up was suspended in THF (100 ml) and Et_3N (1 ml, 6 mmol) was added. Phenyl chloroformate (1 g, 6 mmol) in THF (30 ml) was added dropwise to the rapidly stirring mixture. After 1 hr addition was complete and Et_3N·HCl had separated. TLC in solvent A indicated one major component, R_f 0.5, and several minor components. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in dry pyridine (10 ml) and treated with 2-cyanoethyl phosphate (from 15 mmol of the barium salt) in dry pyridine (10 ml). DCC (10 g) was added and the mixture was stirred for 72 hr. Water (10 ml) was added and after 0.5 hr 2 *N* NaOH (30 ml) was added. The mixture was stirred at 22° for 0.5 hr, filtered, and evaporated. The residue was dissolved in H_2O (30 ml) and the pH was adjusted to 1.5 with concentrated HCl. The solution was heated at 70° for 1.5 hr. After cooling, the pH was adjusted to 3.5 with 1 *N* NaOH and the product was purified by adsorption onto charcoal (10 g) in the normal manner. After elution the nucleotide fraction was concentrated (ca 10 ml) and applied to Dowex-1 (HCO_3^-) (4.5 × 32 cm). This was eluted stepwise with 0–1.0 *M* Et_3NHCO_3 (0.1 *M* increments/l.). With 0–0.2 *M* salt ca. 40,000 OD_{260} units were eluted; with 0.5 *M* salt compound **18a** or **18b** was eluted (8,000 OD_{260} units, 10% yield) and was obtained as a white, chromatographically homogenous triethylammonium salt after desalting it by coevaporating the partially evaporated eluate with ethanol. An analytical sample was prepared by dissolving a portion of the powdery salt in MeOH and adding 1 *M* NaI in acetone. Precipitation with acetone gave **18a** or **18b** as the monosodium salt, presumably because as the free acid, **18a** or **18b** exists as an inner salt: uv max (pH 2) 257 nm (ε 15,100, (pH 12) 259 nm (ε 15,300).

Anal. Calcd for $C_{11}H_{16}N_6O_7PNa \cdot H_2O$: C, 31.65; H, 4.56; N, 20.14; P, 7.43. Found [dried at 25° (0.01 mm)]: C, 32.08; H, 4.88; N, 20.33; P, 6.88.

A solution of the triethylammonium salt of **18a** was treated with EEDQ and the required carboxylic acid under conditions employed in method B and heated at 35° for 3 hr. The methanol was

evaporated and the residue was triturated several times with petroleum ether. The residue was dissolved in water and purified on Whatman 3MM paper in solvent D. The products obtained were identical with those from method C.

9-(6-Cyanoethylaminomethyl-6-deoxy-5-*O*-phosphoryl-β-D-allofuranosyl)adenine (19a). Elution of the above ion-exchange column with 0.6 *M* Et_3NHCO_3 gave a mixture of **18a** with **19a** (2000 OD_{260} units) and 0.7 *M* gave homogeneous **19a** (12,000 OD_{260} units, 15% yield). The triethylammonium salt of **19a** was obtained as described for the same salt of **18a** and was converted to the sodium salt with sodium iodide in acetone: uv max (pH 2) 257 nm (ε 15,100), (pH 12), 259 nm (ε 15,500); NMR (D_2O) 8.85 (s, 1, H-8), 8.50 (s, 1, H-2), 6.45 (d, 1, J = 5 Hz, H-1′), 4.63 (m, 1, H-4′ or H-5′), 3.85 (m, 4, $-CH_2NHCH_2-$), 3.58 ppm (t, 2, J = 6 Hz, $-CH_2CN$). The HDO peak at 5.20 obscured the remaining sugar protons.

Anal. Calcd for $C_{14}H_{18}N_7O_7PNa_2 \cdot 2.5\ H_2O$: C, 32.43; H, 4.12; N, 18.92; P, 5.98. Found [dried at 25° (0.01 mm)]: C, 32.38; H, 4.18; N, 18.61; P, 5.90.

9-(6-Acetamido-6-deoxy-5-*O*-phosphoryl-β-D-allofuranosyl)adenine (14a). Application of method C to compound **10a** (100 mg, 0.27 mmol) gave the disodium salt of **14a** (32 mg) as a white powder: ir 1610 (C=O), 1240 (P=O), 1100 cm^{-1} (P-O-C); uv max (pH 2) 257 nm (ε 14,800), (pH 12) 259 nm (ε 14,900); NMR (D_2O) 8.89 (s, 1, H-8), 8.60 (s, 1, H-2), 6.29 (d, 1, J = 6 Hz, H-1′), 5.30 (t, 1, H-2′), 5.13 (H-3′, partially obscured by HDO peak), 4.80 (m, 1, H-4′), 4.56 (m, 1, H-5′), 3.92 (m, 2, H-6′, H-6″), 2.41 ppm (s, 3, $-CH_3$).

Anal. Calcd for $C_{13}H_{17}N_6O_8PNa_2 \cdot 2H_2O$: C, 31.33; H, 4.22; N, 16.87; P, 6.22. Found [dried at 25° (0.01 mm)]: C, 31.42; H, 4.32; N, 16.62; P, 6.41.

Compound **14a** was obtained in 87% yield from **18a** (81% conversion) by method D.

9-(6-Acetamido-6-deoxy-5-*O*-phosphoryl-α-L-talofuranosyl)adenine (14b). Phosphorylation of **10b** (0.36 mmol) by method C gave 0.19 mmol of chromagraphically homogeneous ammonium salt. From this the disodium salt of the nucleotide was obtained as a white powder in the usual manner: ir 1620 (C=O), 1230 (P=O), 1100 cm^{-1} (P-O-C); uv max (pH 2) 257 nm (ε 14,900), (pH 12) 259 nm (ε 15,100); NMR (D_2O) 8.97 (s, 1, H-8), 8.40 (s, 1, H-2), 6.43 (d, 1, J = 6 Hz, H-1′), 5.33 (H-2′, partially obscured by HDO peak), 5.17 (m, 1, H-3′), 4.94 (m, 1, H-4′), 4.77 (s, 1, H-5′), 3.98 (d, 2, J = 6 Hz, H-6′, 6″), 2.43 ppm (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{17}N_6O_8PNa_2 \cdot 2H_2O$: P, 6.22. Found [dried at 25° (0.01 mm)]: P, 6.38, 6.35.

Compound **14b** was obtained in 91% yield from **18b** (85% conversion) by method D.

9-(6-Deoxy-5-*O*-phosphoryl-6-propionamido-β-D-allofuranosyl)adenine (15a). This was obtained as a chromatographically and electrophoretically homogeneous ammonium salt (0.14 mmol) by application of method C to **11a** (0.57 mmol). This was converted in high yield to the disodium salt (a white powder) with sodium iodide in acetone: ir 1655 (C=O), 1230 (P=O), 1100 cm^{-1} (P-O-C); uv max (pH 2) 257 nm (ε 14,900), (pH 12) 259 nm (ε 15,100); NMR (D_2O) 8.88 (s, 1, H-8), 8.56 (s, 1, H-2), 6.50 (d, 1, J = 6 Hz, H-1′), 5.30 (t, 1, H-2′), 5.14 (H-3′, partially obscured by HDO peak), 4.86 (m, 1, H-4′), 4.64 (m, 1, H-5′), 3.98 (m, 2, H-6′, 6″), 2.70 (q, 2, J = 7 Hz, $-COCH_2-$), 1.52 (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_{14}H_{19}N_6O_8PNa_2 \cdot 2H_2O$: P, 6.05. Found [dried at 25° (0.01 mm)]: P, 6.10, 6.12.

Compound **15a** was obtained in 84% yield from **18a** (82% conversion) by method D.

9-(6-Deoxy-5-*O*-phosphoryl-6-propionamido-α-L-talofuranosyl)adenine (15b). This was obtained as a chromatographically and electrophoretically homogeneous ammonium salt (0.13 mmol) by application of method C to **11b** (0.4 mmol). From this the disodium salt was prepared as above: ir 1610 (C=O), 1235 (P=O), 1100 cm^{-1} (P-O-C); uv max (pH 2) 257 nm (ε 15,000), (pH 12) 259 nm (ε 15,300); NMR (D_2O) 9.00 (s, 1, H-8), 8.53 (s, 1, H-2), 6.51 (d, 1, J = 6 Hz, H-1′), 5.20 (H-2′, partially obscured by HDO peak), 5.08 (m, 1, H-3′), 4.91 (m, 1, H-4′), 4.80 (s, 1, H-5′), 3.99 (d, 2, J = 6 Hz, H-6′, 6″), 2.63 (q, 2, J = 7 Hz, $-COCH_2-$), 1.42 (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_{14}H_{19}N_6O_8PNa_2 \cdot 2H_2O$: P, 6.05. Found [dried at 25° (0.01 mm)]: P, 5.98, 6.02.

9-(6-Benzamido-6-deoxy-5-*O*-phosphoryl-β-D-allofuranosyl)adenine (16). A. From Method C. Compound **16** was obtained as its ammonium salt (0.08 mmol) by application of method C to **12** (0.25 mmol): ir 1620 (C=O), 1230 (P=O), 1100 cm^{-1} (P-O-C); uv (disodium salt) max (pH 2) 257 nm (ε 14,900), (pH 12) 259 nm (ε 15,100); NMR (D_2O) 8.83 (s, 1, H-8), 8.51 (s, 1, H-2), 7.80–8.20 (m, 5, aromatic), 6.48 (d, 1, J = 6 Hz, H-1′), 5.41 (t, 1, H-2′), 5.10 (H-3′, partially obscured by HDO peak), 4.61 (m, 1, H-4′), 4.45 (m, 1, H-5′), 3.90 (m, 2, H-6′, H-6″).

Anal. Calcd for $C_{18}H_{19}N_6O_8PNa_2 \cdot 2H_2O$: P, 5.54. Found [dried at 25° (0.01 mm)]: P, 5.42, 5.46.

B. By Benzoylation of 18a. Compound **18a** (2600 OD_{260} units; 190 μmol) and Na_2CO_3 (14.8 mg, 140 μmol) were dissolved in H_2O (700 μl) and stirred at 0°. Benzoyl chloride (23.3 μl, 200 μmol) in ether (300 μl) was added slowly. Stirring was then continued at 0° for 10 min, then at ca. 22° for 3 hr. Chromatography on Whatman No. 3MM paper (two sheets, 20 × 46 cm) in solvent D gave, after elution and lyophilization, compound **18a** (500 OD_{260} units, 19.3% recovered) and compound **16** (1700 OD_{260} units, 81% yield and 85% conversion) identical with that prepared by method C in the solvent systems listed in Table I.

C. From Method D. Paper chromatographic analysis (solvent C) of the mixture obtained upon application of method D gave **16** (57%, spectrophotometrically determined), unchanged **18a** (17%), and an additional nucleotide (23%, R_f 0.42 in solvent C). The unknown compound had R_f 0.27 in solvent B and an electrophoretic mobility (AMP = 1) at pH 7.5 of 0.89. Compound **16** and the unknown showed a large difference in the 260/235 nm ratio of uv absorption (1.05 and 2.92, respectively).

9-(6-Acetamido-6-deoxy-5-*O*-triphosphoryl-β-D-allofuranosyl)adenine (3). The homogeneous ammonium salt of compound **14a** (1200 OD_{260} units, 80 μmol) (purified by chromatography in solvent D; see method C) was suspended in MeOH (5 ml) and tri-*n*-butylamine (300 μl) was added. The mixture was warmed until homogeneous; then the MeOH was evaporated. The residue was rendered anhydrous by three evaporations in vacuo with pyridine (2 ml). Dioxane (0.5 ml) and *N,N*-dimethylformamide (0.3 ml) were added followed by diphenyl phosphorochloridate (30 μl) and tri-*n*-butylamine (40 μl). The mixture was stirred at room temperature for 3 hr. Solvents were removed in vacuo at 25° and ether (50 ml) was added to the residue with shaking. The mixture was kept at 0° for 1 hr. The ether was decanted and dioxane (1 ml) was added, after which the mixture was evaporated to a syrup. A solution of di(tri-*n*-butylammonium) pyrophosphate (0.1 mmol) in pyridine (200 μl) was added and the solution was kept at room temperature for 1 hr. The pyridine was removed in vacuo and ether (50 ml) was added to precipitate the nucleotide and then decanted off. The precipitate was dissolved in water and streaked on two sheets (20 × 46 cm) of Whatman 3MM paper. This was developed for 24 hr in solvent E. The zone corresponding to **3** was eluted into water and the solution was lyophilized. The product (405 OD_{260} units) was chromatographed in solvent F to remove the corresponding nucleoside diphosphate (30 OD_{260} units). The developed chromatogram was soaked in 1-propanol to remove ammonium butyrate, after which the product was eluted into water and obtained as a solid by lyophilization. It was converted to the tetrasodium salt (320 OD_{260} units, 27% yield) by the procedure used to prepare disodium salts of the monophosphates, uv max (pH 2) 257 nm (ε 14,900), (pH 12) 259 nm (ε 15,600).

Anal. Calcd for $C_{13}H_{17}N_6O_{14}P_3Na_4 \cdot 1.5H_2O$: P, 13.57. Found: P, 13.72.

The product (12.36 OD_{260} units) was kept for 60 min at 22° in 1 ml of Tris buffer, pH 10.4, containing 0.02 mg of alkaline phosphatase of calf intestinal mucosa (Type VII, from Sigma Chemical Co.). The ratio of inorganic phosphate[23] to 5′-*C*-acetylaminomethyladenosine was 2.92:1.

9-(6-Acetamido-6-deoxy-5-*O*-triphosphoryl-α-L-talofuranosyl)adenine (4). Compound **14b** (1200 OD_{260} units) was converted to **4** by the foregoing procedure. Purification in solvent E gave 435 OD units of **4**, which showed no trace of the nucleoside diphosphate or other impurity in solvent F. Compound **4** was isolated as its tetrasodium salt (350 OD_{260} units, 29% yield) as described for its 5′ epimer, uv max (pH 2) 257 nm (ε 14,800), (pH 12) 259 nm (ε 15,200).

Anal. Calcd for $C_{13}H_{17}N_6O_{14}P_3Na_4 \cdot 1.0H_2O$: P, 13.74. Found: P, 13.85.

The ratio of the inorganic phosphate released by alkaline phosphatase to 5′-*C*-acetylaminomethyladenosine (determined as for **3**) was 3.14:1.

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cer Research (USPHS Grants CA-06927 and RR-05539 and an appropriation from the Commonwealth of Pennsylvania).

Registry No.—3 tetrasodium salt, 54677-85-9; 4 tetrasodium salt, 54677-86-0; **5**, 50304-49-9; **8a**, 54677-87-1; **8b**, 54677-88-2; **10a**, 54677-89-3; **10b**, 54677-90-6; **11a**, 54677-91-7; **11b**, 54724-59-3; **12**, 54677-92-8; **13**, 54677-93-9; **14a** disodium salt, 54677-94-0; **14a** ammonium salt, 54677-95-1; **14b** disodium salt, 54677-96-2; **15a** disodium salt, 54677-97-3; **15b** disodium salt, 54677-98-4; **16** disodium salt, 54677-99-5; **18a** sodium salt, 54678-00-1; **18b** sodium salt, 54678-01-2; **19a** disodium salt, 54678-02-3; 2′,3′-*O*-isopropylideneadenosine, 362-75-4.

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(16) This reagent had previously proved useful for selective N-acylation of other nucleotides in this laboratory (Slotin and Hampton, in preparation).
(17) An external concentric capillary of Me_4Si was used for determination of all ^1H NMR spectra and caused a downfield shift of 0.4–0.5 ppm for all protons.
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(21) Darco G-60 charcoal was used for adsorbing nucleotides and was activated prior to use by the method of Lipkin et al.[22] Petroleum ether employed in purifications boiled at 30–60°. Thin layer chromatograms were obtained with Merck F-254 silica gel plates in chloroform–methanol (9:1) (system A). Preparative layer chromatography was conducted with 2-mm layers of silica gel on glass. Paper chromatography (descending) employed Whatman No. 1, 3MM or 17 papers in (B) 2-propanol–concentrated NH_4OH–water (7:1:2); (C) 1-butanol–acetic acid–water (5:2:3); (D) 1-propanol–concentrated NH_4OH–water (7:1:2); (E) 1-propanol–concentrated NH_4OH–water (55:10:35); (F) isobutyric acid–1 *M* NH_4OH (10:6); (G) 1-butanol–acetic acid–water (4:1:5, upper layer); (H) 1-butanol–pyridine–water (3:1:1); (J) 1-butanol–pyridine (2:1). Electrophoresis was performed on Whatman No. 1 paper at 40–80 V/cm for 30–60 min at pH 7.5 [0.05 *M* $(Et)_3NHCO_3$, pH 4.5 (0.05 *M* acetate), or pH 3.5 (0.015 *M* citrate)]. Mobility values (M_{AMP}) are relative to those of adenosine 5′-phosphate (AMP). Spots on chromatograms were detected by their ultraviolet absorption and (in the case of silica gel chromatograms) by spraying with the Molisch reagent. Melting points (uncorrected) were determined by the capillary method. Ultraviolet spectra were determined with a Cary Model 15 spectrophotometer. Infrared spectra were determined in KBr disks with a Perkin-Elmer spectrophotometer Model 137, and ^1H NMR spectra were obtained with a Varian XL-100-15 spectrometer and are recorded as parts per million downfield from an external standard (concentric capillary) of $SiMe_4$. Infrared and NMR spectra of nucleotides were usually obtained on ammonium salts from which the analytically pure sodium salts were obtained. Specific rotations were determined with a Bendix automatic polarimeter 1169. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga., and Midwest Microlab, Ltd., Indianapolis, Ind.
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Nucleotides. V. Syntheses of 2′-*O*- and 3′-*O*-(3-Methyl-2-picolyl 1-oxide) Ribonucleosides and Diribonucleoside Monophosphates by Application of 3-Methyl-2-picolyl 1-Oxide Protection[1]

Yoshihisa Mizuno,* Takeshi Endo, and Kazuyoshi Ikeda

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

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The alkylation of ribonucleosides (uridine series, **3** and **6**; adenosine series, **16** and **19**) with 1-oxido-3-methyl-2-pyridyldiazomethane (**2**) afforded an isomeric mixture of 2′-*O*- and 3′-*O*-(3-methyl-2-picolyl 1-oxide) ribonucleosides in 63–91% yields. 2′-*O*-(3-Methyl-2-picolyl 1-oxide)uridine (**4**) and 2′-*O*- (**17**), and 3′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine (**18**) could be isolated by fractional crystallization of the respective isomeric mixture, whereas 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-benzoyluridine (**7**) and 2′-*O*-(3-methyl-2-picolyl 1-oxide)-$O^{5'}$,N^6-dibenzoyladenosine (**20**) were isolated by column chromatography on silica gel. The stability of 3-methyl-2-picolyl 1-oxide group toward tritylation, benzoylation, and especially phosphorylation by the general method (phosphate in the presence of TPS) and its removability were found to be compatible with the oligoribonucleotide synthesis. Thus, the synthesis of 2′-*O*-(3-methyl-2-picolyl 1-oxide)uridylyl(3′–5′)-$O^{2'}$,$O^{3'}$,N^6-triacetyladenosine (**26**) and uridylyl(3′–5′)adenosine (UpA, **27**) was achieved by the application of 3-methyl-2-picolyl protection.

Requirements for protecting groups in the oligoribonucleotide synthesis have been recently discussed by Christen and Broom.[2] The development of the synthesis by a "phosphotriester approach",[3] in particular, has depended to a significant extent on the design of a new protecting group for 2′-hydroxyl function which meets the requirements.[4] Since 2′-*O*-(2-picolyl 1-oxide) ribonucleoside might be useful key intermediates for the oligonucleotide synthesis, our interest is selective and direct introduction of a removable blocking group of this type into the *cis*-glycol system of ribonucleosides. We have therefore prepared a series of nitrogenous heterocyclic *N*-oxides bearing a diazomethylene group and it was concluded that out of these diazoalkanes, 1-oxido-3-methyl-2-pyridyldiazomethane (**2**), might be a reagent of choice for the monoalkylation of the *cis*-glycol system of the ribonucleosides because of its easy accessibility and comparatively small δ value of the signal due to the diazomethylene proton in its NMR spectrum.[5]

Table I
NMR Data[a] of 2′-*O*- and 3′-*O*-(3-Methyl-2-picolyl 1-oxide) Nucleosides

O-(3-Methyl-2-picolyl 1-oxide) of	Anomeric proton		3″-Methyl proton	
	2′-O-	3′-O-	2′-O-	3′-O-
Uridine[c]	5.93	5.77	2.37	2.44
Adenosine	5.76	5.59	2.30	2.50
5′-*O*-Benzoyluridine	5.90	5.67	2.46	2.42
$O^{5'}$,N^{6}-Dibenzoyl-adenosine	6.16	6.11	2.37	2.45

[a] In $CDCl_3$, in parts per million (δ). [b] Reference 6. [c] In DMSO-d_6.

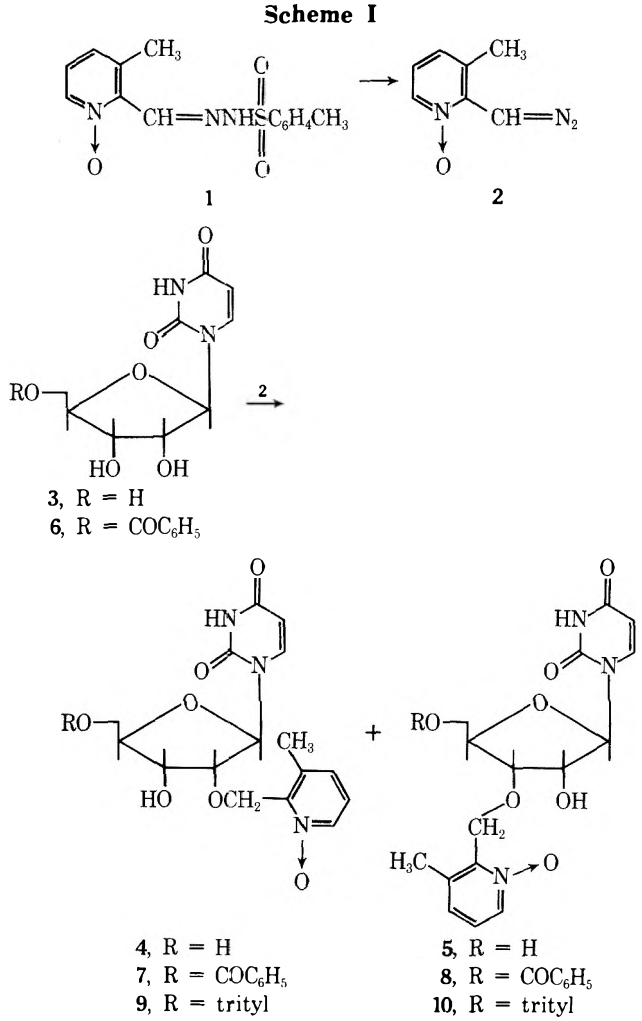
The present paper deals with the synthesis of 2′-*O*- and 3′-*O*-(3-methyl-2-picolyl 1-oxide) ribonucleosides (uridine series, **4**–**10**; adenosine series, **17**–**23**) by the use of **2** and the synthesis of uridylyl(3′–5′)adenosine (UpA) by the application of 1-oxido-3-methyl-2-picolyl protection.

Alkylation of uridine (**3**) with freshly prepared **2** in the presence of $SnCl_2$ (Scheme I) was performed essentially according to Christensen and Broom's procedure.[2] The reaction took place smoothly with evolution of nitrogen gas and within 12 hr the starting nucleoside (**3**) disappeared in the reaction mixture. After work-up, a 1:1 mixture of 2′-*O*- (**4**) and 3′-*O*-(3-methyl-2-picolyl 1-oxide)uridine (**5**) was obtained as a solid in combined yield of 91%. Recrystallization of this isomeric mixture from water afforded pure 2′-O isomer (**4**) in 25% yield. Attempted chromatography (silica gel) of the mother liquor failed to separate 3′-*O*-(3-methyl-2-picolyl 1-oxide)uridine (**5**) from **4**. The mixture was therefore treated with trityl chloride in pyridine to give monotritylated derivatives (**9** and **10**) from which 3′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (**10**) was isolated in 39% yield by column chromatography. A pure sample of **5** was prepared by detritylation of **10** in 90% yield. The purity of **4** and **5** could be readily demonstrated by examination of the signals, particularly by examination of the signals for 3″-CH_3[6] which appeared as a three-proton singlet at 2.37 and 2.44 ppm, respectively (see Table I). Structural assignments of **4** and **5** rest upon elemental and spectral (uv and NMR) analysis. As pointed out earlier by Reese and coworkers,[7] among a pair of 2′-O and 3′-O isomers, NMR signals due to the anomeric proton of the former all appeared at lower field (Table I). The fact that uridylyl(3′–5′)adenosine prepared starting from **4** was completely hydrolyzable with bovine pancreatic RNase to uridine 3′-phosphate and adenosine (vide infra) confirmed the structural assignment of **4** and hence **5**.

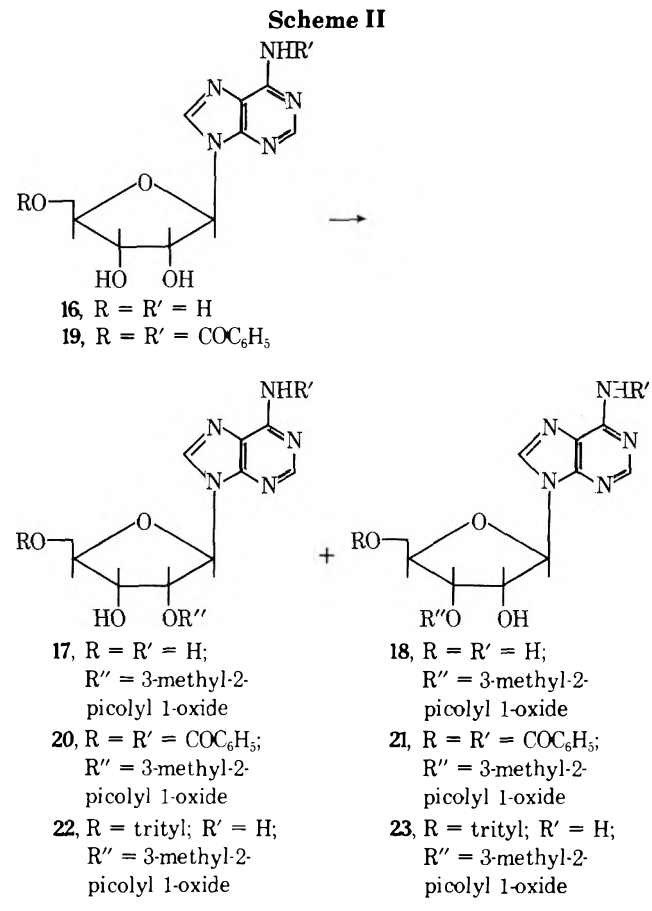
Parallel experiments with adenosine (**16**) and **2** afforded a 1:1 mixture of 2′-*O*- (**17**) and 3′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine (**18**) in 90% yield (Scheme II). Separation of each isomer was achieved by taking advantage of a large difference in their methanol solubility. Thus, on trituration of this isomeric mixture with methanol, a large proportion of 3′-O isomer (**18**) was dissolved in the solvent, 2′-O isomer (**17**) remaining undissolved. Recrystallization of the latter (**17**) from water afforded, after evaporation of the solvent followed by crystallization from ethanol, a pure sample of 3′-O isomer (**18**) in 13% yield. These structural assignments again rest upon both elemental and spectral (uv and NMR) analysis. NMR spectral trends follow the uridine case (Table I).

It is worthy of note that the solubility both in water and in methanol was remarkably different between the 2′-O

Scheme I



Scheme II



and 3′-O isomers in the adenosine series as well as the uridine series. Thus the 3′-O isomers (**5** and **18**) are nearly freely soluble in water whereas the 2′-O isomers (**4** and **17**) have a low solubility in water, which may serve as a suitable solvent for recrystallization of the latter.

In addition to the above studies with the free nucleosides (**3** and **16**), the alkylation of 5′-*O*-benzoyluridine (**6**) and $O^{5'},N^6$-dibenzoyladenosine (**19**) was also undertaken. As far as we know, the nucleoside **6** has never been described in the literature and **6** was therefore prepared in the following way. Benzoylation of 2′,3′-*O*-isopropylideneuridine afforded the corresponding 5′-*O*-benzoyl derivative, which in turn was treated with 80% aqueous acetic acid (100°, 4 hr) to afford the required **6** in 54% overall yield. The structure was confirmed by both combustion values and NMR analysis. The nucleoside **6** was treated with freshly prepared **2** as in the case of uridine. Evaporation of the solvent left crude products (**7** and **8**) contaminated with by-products. Attempted fractional recrystallization failed because of the slight difference in the solubility in water between two isomers. The mixture was therefore separated with the aid of silica gel chromatography. The yields of 2′-*O*- (**7**) and 3′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-benzoyluridine (**8**) were 34.4 and 18.7%, respectively. These structural assignments rest upon the fact that among a pair of isomers, an NMR signal due to the anomeric proton **7** appeared at relatively lower field (see Table I).[7] It is worthy of note, however, that the signal due to the 3″-methyl proton[6] of the 3′-O isomer (**8**) appeared upfield in the NMR spectrum relative to that of the 2′-O isomer (**7**) and this contrasts with other pairs of isomers (see Table I) where the signals due to 3″-methyl protons of the 2′-O isomers appeared relatively upfield.

$O^{5'},N^6$-Dibenzoyladenosine (**19**), which was prepared from 2′,3′-*O*-ethoxymethylene-$O^{5'},N^6$-dibenzoyladenosine by acid hydrolysis was treated with **2** to afford a mixture of 2′-*O*- (**20**) and 3′-*O*-(3-methyl-2-picolyl 1-oxide)-$O^{5'},N^6$-dibenzoyladenosine (**21**). The relative yields of two isomers were determined as roughly 1:1 by relative areas of the 3″-methyl[6] absorption in the NMR spectrum. Since once again the solubility difference in both water and methanol between these isomers was not large enough to permit the fractional recrystallization, the mixture was subjected to chromatographic (silica gel) separation. The compound (**20**) was isolated pure in 25% yield and the structure was determined on the basis of elemental analysis and Reese's rule.[7] However, even by this chromatographic technique we failed to obtain pure **21**.

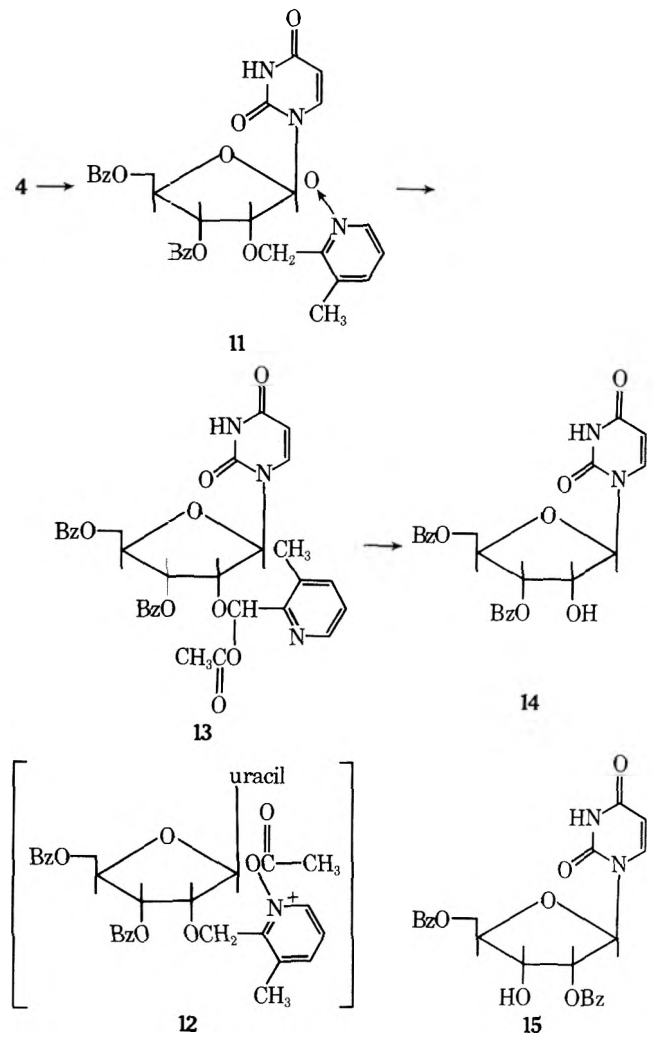
Alkylation of 5′-*O*-trityluridine[8] with **2** in the presence of $SnCl_2$ was found to be accompanied by detritylation to give an isomeric mixture of **4** and **5**.

In the connection, with the catalyst $SnCl_2$ it must be emphasized that the alkylation in the presence of an excess of the catalyst afforded a substantial amount of uv-absorbing by-product(s) of unknown structure[9] and the yield of required products was accordingly reduced to a significant extent.

Our next objective was to examine the stability of the 3-methyl-2-picolyl 1-oxide group toward a variety of reagents encountered in the nucleotide synthesis: tritylation, benzoylation, and phosphorylation [in the presence of 2,4,6-triisopropylbenzenesulfonyl chloride (TPS)],[10] and its removability under required conditions.

Tritylation of 2′-*O*-(3-methyl-2-picolyl 1-oxide)uridine (**4**) by a conventional method afforded the corresponding 5′-*O*-trityl derivative (**9**) in almost quantitative yield.[8b] Benzoylation of **4** with benzoyl chloride (1.86 equiv) afforded 3′,5′-di-*O*-benzoyl-2′-*O*-(3-methyl-2-picolyl 1-oxide)uridine (**11**) in 58% yield (Scheme III). The structural assignment rests upon the combustion values and spectral data.

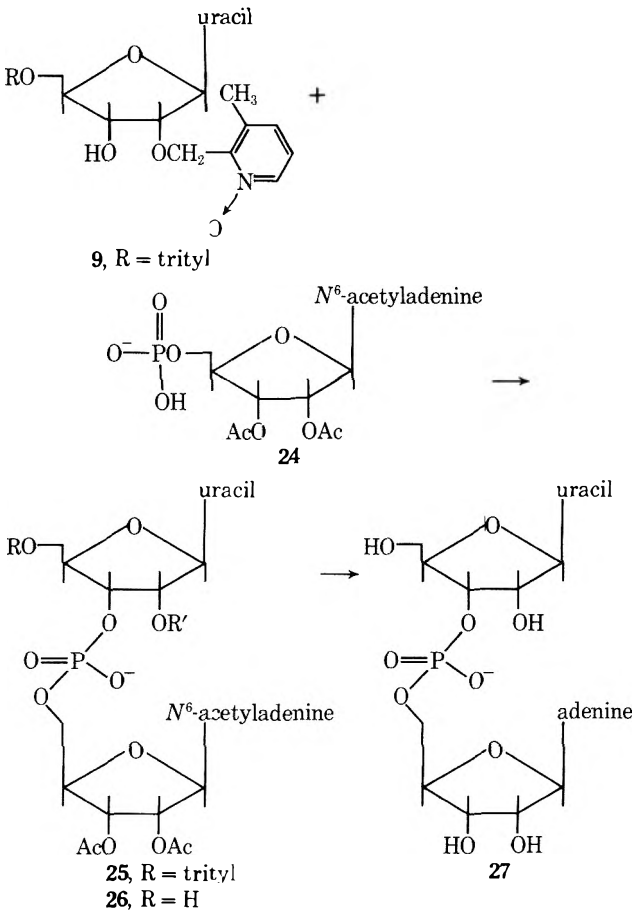
Scheme III



A deblocking experiment was carried out taking **11** as an example in the following way. The nucleoside **11** was treated with acetic anhydride at 43°. The progress of the reaction was monitored by TLC. Shortly (10 min) after the start of the reaction, the formation of an intermediate (presumably *N*-acetoxypyridinium acetate derivative, **12**)[11] was observed on TLC. After 14 hr, the formation of 3′,5′-di-*O*-benzoyl-2′-*O*-(3-methyl-2-pyridylacetoxymethyl)uridine (**13**) was observed. After 6 days both **11** and **12** completely disappeared in the reaction mixture, after which time the reaction mixture was worked up and a product (**13**) was isolated pure by silica gel chromatography. Although we failed to crystallize this nucleoside because of the epimeric mixture, it was found to be homogeneous on the criteria of chromatographic behavior and NMR spectra. Its combustion values were also compatible with the structure assigned. The yield of **13** was quantitative. Acidic hydrolysis (50% aqueous acetic acid, 70°, 3 hr) converted **13** into crystalline 3′,5′-di-*O*-benzoyluridine (**14**) in almost quantitative yield. Spectral (NMR) analysis showed that this was indeed 3′,5′-di-*O*-benzoyluridine and not 2′,5′-*O*-benzoyluridine.[12]

The remainder of this section deals with the synthesis of uridylyl(3′–5′)adenosine (UpA, **27**). Treatment of 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (**9**) with $O^{2'},O^{3'},N^{6'}$-triacetyladenosine 5′-phosphate (**24**) in the presence of TPS (Scheme IV) afforded 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-tritylurid ylyl(3′–5′)-$O^{2'},O^{3'},N^6$-tria-

Scheme IV



cetyladenosine (**25**). Acidic treatment of **25** under mild conditions afforded the corresponding dinucleoside monophosphate derivative (**26**), which might be of use for further chain elongation. For the complete deblocking the nucleoside **26** was first treated with acetic anhydride (at 43° for 6 days) and then with methanolic ammonia (at room temperature) to give **27** in 92% yield. As already mentioned, this sample of **27** was found to be completely hydrolyzable with pancreatic RNase[13] to give uridine 3′-phosphate and adenosine in 1:1 molar ratio.[14]

Thus ease of introduction, stability, and removability under required conditions of the 3-methyl-2-picolyl 1-oxide group was found to be completely compatible with the oligonucleotide synthesis. Our approach by the application of this novel 2′-O-protecting group might have a considerable merit in the oligonucleotide synthesis starting from synthetic modified nucleosides (e.g., 1- or 3-deazaadenosine). The synthesis of oligoribonucleotides containirg the modified nucleosides as well as cytidine and guanosine and the oligonucleotides of higher chain length is now underway in our laboratory.

Experimental Section

General. Melting points were taken on a Yamato MP-1 capillary apparatus and are uncorrected. Ultraviolet absorption (uv) spectra were determined on a Hitachi spectrophotometer, Type 14. Infrared (ir) spectra were determined on a Model DS-701G spectrometer (Nippon Bunko Co.). Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi high-resolution NMR spectrometer, Model R-24, and NMR signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; bs, broad singlet; bd, broad doublet. The chemical shifts were reported in parts per million downfield from Me_4Si (an internal standard). Elemental analyses were performed by a staff of the analytical room, Faculty of Pharmaceutical Sciences, Hokkaido University. Thin layer chromatography (TLC) was run on glass plates coated with silicic acid. Paper electrophoresis was performed on Toyo Roshi filter paper No. 51A at pH 7.5 using 0.05 *M* triethylammonium bicarbonate (TEAB) solution (20 V/cm, 1 hr). DEAE cellulose was a product of Jujo Paper Co. and a gift therefrom. RNase was obtained from Worthington Biochemicals. Digestion with this enzyme was performed as reported.[15] Unless otherwise stated, solvent was removed under reduced (aspirator) pressure with a rotating evaporator.

2′-*O*-(3-Methyl-2-picolyl 1-oxide)uridine (4) and an Isomeric Mixture of 4 and 3′-*O*-(3-Methyl-2-picolyl 1-oxide)uridine (5). To a stirred solution of uridine (**3**, 5.2 g, 21 mmol) and $SnCl_2 \cdot 2H_2O$ (100 mg) in DMF (50 ml) was added in three portions a DMF solution (1 ml) of 1-oxido-3-methyl-2-pyridyldiazomethane (**2**)[5] prepared from 16.49 g (54 mmol) of 3-methyl-2-formylpyridine 1-oxide *p*-tosylhydrazone (**1**). After 2 hr, a further amount of $SnCl_2 \cdot 2H_2O$ (100 mg) was added. The stirring was continued at room temperature overnight. After it was ascertained by TLC that the reaction was almost complete, the solvent was evaporated to leave an oily residue which was triturated with ethanol to precipitate a solid which was collected by filtration and dried, yield 7.0 g (91%). Recrystallization from water afforded **4**, yield 1.9 g (25%). This sample was found to be completely free of the 3′-O isomer (**5**) on the criterion of the NMR spectra: NMR (DMSO-d_6) δ 8.20 (q, J = 7.5 Hz, 1, H-6″[6]), 7.92 (d, J = 10 Hz, 1, H-6), 5.93 (d, J = 7.0 Hz, 1, H-1′), 5.65 (bd, J = 10 Hz, 1, H-5), 4.9 (s, 2, H-7″), 2.37 (s, 3, 3″-CH_3); mp 266–268° dec.

Anal. Calcd for $C_{16}H_{19}N_3O_7 \cdot \frac{1}{2}H_2O$: C, 51.47; H, 5.09; N, 11.26. Found: C, 51.70; H, 5.30; N, 11.32.

3′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (10). To the above isomeric mixture (**4** and **5**, 3.05 g, 8.35 mmol) in pyridine (30 ml) was added with stirring trityl chloride (3 g, 11 mmol). The stirring was continued at room temperature until the starting materials were almost completely consumed (for 2 days). Evaporation of the solvent left a foam which was applied to a column (silica gel, 90 g). The column was washed with $CHCl_3$–EtOH (25:1). The eluate was monitored by TLC. The faster travelling fraction afforded, after removal of the solvent, a mixture of 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (**9**) and the 3′-O isomer (**10**) (0.8 g) and slower travelling fraction (free from **9**) was pooled, and concentrated to dryness. The residue was crystallized from methanol to give **10**: mp 246–248°; yield 2.0 g (39%); NMR ($CDCl_3$) δ 8.86 (d, $J_{5,6}$ = 10 Hz, 1, H-6), 8.25 (bt, 1, H-6″[6]), 5.96 (bs, 1, H-1′), 5.40 (d, $J_{5,6}$ = 10 Hz, H-5), 2.37 (s, 3, 3″-CH_3[6]).

Anal. Calcd for $C_{35}H_{33}N_3O_7$: C, 69.19; H, 5.43; N, 6.91. Found: C, 69.25; H, 5.40; N, 6.83.

3′-*O*-(3-Methyl-2-picolyl 1-oxide)uridine (5). 3′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (**10**, 500 mg) was dissolved in 25 ml of aqueous acetic acid [AcOH–H_2O (20:5)]. The solution was allowed to stand at room temperature for 2 days, during which time triphenylmethyl alcohol (160 mg) precipitated and filtered off. The filtrate was concentrated to dryness. The residue was recrystallized from methanol: mp 216–218°; yield 270 mg (90%); NMR (DMSO-d_6) δ 5.77 (d, 4.0 Hz, 1, H-1′), 2.44 (s, 3, 3″-CH_3[6]).

Anal. Calcd for $C_{16}H_{19}N_3O_7$: C, 52.60; H, 5.20; N, 11.51. Found: C, 52.30; H, 5.15; N, 11.25.

2′-*O*-(3-Methyl-2-picolyl 1-oxide)-3′,5′-di-*O*-benzoyluridine (11). To a stirred suspension of **4** (1.65 g, 4.4 mmol) in pyridine (30 ml) was added in portions benzoyl chloride (1.14 g, 8.1 mmol) at 0°. The stirring was continued at room temperature overnight. Evaporation of the solvent left a solid which was purified by column chromatography [silica gel, solvent system $CHCl_3$–EtOH (25:1)], yield 1.5 g (58%). Recrystallization from methanol afforded an analytical sample: mp 129–131°; NMR ($CDCl_3$) δ 6.61 (d, J = 6 Hz, 1, H-1′), 2.18 (s, 3, 3″-CH_3[6]).

Anal. Calcd for $C_{30}H_{27}N_3O_9 \cdot \frac{1}{2}H_2O$: C, 61.85; H, 8.84; N, 7.21. Found: C, 61.80; H, 4.88; N, 7.13.

3′,5′-Di-*O*-benzoyluridine (14). Conversion of 11 into 14 via 13. A solution of **11** (800 mg, 1.37 mmol) in acetic anhydride (30 ml) was allowed to stand at 43° (bath temperature). The progress of the reaction was followed by TLC [solvent system $CHCl_3$–EtOH (7:1)]. In the very early stage of reaction (10 min) a new spot appeared on TLC which was assumed to correspond to *N*-acetoxypyridinium salt (**12**),[11] but it was not confirmed. After 14 hr another new spot due to **13** began to appear, with concomitant decrease in the area due to **12**. The reaction was considered to be complete when the spot due to **12** was scarcely discernible on TLC. It took 6 days. The mixture was then concentrated to dryness and the residue was applied to a silica gel column. The column was washed with $CHCl_3$–EtOH (33:1). The fraction containing 3′,5′-di-*O*-ben-

zoyl-2′-*O*-(3-methylpyridylacetoxymethyl)uridine (13) was collected. Evaporation of the solvent left a colorless and homogeneous foam, yield 845 mg (97%), which was treated with 80% aqueous acid (100 ml) at 70° for 3 hr. The cooled solution was concentrated to dryness. The residue was crystallized from methanol or aqueous methanol to afford an analytical sample of **14**, mp 187–189°, yield 535 mg (quantitative).

Anal. Calcd for $C_{23}H_{20}N_2O_8$: C, 61.06; H, 4.42; N, 6.19. Found: C, 61.02; H, 4.32; N, 6.25.

2′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-trityluridine (9). To a solution of 2′-*O*-(3-methyl-2-picolyl 1-oxide)uridine (**4**, 3.0 g, 8 mmol) in pyridine (50 ml) was added with stirring trityl chloride (3.4 g, 12 mmol) at 0°. The stirring was continued at 36° for 4 days. After work-up, the product was purified by column chromatography [silica gel, 90 g; solvent system $CHCl_3$–EtOH (25:1)]. Evaporation of the fraction containing **9** left a homogeneous foam, yield 4.5 g (92%).

Anal. Calcd for $C_{35}H_{33}N_3O_7$: C, 69.17; H, 5.47; N, 6.91. Found: C, 69.22; H, 5.56; N, 7.01.

5′-*O*-Benzoyluridine (6). To a cooled solution of 2′,3′-*O*-isopropylideneuridine (5.7 g, 20 mmol) in pyridine (20 ml) was added with stirring a pyridine solution (10 ml) of benzoyl chloride (3.1 g, 22 mmol) over a period of 30 min. The stirring was continued at room temperature overnight. The mixture was then concentrated to dryness and the residue was dissolved in chloroform (100 ml). The solution was successively washed with water and 5% sodium hydrogen carbonate solution, and dried (Na_2SO_4). The salt was filtered off and the filtrate was concentrated to dryness. The residue was dissolved in 80% acetic acid (100 ml) and the solution was heated at 100° for 4 hr. The solvent was removed to give a product which was dried by codistillation with ethanol. The final residue was dissolved in ethanol (50 ml). There was then added dry ether (150 ml) to give crystalline (homogeneous) product (6.0 g). Recrystallization from ethanol or chloroform afforded an analytical sample, mp 169–170°, yield 4.4 g (63%).

Anal. Calcd for $C_{16}H_{16}N_2O_7$: C, 55.17; H, 4.60; N, 8.05. Found: C, 55.21; H, 4.60; N, 7.99.

2′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-benzoyluridine (7) and 3′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-O-benzoyluridine (8). To a stirred suspension of 5′-*O*-benzoyluridine (**6**, 2.0 g, 5.74 mmol) and $SnCl_2{\cdot}2H_2O$ (100 mg) in DMF (20 ml) was added a chloroform solution (1 ml) of **2**,[5] prepared from **1** (4.4 g, 14.5 mmol) and sodium (322 mg, 14 mmol). The stirring was continued at room temperature overnight, during which time a clear solution resulted. After work-up, the crude products were dissolved in methanol (100 ml) and the insoluble material (900 mg)[9] was filtered off. Evaporation of the filtrate left crude products which were dissolved in chloroform and applied to a silica gel column (silica gel, 100 g). The column was washed with $CHCl_3$–EtOH (25:1). The fraction containing 2′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-benzoyluridine (**7**) was collected. Evaporation of the solvent left **7** as a homogeneous foam. From the subsequent fraction an almost pure sample of **7** (820 mg) was obtained, which was rechromatographed over silica gel with the same solvent. Evaporation of the solvent afforded a further crop of **7** as a homogeneous foam, combined yield 1.0 g (34.4%). On the basis of the δ value of the signal due to the anomeric proton (5.90 ppm),[7] compound **7** was assigned as the 2′-O isomer. The third fraction afforded after evaporation of the solvent a mixture of 3′-*O*-(3-methyl-2-picolyl 1-oxide)-5′-*O*-benzoyluridine (**8**) and **7**, yield 200 mg. The fourth fraction afforded on similar treatment a pure sample of **8** (500 mg, 18.7%): NMR ($CDCl_3$) δ 5.67 (d, J = 1 Hz, 1, H-1′), 2.42 (s, 3, 3″-CH_3[6]). On the basis of the δ value, compound **8** was assigned as the 3′-O isomer.

Anal. Calcd for $C_{23}H_{23}N_3O_8$: C, 55.84; H, 4.90; N, 8.95. Found: C, 58.69; H, 4.73; N, 8.88.

2′-*O*- (17) and 3′-*O*-(3-Methyl-2-picolyl 1-oxide)adenosine (18). A mixture of adenosine (**16**, 10 g, 37.8 mmol) and $SnCl_2{\cdot}2H_2O$ (100 mg) in DMF (200 ml) was heated until a clear solution resulted. To the cooled solution was added at room temperature a chloroform solution (1 ml) of **2**, freshly prepared from **1** (19.02 g, 62 mmol, 2 equiv). After 18 hr the solvent was evaporated to leave a product (crude yield of **17** and **18**, 90%) which was triturated with hot ethanol (150 ml). The insoluble material was collected by filtration and washed with methanol to give **17** (6.0 g, 41%). Recrystallization from water afforded an analytical sample of **17** (5.0 g, 34.1%). This compound was tentatively assigned as the 2′-O isomer on the basis of δ values of the anomeric proton (5.76 ppm) and 3″-methyl protons[6] (2.30 ppm).

Anal. Calcd for $C_{17}H_{20}N_6O_5$: C, 52.24; H, 5.24; N, 21.67. Found: C, 52.24; H, 5.24; N, 21.67.

The above filtrate (ethanol solution) deposited a mixture of **17** and **18** (7.0 g) after standing at room temperature for 3 days. The mixture was collected by filtration and triturated with methanol (50 ml) to give a further crop of **17** (500 mg, 3.3%) as the insoluble fraction. Concentration of the mother liquor left oily residue which was triturated with ethanol and the insoluble fraction was collected by filtration and recrystallized from ethanol to afford an analytical sample of **18**, yield 2.0 g(13%). This sample was found to be very hygroscopic. Compound **18** was assigned as the 3′-O isomer on the basis of δ values of the signals due to the anomeric proton (5.59 ppm) as well as 3″-methyl protons[6] (see Table I).

Anal. Calcd for $C_{17}H_{20}N_6O_5$: C, 52.53; H, 5.24; N, 21.67. Found: C, 52.44; H, 5.24 N, 21.78.

$O^{5'}$,N^6-Dibenzoyladenosine (19). To a stirred suspension of adenosine (**16**, 10.0 g, 37.6 mmol) in ethyl orthoformate (40 ml) was added *p*-toluenesulfonic acid (monohydrate, 8.0 g). The stirred suspension was refluxed for 45 min, during which period a clear solution resulted. The cooled solution was neutralized with 80 ml of 0.4 *M* methanolic sodium methoxide. The sodium tosylate which precipitated was removed by filtration. The filtrate was concentrated to dryness, the residue was dissolved in chloroform (200 ml), and the insoluble material was filtered off. The residue, obtained by evaporation of the filtrate, was purified by silica gel chromatography; the yield of 2′,3′-*O*-ethoxymethylideneadenosine was 10.0 g. The adenosine derivative was dissolved in pyridine (100 ml) and treated with benzoyl chloride (20 g) at room temperature overnight. The mixture was concentrated to a half of its volume and then poured into a saturated sodium carbonate solution (150 ml) at around 5°. The product was extracted with three 150-ml portions of chloroform. The organic layer was washed with water and dried over sodium sulfate. The inorganic salt was filtered off and the filtrate was concentrated to dryness. The residue (crude 2′,3′-*O*-ethoxymethylidene-$O^{5'}$,N^6-dibenzoyladenosine) was dissolved in a mixture of acetic acid (80 ml) and water (200 ml). The solution was allowed to stand at room temperature overnight and then concentrated to dryness. The residue was partitioned between chloroform (50 ml) and saturated sodium carbonate solution (20 ml). The organic layer was separated and dried over sodium sulfate. The inorganic salt was filtered off and the filtrate was concentrated to dryness. The residue was applied to a column [silica gel, 200 g; solvent system $CHCl_3$–EtOH (100:3)]. The fraction containing the required product (**19**) was pooled and concentrated to give a colorless and homogeneous foam (8.4 g, 45%). This sample showed the positive test toward the *cis*-glycol–metaperiodate–benzidine test.[16] The structure was also confirmed by spectral (uv and NMR) as well as combustion analyses, uv (EtOH) λ_{max} 230, 279 nm,[17] NMR spectra showing the presence of ten aromatic protons (dibenzoyl).

Anal. Calcd for $C_{24}H_{21}N_5O_6H_2O$: C, 58.41; H, 4.66; N, 14.19. Found: C, 58.08; H, 4.25; N, 14.26.

2′-*O*-(3-Methyl-2-picolyl 1-oxide)-$O^{5'}$,N^6-dibenzoyladenosine (20) and 3′-*O*-(3-methyl-2-picolyl 1-oxide)-$O^{5'}$,N^6-dibenzoyladenosine (21). To a stirred solution of **19** (2.0 g, 4.21 mmol) and $SnCl_2{\cdot}2H_2O$ (20 mg) in DMF (30 ml) was added in portions a chloroform solution (1 ml) of **2** which was freshly prepared from **1** (2.0 g, 7.6 mmol) and sodium (147.4 mg) in ethanol (30 ml). The stirring was continued at room temperature for 8 hr. The mixture was then concentrated to dryness. The residue was applied to a silica gel column (silica gel, 100 g). The column was washed with $CHCl_3$–EtOH (25:1). The fraction containing **20** was collected. Evaporation of the solvent left a homogeneous foam (100 mg): uv (EtOH λ_{max} 230, 279 nm; NMR ($CDCl_3$) δ 8.70 (s, 1, H-8 or H-2), 8.21 (s, 1, H-2 or H-8), 6.16 (d, $J_{1',2'}$ *1, H-1′)*, = 7 Hz, 2.37 (s, 3, 3″-CH_3[6]). On the basis of δ values of the anomeric proton and 3″-methyl,[6] compound **20** was assigned as the 2′-O isomer (see Table I).

Anal. Calcd for $C_{31}H_{28}N_6O_7{\cdot}\frac{1}{2}H_2O$:C, 61.48; H, 4.79; N, 13.88. Found: C, 61.78; H, 4.80; N, 13.63.

The subsequent fraction afforded after evaporation of the solvent a mixture of **20** and **21**, yield 3.02 g, uv (EtOH) λ_{max} 230, 279 nm. Since every signal in the NMR spectra of **20** had been assigned (vide ante), signals of **21** could be assigned from the NMR spectra of the mixture as follows: NMR ($CDCl_3$) δ 6.05 (d, J = 1 Hz, 1, H-1′), 2.30 (s, 3, 3″-CH_3[6]).

3′-*O*-(3-Methyl-2-picolyl 1-oxide)-5′-*O*-trityladenosine (23). To a solution of 3′-*O*-(3-methyl-2-picolyl 1-oxide)adenosine (**18**, 500 mg, 1.286 mmol) in pyridine (30 ml) was added trityl chloride (700 mg, 2.51 mmol). The mixture was stirred for 4 days at room temperature and then concentrated to dryness. The residue was dissolved in a mixture of methanol (20 ml) and saturated sodium carbonate solution (50 ml). The resulting solution was extract-

ed with four 30-ml portions of chloroform. The combined chloroform solution was dried (Na_2SO_4) and filtered. The filtrate was concentrated to dryness. The residue was applied to a column silica gel, 11 g). The column was washed with $CHCl_3$–EtOH (25:1). The eluate was monitored by TLC [solvent system $CHCl_3$–EtOH (7:1)]. The fraction containing **23** was pooled and concentrated to dryness (homogeneous foam): yield 520 mg (76%); NMR ($CDCl_3$) δ 8.27 (s, 1, H-8 or H-2), 8.04 (s, 1, H-2 or H-8), 6.05 (d, J = 4.9 Hz, 1, H-1'), 2.36 (s, 3, 3''-CH_3[6]).

Anal. Calcd for $C_{36}H_{34}N_5O_5 \cdot \frac{1}{2}H_2O$: C, 65.75; H, 5.63; N, 12.78. Found: C, 65.87; H, 5.24; N, 12.64.

Uridylyl(3'-5')adenosine (27). A stock solution[18] of $O^{2'},O^{3'},N^6$-triacetyladenosine 5'-phosphate (8.3 ml) was dissolved in dry pyridine (15 ml). The resulting mixture was concentrated to dryness in vacuo. This process was repeated four times. The final residue and 2'-O-(3-methyl-2-picolyl 1-oxide)-5'-O-trityluridine (**9**, 141.2 mg, 0.23 mmol) were dissolved in pyridine (15 ml). The mixture was then three times codistilled with dry pyridine (3 × 15 ml). The final residue was dissolved in pyridine (30 ml) containing triisopropylbenzenesulfonyl chloride (1.035 g, 0.345 mmol). The solution was kept at room temperature overnight. Water (1 ml) was then added and the solution was concentrated to dryness in vacuo.

Detritylation. The above residue was dissolved in acetic acid (40 ml) and water (20 ml). The mixture was allowed to stand at 45° overnight. After it was ascertained by paper electrophoresis (0.05 M TEAB solution, pH 7.5, 20 V/cm, 1.5 hr) that detritylation was complete, the mixture was concentrated to dryness. The residue was applied to DEAE cellulose column (column size 15 × 3 cm). Elution was performed by a linear gradient of 0.02 M TEAB (1 l.) and H_2O (1 l.), fraction size being 16 ml. Fractions 31–41 (TOD, A_{260nm} 1900 units) were pooled and concentrated to dryness in vacuo.

UpA. The above residue was dissolved in acetic anhydride (50 ml) and the solution was allowed to stand at 43° for 6 days (within 18 hr, a complete solution resulted). The solution was concentrated to dryness in vacuo and the residue was dissolved in methanol (50 ml) saturated with ammonia at 0°. The solution was allowed to stand at room temperature overnight and concentrated to dryness. The residue was applied to a DEAE cellulose column (15 × 3 cm). Elution was performed first with H_2O (1 l.), followed by 0.1 M TEAB solution (700 ml). The fraction containing UpA was pooled (A_{260nm} 1400 units) and concentrated to dryness, yield 92%, based on the assumption that the molecular extinction coefficient of **9** was 15,000. On the Varian LCS 1000 column chromatography this sample behaved similarly to an authentic sample of UpA.[20]

Digestion of the Dinucleoside Monophosphate (UpA) with Pancreatic Ribonuclease. The reaction mixture contained 40 μl of the sample of UpA (A_{260} nm 20 units), 20 μl of RNase (1 mg/1 ml), and 40 μl of Tris-HCl (pH 7.5) in a total volume of 100 μl. This mixture was incubated at 37° for 24 hr. After this period, paper electrophoresis (the conditions were the same as above) showed that UpA was completely hydrolyzed with the enzyme to afford uridine 3'-phosphate and adenosine in a molar ratio of 1:1.

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Registry No.—**1**, 54613-02-9; **2**, 54618-03-0; **3**, 58-96-8; **4**, 54618-04-1; **5**, 54618-05-2; **6**, 54618-06-3; **7**, 54618-07-4; **8**, 54618-08-5; **9**, 54618-09-6; **10**, 54618-10-9; **11**, 54657-21-5; **14**, 54618-11-0; **16**, 58-61-7; **17**, 54657-22-6; **18**, 54618-12-1; **19**, 33485-36-8; **20**, 54618-13-2; **21**, 54618-14-3; **23**, 54618-15-4; **24**, 23197-78-6; **27**, 3256-24-4; trityl chloride, 76-83-5; benzoyl chloride, 98-88-4; 2',3'-O-isopropylideneuridine, 362-43-6.

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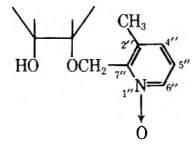

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(19) A column used was packed with PA 38 pellicular anion exchange resin (column size 300 cm × 1 mm); temperature 70°; flow rate 10 ml/hr; elution was performed by a linear gradient from 0.02 M KH_2PO_4 (pH 3.25) to 1.0 M KH_2PO_4 (pH 3.85); initial gradient chamber volume, 40 ml; gradient delay, 10 min. Under these conditions, the retention time of UpA was 56 min (a single peak).

Protecting Groups. V. Preparation of 2-Pyridyl-, 2-Quinolyl-, and 1-Isoquinolyldiazomethane *N*-Oxides and Alkylation of Acidic Hydroxylic Functions[1]

Yoshihisa Mizuno,* Takeshi Endo, and Takac Nakamura

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

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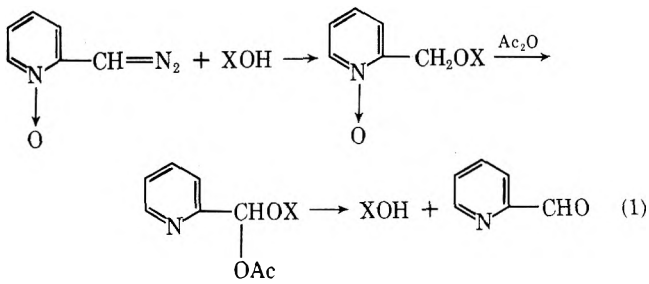
A number of new heterocyclic *N*-oxides bearing a diazomethylene group (**3b–g**) have been prepared by the adoption of the Bamford–Stevens method to search for a diazoalkane suitable for the monoalkylation of the *cis*-glycol system of ribonucleosides. Alkylation of acidic substances (whose pK_a values range from 3.4 to 10.0) with these diazoalkanes was carried out under comparable conditions. 1-Oxido-3-methyl-2-pyridyldiazomethane (**3b**) would be a most promising reagent for the above purpose because of its easy accessibility and comparatively small δ value of a signal due to the diazomethylene proton in the NMR spectrum.

1-Oxido-2-pyridyldiazomethane (**3a**) is capable of alkylating hydroxyl groups of phosphates, carboxylic acids, and phenols and the 2-picolyl 1-oxide group introduced can be readily removed by treatment with acetic anhydride, followed by hydrolysis (eq 1).[2,3]



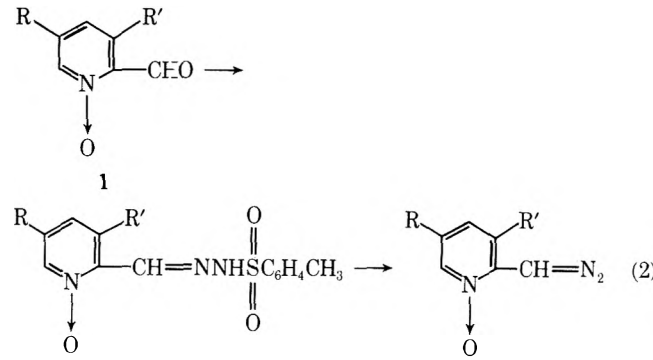
(1)

2′-*O*-(2-Picolyl 1-oxide) ribonucleosides might be potentially useful key intermediates for the derivatization of the ribonucleosides, particularly for the oligoribonuclotide synthesis,[4,5] provided that selective and direct introduction of this easily removable blocking group[6] into the *cis*-glycol system (whose pK_a value is estimated to be 12.35)[7] of the ribonucleosides could be achieved.[8]

Our initial attempts to use **3a**[9] for the monoalkylation of the *cis*-glycol system of the ribonucleosides proved unrewarding, because treatment of the ribonucleosides with **3a** (in the absence of added catalyst) resulted in no reaction and a combination of **3a** with $SnCl_2$[5,10] afforded a complex mixture leading to a poor yield of the desired ribonucleoside derivatives. This prompted us to initiate a study to search for diazoalkane derivatives which might be more suitable for the above purpose.

The present paper deals with the preparation of a series of aromatic *N*-oxides (**3b–g**) bearing a diazomethyl group on the α position with respect to the *N*-oxide group and also with experiments whereby we were able to reach a conclusion that 1-oxido-3-methyl-2-pyridyldiazomethane (**3b**) might be a reagent of choice for the direct monoalkylation of the *cis*-glycol system of the ribonucleosides. The alkylation of unprotected ribonucleosides with **3b** will be dealt with in the subsequent paper.[11]

1-Oxido-3-methyl-2-pyridyl- (**3b**), 1-oxido-5-methyl-2-pyridyl- (**3c**), 1-oxido-3-methoxy-2-pyridyl- (**3d**), and 1-oxido-5-methoxypyridyldiazomethane (**3e**) were prepared from the corresponding *p*-tosylhydrazones (**2b–e**) by the Bamford–Stevens process[12] (eq 2), with slight modifications of an earlier report.[3] Aldehyde 1-oxides (**1b–e**) which were prerequisite to the synthesis of the *p*-tosylhydrazones **2b–e**) were prepared by either of the following methods. Selenium dioxide oxidation in pyridine of the corresponding methylated heterocycle 1-oxides afforded **1b,c** in 50–70% yields. Since the oxidation of 3-methoxy-2-picoline 1-oxide (**4**) under comparable conditions failed to give **1d**, the starting material being recovered almost quantitatively, **4** was treated with acetic anhydride to give 3-methoxy-2-picolyl acetate, which in turn was converted into 3-methoxy-2-picolyl alcohol 1-oxide. Oxidation of the latter with selenium dioxide in refluxing pyridine afforded 3-methoxy-2-formylpyridine 1-oxide (**1d**) in 31% overall yield (based on **4**). 5-Methoxy-2-formylpyridine 1-oxide (**1e**) was prepared analogously from 5-methoxy-2-picoline 1-oxide. *p*-Tosylhydrazones (**2b–e**) were prepared as in the synthesis of **2a**.[3] Yields of the diazoalkanes (**3a–e**) were much improved by the following modifications. The *p*-tosylhydrazones (**2a–e**) were suspended at ambient temperature in absolute ethanol containing sodium ethoxide equivalent to *p*-toluenesulfinic acid formed. After the suspension was stirred for 30 min at the same temperature, the mixture was heated at 50–55° until the solution resulted (usually 20 min). Prolonged heating in the presence of excess sodium ethoxide resulted in considerable decomposition of the diazoalkanes formed. After work-up (see Experimental Section), these diazoalkanes (**3a–e**) could be isolated in 60–80%



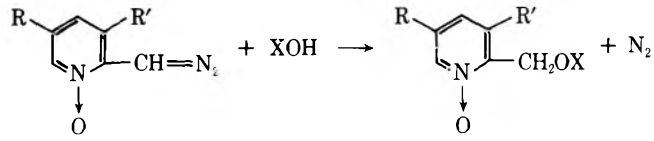
(2)

a, R = R′ = H
b, R = H; R′ = CH_3
c, R = CH_3; R′ = H
d, R = H; R′ = OCH_3
e, R = OCH_3; R′ = H

yield, usually in the semisolid or solid state, and except for **3a** these were found to be quite stable; the diazoalkane **3f** can be stored in a desiccator for at least 1 month without any decomposition.[13]

The structural confirmation of these diazoalkanes (**3b–e**) rests upon the presence of the absorption due to the diazo group (2040–2080 cm^{-1}) and *N*-oxide (1235–1260 cm^{-1}) in ir spectra and the presence of a one-proton signal due to the methine proton of the diazomethyl group in NMR spectra at 5.3–5.9 ppm downfield from tetramethylsilane which disappeared in addition of CH_3COOD. It is to be

Table I
Reactions of 3a–e with Acidic Substances in Chloroform at 20° for 3 Hr



Reagent	XOH	Registry no.	pK_a	Product: Mp,[a] °C	Product: Yield, %	Product: Registry no.
	p-$NO_2C_6H_4COOH$	62-23-7	3.4	155–157	Quant[d]	50908-24-2
3a	C_6H_5COOH	65-85-0	4.2	125–126	Quant[d]	50908-25-3
	p-$NO_2C_6H_4OH$	100-02-7	7.1	221–223	71[d]	50908-27-5
	m-$NO_2C_6H_4OH$	554-84-7	8.4	158–160	40[e]	54618-30-3
3b	C_6H_5OH	108-95-2	10.0	*b*		
	p-$NO_2C_6H_4COOH$		3.4	218–220	40[e]	54618-31-4
	CH_3CH_2COOH	79-09-4	4.8	125–127	Quant[d]	54618-32-5
3c	p-$NO_2C_6H_4OH$		7.1	170–172	40[e]	54618-33-6
	m-$NO_2C_6H_4OH$		8.4	158–160	38[e]	54618-34-7
	C_6H_5OH		10.0	*b*		
	p-$NO_2C_6H_4COOH$		3.4	173–175	40[e]	54618-35-8
3d	p-$NO_2C_6H_4OH$		7.1	187–189	38[e]	54618-36-9
	m-$NO_2C_6H_4OH$		8.4	158–160	25[e]	54618-37-0
	C_6H_5OH		10.0	*c*		
3e	p-$NO_2C_6H_4OH$		7.1	166–168	39[e]	54618-38-1

[a] Crystallized from one of the following solvents: ethanol, DMF, and benzene-*n*-hexane. [b] No reaction. [c] Discernible reaction took place, but product(s) failed to be isolated. [d] Yield based on acidic substrate on reaction with excess diazoalkane; yield based on *p*-tosylhydrazone which was used for the preparation of the diazoalkane.

noted that the NMR spectra could be conveniently used to check the purity of diazoalkanes obtained. Further structural confirmation comes from the characterization of the products (*p*-nitrophenyl 1-oxide 2-picolyl ethers) on treatment of *p*-nitrophenol with these diazoalkanes. Yields of **3b–e** were estimated on the yields of the above ethers formed on reactions of the diazoalkanes with excess *p*-nitrophenol on the assumption that the alkylations were quantitative.

Diazoalkanes of condensed heteroaromatic series, 1-oxido-2-quinolyl- (**3b**) and 2-oxido-1-isoquinolyldiazomethane (**3f**), were prepared and characterized analogously. Yields of these diazoalkanes (**3f–g**) were also satisfactory (80–81%).

The alkylation of a variety of substrates (phenol, *m*-nitrophenol, *p*-nitrophenol, propionic acid, benzoic acid, and *p*-nitrobenzoic acid) with the diazoalkanes (**3a–g**), including phenyldiazomethane (**3h**)[12b,14] as a reference compound, was performed under comparable conditions (in chlororform, 20°, 3 hr). The reaction was monitored with respect with nitrogen evolution. The products and the starting materials, if any, were isolated by column chromatography on silica gel and characterized by spectra and elemental analysis. Results obtained are listed in Tables I and II. One point of special interest is that among these diazoalkanes (**3a–h**) a noticeable difference in reactivities with respect to alkylation was observed. For example, phenyldiazomethane (**3h**) rapidly reacted with phenol (pK_a 10) to give benzyl phenyl ether (mp 40°, the structure was confirmed by its NMR spectrum), whereas no discernible reaction of **3b** with the same phenol was observed over the period of 3 hr. The reaction of **3b** with *m*-nitrophenol (pK_a 8.4) rapidly took place to give (*m*-nitrophenyl) (3-methyl-2-pyridyl 1-oxide) ether, whereas **3a** did not show any detectable reaction with the phenol under comparable conditions of reaction. In trying to understand better the factors on which their reactivities with respect to alkylation depend, we determined the δ values of diazomethylene proton signals of **3a–h.**[15] A noteworthy feature of the NMR spectra in chloroform is the substantial upfield shift (by 0.6 ppm with respect to that of **3b**) of the diazomethylene proton signal of **3h.** The signal due to the proton of the diazomethylene of **3b** showed an upfield shift of 0.6 ppm with respect to that of **3a.** These data suggest that a possible correlation might exist between the δ values and the reactivities of these alkanes with respect to alkylation. It is also worthy of note that among pairs of diazoalkanes (**3b** and **3c, 3d** and **3c, 3f** and **3g**), the "3"-substituted[18] derivative of each pair was found to have a comparatively smaller δ value (see Experimental Section).[19]

In conclusion, with respect to easy accessibility and smaller δ value of the diazomethylene proton signal in the NMR spectrum, 1-oxido-3-methylpyridyldiazomethane (**3b**) appears to the most promising reagent for the direct monoalkylation of the *cis*-glycol system of the ribonucleosides.[11]

Experimental Section[20]

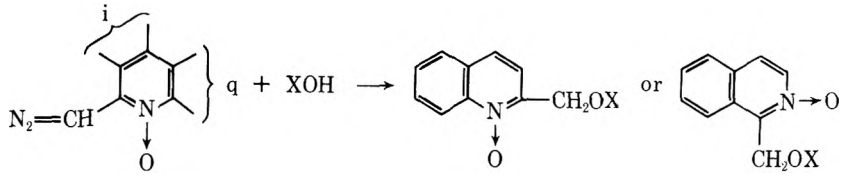
***N*-Oxides of 2-Picoline, 2,3- and 2,5-Lutidine, 3- and 5-Methoxy-2-picoline, Quinaldine, and 1-Methylisoquinoline.** The preparation of 1-methylisoquinoline[21] and 3-methoxy-2-picoline[22] followed literature directions. 5-Methoxy-2-picoline was prepared by methylation of 5-hydroxy-2-picoline with diazomethane by application of Lagotheis's method.[22] *N*-Oxides were prepared according to a general procedure.[23] 2-Picoline[23] [bp 123–124° (15 mm)] and 2,5-lutidine 1-oxide[24] [bp 124° (4 mm), picrate bp 130–131°] were purified by distillation. 2,3-Lutidine 1-oxide[25] and 3- and 5-methoxy-2-picoline 1-oxide were purified by silica gel column chromatography [solvent system $CHCl_3$–EtOH (100:3)]. Recrystallization of 3-methoxy-2-methylpyridine 1-oxide from acetone–ethyl ether afforded the analytical sample, mp 64–66°, 108–110° (picrate).

Anal. Calcd for $C_7H_9NO_2 \cdot \frac{1}{2}H_2O$: C, 57.90; H, 6.66; N, 9.65. Found: C, 58.75; H, 6.71; N, 9.72.

Quinaldine 1-oxide[26] and 1-methylisoquinoline 2-oxide[27] were used for the subsequent step without distillation. However, the structures of these *N*-oxides were confirmed by NMR spectra.

2-Hydroxymethyl-3-methoxypyridine. A solution of 2-methyl-3-methoxypyridine 1-oxide (16.96 g, 0.15 mol) in dioxane

Table II
Reactions of 3f–g with Acidic Substances in Chloroform at 20° for 3 Hr



3f, i = isoquinoline;
3g, q = quinoline

Reagent	XOH	pK_a	Product: Mp, °C	Product: Yield, %	Registry no.
	CH_3COOH[j]	4.8	116–118[a]	85[c]	54657-20-4
	p-$NO_2C_6H_4OH$	7.1	177–179[a]	40[c]	54618-39-2
3f	m-$NO_2C_6H_4OH$	8.4	170–171[b]	40[c]	54618-40-5
	C_6H_4OH	10.0	*d*		
	p-$NO_2C_6H_4COOH$	3.4	209–210[e]	34[c,f]	54618-41-6
	C_6H_5COOH	4.2	110–111[e]	50[c,g]	54618-42-7
3g	p-$NO_2C_6H_4OH$	7.1	219–220[h]	26[c]	54618-43-8
	m-$NO_2C_6H_4OH$	8.4	179–181[i]	25[c]	54618-44-9
	C_6H_4OH	10.0	No reaction		

[a] Recrystallized from benzene–*n*-hexane. [b] From acetone. [c] Yield based on *p*-tosylhydrazone which was used for the preparation of diazoalkane. [d] Discernible reaction took place, but the product(s) failed to be characterized. [e] Recrystallized from EtOH. [f] Nitrobenzoic acid was recovered in 59% yield. [g] Benzoic acid was recovered in 33% yield. [h] From AcOH–MeOH. [i] From acetone. [j] Registry no., 64-19-7.

(50 ml) was treated with acetic anhydride (100 ml) at 100° for 1 hr. A solution of the residue obtained by evaporation of the solvent in concentrated hydrochloric acid (60 ml) and water (90 ml) was refluxed for 1 hr. The mixture was concentrated to dryness and the residue was neutralized (Na_2CO_3), dissolved in chloroform, and purified on a silica gel column [silica gel, 350 g; solvent system $CHCl_3$–EtOH (25:1)]. Crystallization from ethyl ether afforded a pure sample, mp 72–75°, yield 15.3 g (90%). The structure was confirmed by NMR spectrum.

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.60; H, 6.61; N, 10.22.

2-Hydroxymethyl-3-methoxypridine 1-Oxide. Oxidation of 2-hydroxymethyl-3-methoxypyridine (14.4 g, 0.104 mol) with a mixture of acetic acid (35 ml) and hydrogen peroxide (35%, 15 ml) at 65–70° for 18 hr and work-up afforded a product which after recrystallization from methanol–ether yielded crystals, mp 142–145°, yield 14.37 g (89.5%).

Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.02; H, 5.78; N, 9.19.

2-Formyl-3-methoxypyridine 1-Oxide (1d). A solution of 2-hydroxymethyl-3-methoxypyridine 1-oxide (1 g) in pyridine (20 ml) was refluxed for 5 hr with selenium dioxide (0.358 g). The solution was filtered and the filtrate was codistilled with water (2 × 20 ml). The residue was triturated with methanol and filtered. Removal of the solvent left crude product(s). NMR spectral examination showed that the product contained the required 2-formyl derivative (**1d**) and the corresponding methanol hemiacetal. This crude product was used for the synthesis of *p*-tosylhydrazone **2d.**

2-Formyl-5-methoxypyridine 1-Oxide (1e). A solution of 5-methoxy-2-picoline 1-oxide (4.98 g, 35.8 mmol) in acetic anhydride (50 ml) was refluxed for 3 hr. The cooled solution was concentrated to dryness in vacuo. For hydrolysis the residue was dissolved in aqueous ethanol [EtOH–H_2O (2:1), 30 ml] containing concentrated hydrochloric acid (20 ml). The solution was refluxed for 3 hr. The cooled solution was concentrated to dryness. The residue was dissolved in water (30 ml). The neutralized (with sodium carbonate) solution was treated with four 20-ml portions of chloroform. Combined chloroform extracts were evaporated to leave a gummy substance which was applied to a silica gel column [silica gel, 100 g; solvent system $CHCl_3$–EtOH (25:1)]. The fraction containing 5-methoxy-2-picolyl alcohol was concentrated to dryness, yield 3.94 g (79.1%). The alcohol (3.93 g, 28.3 mmol) was converted into the corresponding 1-oxide by a general procedure[23] by the use of 40 ml of acetic acid and 9 ml of 35% hydrogen peroxide (at 67° for 2 days). The purity was checked by TLC [solvent system $CHCl_3$–EtOH (7:1)] and NMR spectrum. The title compound (**1e**) was prepared by selenium dioxide oxidation of 5-methoxy-2-picolyl alcohol 1-oxide; a solution of the 1-oxide (476 mg, 3.0 mmol) and selenium dioxide (171 mg, 1.5 mmol) in pyridine (20 ml) was refluxed for 4 hr. Evaporation of the solvent left a product which was purified by preparative silica gel TLC [solvent system $CHCl_3$–EtOH (7:1)]: ir (KBr) 1680 cm^{-1} (C=O); NMR spectra were consistent with the structure assigned; yield 122 mg (27%), the starting material being recovered in 44% yield. The structure was further confirmed by conversion into the *p*-tosylhydrazone.

Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.71; N, 13.08; S, 9.98. Found: C, 52.22; H, 4.59; N, 13.07; S, 9.78.

***p*-Tosylhydrazones (2a–g) of 2-Formylpyridine 1-Oxides, 2-Formylquinoline 1-Oxide, and 1-Formylisoquinoline 1-Oxide.** Prerequisite formyl derivatives except **1d** and **1e** were obtained by selenium dioxide oxidation of the corresponding well-dried active methyl derivatives by slight modifications of a reported procedure.[28] The *N*-oxide (1 mol) and selenium dioxide (1.1 mol) were dissolved in dry pyridine (ca. 800 ml). The solution was refluxed with vigorous stirring for 5–9 hr. After it was ascertained that the oxidation was almost complete by TLC [silica gel, $CHCl_3$–EtOH (7:1)], the solution was filtered. Water (ca. 300 ml) was then added to the filtrate. The solution was again filtered. The filtrate was concentrated to dryness. Crude yields were 50–70%. After the absence of a signal (s, 3, 2.51–2.81 ppm) due to an active methyl was checked by NMR, the above residue was employed for the subsequent reaction.

The title compounds (**2a–g**) were prepared by adding a methanol solution (1 l.) of *p*-tosylhydrazine (2 equiv) to a methanol solution (200 ml) of the residue (0.3 mmol). The mixture was concentrated to dryness. Crystallization from DMF–H_2O or DMF–MeOH, or precipitation of an acetic acid solution (50–60°) of the residue by addition of water, afforded an analytical sample; yields, melting points, and combustion values are listed in Table III.

General Procedure for Preparation of Diazoalkanes (3a–g). To an ethanol solution (55 ml) containing 10 mmol of sodium ethoxide was added with stirring the *p*-tosylhydrazone (**2a–g,** 10 mmol). Stirring was continued at room temperature for 30 min. The solution was then heated at 50–55° until the clear solution resulted. The solution was allowed to return to ambient temperature, during which period insoluble material precipitated and was filtered off. The filtrate was carefully concentrated to dryness in vacuo: ir (KBr) of the residue 2040–2080 ($^+N{=}N$), 1235–1260 cm^{-1} (*N*-oxide). The residue was dissolved in 50 ml of chloroform. Insoluble material was filtered off and the filtrate was usually employed for alkylation. When it was necessary to know the concentration, the solution was subjected to the benzoic acid assay.[3] For the determination of NMR spectra the residue was used which had been obtained by evaporation of the chloroform. Values of the signal due to the diazomethylene proton are given in Table IV.

Under the above reaction conditions, especially in cases where

Table III
Melting Points, Yields, and Combustion Values of *p*-Tosylhydrazones

Compd	Mp,[a] °C	Yield, %[b]	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % S	Found, % C	Found, % H	Found, % N	Found, % S
2a	135–137	50	53.61	4.46	14.43	11.00	53.58	4.45	14.40	10.99
2b	138–139	60	55.08	4.92	13.77	10.49	54.94	4.88	13.67	10.51
2c	144–145	46	55.08	4.92	13.77	10.49	54.88	4.91	13.77	10.52
2d	120–122	67.6	52.33	4.70	13.07	9.96	52.31	4.59	12.98	9.81
2e	174–175	61	52.33	4.70	13.07	9.96	52.34	4.58	12.89	9.82
2f	138–139	44	59.82	4.39	12.31	9.38	59.78	4.43	12.12	9.41
2g	140–141	65	59.82	4.39	12.31	9.38	60.09	4.38	12.21	9.24

[a] These compounds (**2a–g**) were recrystallized from DMF–MeOH and melted with decomposition. [b] Percentages refer to overall yields based on *N*-oxides of 2-methyl-, 2,3-dimethyl-, and 2,5-dimethylpyridine, 3-methoxy-2-picoline, 5-methoxy-2-picoline, 1-methylisoquinoline, and quinaldine.

Table IV
Values of Methine Signals in NMR of Diazoalkanes in Chloroform[a]

Diazoalkanes	Pyridine series 3h[b]	3b	3d	3c	3e	3a	Bicyclic series 3f	3g
	4.90	5.30	5.65	5.80	5.80	5.90	5.70	5.89

[a] In parts per million (δ) [b] Phenyldiazomethane reacted with phenol or *m*-cresol to give the corresponding ethers.

Table V
Combustion Values of Alkylation Products[a]

Product		Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
p-$NO_2C_6H_4COOR$	($C_{13}H_{10}N_2O_5$)	56.93	3.65	10.21	56.81	3.49	10.22
C_6H_4COOR	($C_{13}H_{11}NO_3$)	68.11	4.84	6.11	68.12	4.81	6.11
p-$NO_2C_6H_4OR$	($C_{12}H_{10}N_2O_4$)	58.53	4.06	11.38	58.49	4.11	11.29
m-$NO_2C_6H_4OR$*	($C_{13}H_{12}N_2O_4$)	60.00	4.65	10.76	60.22	4.71	10.69
p-$NO_2C_6H_4OR$**	($C_{13}H_{12}N_2O_4$)	60.00	4.65	10.76	59.98	4.59	10.57
CH_3CH_2COOR**	($C_{10}H_{13}NO_3$)	69.11	5.38	5.75	69.00	5.35	5.59
m-$NO_2C_6H_4OR$**	($C_{13}H_{12}N_2O_4$)	60.00	4.65	10.76	60.13	4.61	10.74
p-$NO_2C_6H_4OR3$*	($C_{13}H_{12}N_2O_5$)	56.51	4.38	10.13	56.40	4.32	10.02
m-$NO_2C_6H_4OR3$*	($C_{13}H_{12}N_2O_5$)	56.51	4.38	10.13	56.48	4.29	9.99
p-$NO_2C_6H_4COOR3$*	($C_{14}H_{12}N_2O_6$)	55.26	3.98	9.20	55.21	4.01	9.01
p-$NO_2C_6H_4OR4$*	($C_{13}H_{12}N_2O_5$)	56.51	4.38	10.13	56.50	4.32	10.08
p-$NO_2C_6H_4OR5$*	($C_{16}H_{12}N_2O_4$)	64.93	4.05	9.45	64.88	4.00	9.28
p-$NO_2C_6H_4COOR6$*	($C_{17}H_{12}N_2O_5$)	62.96	3.70	8.64	63.11	3.78	8.88
C_6H_5COOR6*	($C_{17}H_{12}NO_3$)	73.12	4.66	5.01	73.08	4.62	4.97
p-$NO_2C_6H_4OR6$*	($C_{16}H_{12}N_2O_4$)	64.86	4.05	9.45	64.71	4.07	9.46
m-$NO_2C_6H_4OR6$*	($C_{16}H_{12}N_2O_4$)	64.86	4.05	9.45	64.57	4.00	9.27

[a] Abbreviations: R, R*, R**, R3*, R4*, R5*, and R6* stand for 2-picolyl, 3-methyl-2-picolyl, 5-methyl-2-picolyl, 3-methoxy-2-picolyl, 5-methoxy-2-picolyl 1-oxide, 1-isoquinolylmethyl 2-oxide, and 2-quinolyl 1-oxide group, respectively.

the period of heating was limited to 20 min, the amount of by-products (1-oxido-2-picolyl ethyl ethers) was found to be negligibly small and the purity of the diazoalkane was high (on the criteria of sharpness of the NMR signals).

Structure Confirmation of the Diazoalkanes (3b–g) and General Procedure for Alkylation of Acidic Substrates with Diazoalkanes (3a–g). The alkylation of *m*-nitrophenol with **3b** and that of *p*-nitrophenol with **3c** are taken as examples for the general procedure for the alkylation of acidic substances with the diazoalkanes (**3a–g**).

Alkylation of *m*-Nitrophenol with 1-Oxido-3-methyl-2-pyridyldiazomethane (3b). A chloroform solution (40 ml) of **3b** was prepared as above, from sodium (158 mg, 6.88 mmol), *p*-tosylhydrazone (**2b**, 2.1 g, 6.88 mmol), and ethanol (40 ml). There was then added with stirring *m*-nitrophenol (5.0 g, 36 mmol). Stirring was continued at room temperature for 20 hr. The solution was concentrated to dryness. The residue was purified by silica gel column chromatography [solvent system $CHCl_3$–EtOH (20:1)]. The fraction containing the required product was collected. Evaporation of the solvent left the product, which was recrystallized from DMF–MeOH, mp 158–160°, yield 700 mg (40%, based on **2b**) The combustion values are given in Table V.

Alkylation of *p*-Nitrophenol with 1-Oxido-5-methyl-2-pyridyldiazomethane (3c). A chloroform solution (20 ml) of **3c** was prepared according to the above general procedure, from **2c** (1.525 g, 5 mmol), sodium (115 mg, 5 mmol), and ethanol (40 ml). There was then added with stirring *p*-nitrophenol (2.0 g, 14 mmol) to the chloroform solution. Stirring was continued at room temperature for 20 hr. The solution was concentrated to dryness. The residue was crystallized from DMF–MeOH, mp 170–172°, yield 520 mg (40%, based on **2c**). The combustion values are given in Table V.

The preparation and purification, including characterization, of the products listed in Table V were carried out analogously. When necessary, however, preparative TLC was used for purification of the product.

For each diazoalkane (except **3e**) the upper limit of pK_a values of acids which reacted with the diazoalkane was determined by the use of phenol (pK_a = 10.0), *m*- (8.4), *p*-nitrophenol (7.1) pro-

pionic acid (4.85), benzoic acid (4.2), and *p*-nitrobenzoic acid (3.4). For each diazoalkane the approximate upper limit was >10 (**3h**), 10 (**3b** and **3d**), 8 (**3c**), 7 (**3a**), 10 (**3f**), and 8 (**3g**).

Registry No.—**1a**, 7216-40-2; **1b**, 54618-16-5; **1c**, 54618-17-6; **1d**, 54618-18-7; **1e**, 54618-19-8; **2a**, 50908-22-0; **2b**, 54618-02-9; **2c**, 54618-20-1; **2d**, 54618-21-2; **2e**, 54618-22-3; **2f**, 54618-23-4; **2g**, 54618-24-5; **3a**, 50908-23-1; **3b**, 54618-03-0; **3c**, 54618-25-6; **3d**, 54618-26-7; **3e**, 54618-27-8; **3f**, 54618-28-9; **3g**, 54618-29-0; **4**, 35392-65-5; 2-hydroxymethyl-3-methoxypyridine, 51984-46-4; 2-methyl-3-methoxypyridine 1-oxide, 35392-65-5; 2-formylquinoline 1-oxide, 54618-45-0; 1-formylisoquinoline 1-oxide, 54618-46-1.

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(19) This difference in the δ values among a pair of isomers might be not only due to the electronic effect, but also due to the steric effect. Precisely, however, what is involved, induction, hyperconjugation, and steric effects or any combination of the factors, lies beyond the scope of this paper.
(20) Melting and boiling points were uncorrected. Uv absorption spectra were determined on a Hitachi spectrophotometer, Type T4. Ir spectra were determined on a Model DS-701G spectrometer (Nippon Bunko Co.). NMR spectra were determined with a Hitachi high-resolution NMR spectrometer, Model R24. The chemical shifts were reported in parts per million downfield from tetramethylsilane. TLC was run on glass plates coated with silicic acid. Gas chromatography was carried out on a Model G 80 FP gas chromatograph (Yanagimoto Co.).
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Cis Azoxy Alkanes. VI. Cis Azo *N,N'*-Dioxide Synthesis and the Importance of Entropy in the Nitrosoalkane–Azo Dioxide Equilibrium[1a]

James P. Snyder,*[1b] Michael L. Heyman, and Elena N. Suciu

Department of Chemistry, Belfer Graduate School of Science, Yeshiva University, New York, New York, and the Department of General and Organic Chemistry, H. C. Ørsted Institute, University of Copenhagen, 2100 Copenhagen, Denmark

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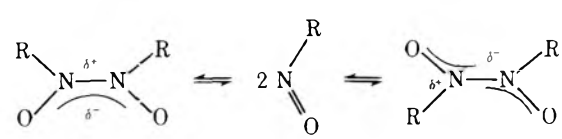
A series of nine cis polycyclic azo *N,N'*-dioxides (nitroso dimers) have been prepared by direct oxidation of the corresponding azo and azoxy alkanes with H_2O_2 and *m*-chloroperbenzoic acid. The synthesis of two bridgehead substituted α-chloro derivatives has also been accomplished by chlorination of polycyclic dioximes. In all cases the corresponding mono-*N*-oxides (azoxy alkanes) were generated independently either by azo oxidation and/or by hexachlorodisilane reduction of the *N,N'*-dioxides. A preliminary study of the thermal behavior of the latter in solution and in the solid state shows that in stark contrast to acyclic nitroso dimers the cyclic derivatives do not deliver the nitroso monomer in observable concentrations on warming to 250°. Estimated ΔH's and ΔS's for the azo dioxide ring opening suggest the source of the experimental result to lie predominantly in the small ΔS term. For highly strained cycles it is concluded that the lack of dedimerization can be attributed either to a kinetic or to a thermodynamic origin. Specifically either the transition state for fragmentation is nonlinear and therefore significantly congested or ground-state azo dioxide strain energies are markedly less than those for the corresponding unsaturated hydrocarbons.

C-Nitroso compounds and their *N,N'*-dioxide dimers have been of interest since the last century.[2a,b] The monomer–dimer equilibrium[2c] operates for a wide range of substituent types and has stimulated the collection of both thermodynamic[3] and kinetic data.[4]



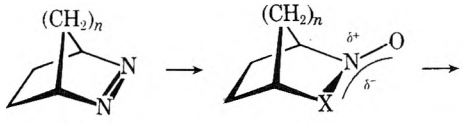
Although a detailed mechanistic understanding is still lacking, recent molecular orbital calculations illuminate certain stereoelectronic facets of the reaction and suggest that dimer formation proceeds by a nonlinear pathway.[5]

Table I
Physical Data for the Polycyclic Cis Azo Dioxides

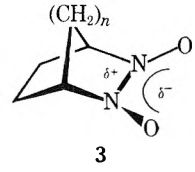
Compd	n	Mp, °C (crystn solvent)	Yield, %	Ir,[a] cm^{-1}	Uv,[b] nm (ε)	^{1}H NMR, τ ($CDCl_3$, TMS)	Formula	Calcd/found, % C	H	N
3	1	142–144 dec (EtOH)	16	1490, 1432, 1290, 1270	265 (8800)	5.22 (2 H, s, $W_{1/2}$ = 4 Hz) 7.3–8.3 (6 H, m)	$C_5H_8N_2O_2$	46.9 47.0	6.3 6.4	21.9 21.9
	2	221–222 dec (EtOH)	41	1475, 1425, 1328, 1309	265 (9000)	5.25 (2 H, s, $W_{1/2}$ = 6 Hz) 7.9 (8 H, broad s)	$C_6H_{10}N_2O_2$	50.7 50.8	7.1 7.0	19.7 19.8
	3	223–224 dec (EtOH)	72	1483, 1412, 1323, 1293	268 (10,500)	5.45 (2 H, s, $W_{1/2}$ = 8 Hz) 7.3–8.5 (10 H, m)	$C_7H_{12}N_2O_2$	53.8 54.0	7.7 7.8	17.9 18.0
	4	216–217 dec (EtOH)	86	1465, 1399, 1331, 1291	270 (13,700)	5.40 (2 H, s, $W_{1/2}$ = 12 Hz) 7.3–8.7 (12 H, m)	$C_8H_{14}N_2O_2$	56.5 56.8	8.3 8.3	16.5 16.7
4b		182–183 dec (EtOH)	14	1496, 1428, 1290, 1258	271 (6900)	5.45 (2 H, s, $W_{1/2}$ = 5 Hz) 7.13 (1 H, s), 7.75 (3 H, s), 8.08 (2 H, s)	$C_7H_8N_2O_2$	55.3 55.3	5.3 5.4	18.4 18.5
5b		238–240 dec (MeOH)	56	1425, 1290, 1270	272 (9300)		$C_8H_8N_2O_2$	58.5 58.5	4.9 5.0	17.1 17.1
6b		182–185 dec (EtOH)	29	1480, 1403, 1340, 1300	267 (7500)	5.09 (2 H, 2, $W_{1/2}$ = 8 Hz) 7.7–8.2 (6 H, m) 8.5–9.0 (2 H, m)	$C_7H_{10}N_2O_2$	54.5 54.6	6.5 6.6	18.2 18.2
9		184–186 dec (EtOH)	91	1460, 1408, 1335, 1275	274 (9000)	7.80 (4 H, s) 8.41 (12 H, s)	$C_8H_{16}N_2O_2$	56.0 55.8	9.6 9.4	16.0 16.3
11[f]		165 dec		1418, 1370, 1320	275[c] (7400)	7.41[d] (br s)				
15	1	238–239 dec (acetone)	23	1421, 1369, 1295	273 (7400)	8.67[e](m), 7.49 (m), 6.73 (m)	$C_{11}H_{14}N_2O_2Cl_2$	47.4 48.0	5.1 5.2	10.1 10.2
16	1	241–242 dec (acetone)	42	1410, 1375, 1270, 1241	276 (5300)	6.6–7.3 (7 H, m) 7.7–9.2 (3 H, m)	$C_{11}H_{10}N_2O_2Cl_2$	48.4 48.6	3.7 3.7	10.3 10.2

[a] KBr. [b] 96% EtOH. [c] CH_2Cl_2. [d] $CDCl_3$, DMSO-d_6. [e] DMSO-d_6. [f] Reference 18.

For the purpose of investigating the dimerization trajectory, the cis dioxide series **3** seemed ideal, since strain energies and thus ring-opening tendencies can be expected to vary markedly as a function of bridge size [$-(CH_2)_n$].



1 **2**



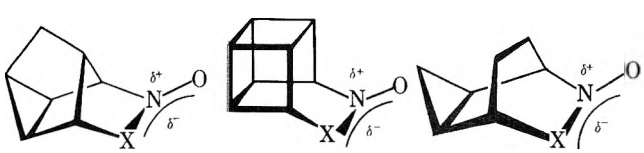
3

The present report describes the preparation of series **2** (n = 1–4) and **3** (n = 1–4) and several closely related compounds by direct oxidation of azo precursors. A second azo dioxide series has been investigated by employing the nitroso dimerization route. In addition a preliminary evaluation of the thermal behavior of the dioxides has been undertaken.

Cis Azoxy Alkanes. The production of substances **2** (n = 1–4), **4a**, and **5a** by oxidation of the corresponding azo alkanes[6] with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 or $CHCl_3$ is unexceptional and proceeds in 70–96% isolated yields. For the cyclopropyl derivative **6a** it is necessary to work at −10°, since the azo parent, generated in situ, has a half-life of 13 min at 12°.[7]

Bicycle **2** (n = 1) has been prepared in an identical fashion,[8] while **2** (n = 1–4), **4a**, and **6a** as well as a variety of unsaturated cis azoxy alkanes may by synthesized by a single hydrolysis–oxidation procedure applied to triazoline–dione adduct precursors.[9]

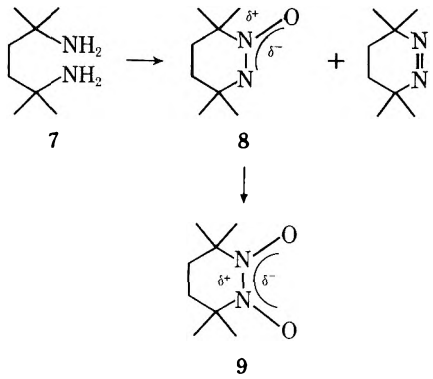
Oxidation. Although azo alkanes are rapidly converted to the corresponding azo *N*-oxides by MCPBA (0–10°, CH_2Cl_2, 1–3 hr), the latter when exposed to the same reagent for longer periods (25°, $CHCl_3$, 2 weeks) allows isolation of low to moderate yields of dioxides **6a** (see Experimental Section) and **7**.[10b] The transformation of pyridazines to pyridazine 1,2-dioxides by the action of 50% hydrogen peroxide in acetic acid,[11] albeit in poor yields, suggested that the generation of azo dioxides could be hastened by utilization of a similar procedure. Accordingly compounds **3** (n = 1–4), **4b**, and **5b** are conveniently prepared by peroxide oxidation of azo alkane precursors[12] (Table I). Substance **6b** is similarly derived from the azoxy precursor **6a**. In the case of dioxides **3** (n = 1, 2), **4b**, and **6b** the low yields simply reflect incomplete conversion under the conditions used. The corresponding monoxides **2** (n = 1, 2) and **4a** are obtained in 70, 17, and 70% yields, respectively, from the same reaction. Likewise for the quadricycle **6b**, 59% of the starting azoxy is recovered unchanged. The oxide mixtures are easily separated (see Experimental Section).



4a, X = N **5a**, X = N_+ **6a**, X = N
b, X = N^+-O^- **b**, X = N^+-O^- **b**, X = N^+-O^-

An unusual transformation occurred in an effort to prepare dioxide **9** by Na_2WO_4-catalyzed peroxide oxidation of 2,5-diamino-2,5-dimethylhexane (**7**). This reagent mixture has been utilized for the conversion of *tert*-butylamine to the nitroso derivative in 24% yield.[3b] Diamine **7** delivers only the monocyclic tetramethyl azoxy **8** (64%) and the corresponding azo alkane (21%). It appears that ring closure occurs after oxidation of only one of the amino groups ei-

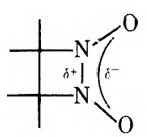
ther to the nitroso or the nitro function. Subsequent oxidation of monoxide 8 with MCPBA produces the desired azo dioxide **9**.



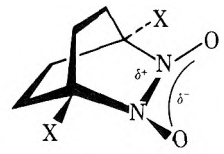
7 8 9

The structures of the dioxides follow from their microanalyses, physical properties, and reaction with hexachlorodisilane. Each exhibits bands in the infrared between 1290 and 1500 cm^{-1} characteristic of aliphatic cis nitroso dimers.[2a,15,16] In the ultraviolet, series **3** shows the expected $\pi-\pi^*$ absorption between 265 and 271 nm (96% EtOH) with a slightly increasing λ_{max} as n increases from 1 to 4. The proton NMR spectra are interpreted in a straightforward manner. Diagnostic are the broad α-nitrogen bridgehead resonances falling in the range τ 5.1–5.45. Not surprisingly, the dioxide values appear at slightly lower field than those of the corresponding monoxides (τ 5.3–5.45).[9a,b] The natural abundance ^{13}C spectrum of **3** [n = 2, δ (CH_2Cl_2, Me_4Si) 25.8 and 70.3 ppm] confirms that oxidation of **2** [n = 2, δ ($CHCl_3$, Me_4Si)[9a] 23.9, 25.6, 57.7, and 71.7 ppm] introduces a molecular symmetry plane. The mass spectra of azo dioxides **3** (n = 1, 2) have already been discussed.[17] The spectroscopic data are assembled in Table I. Finally, treatment of **3** (n = 2) with the effective deoxygenating agent hexachlorodisilane[9a] leads cleanly to azo compound **1** (n = 2) at room temperature.

In addition to compound **10**[10] and the pyridazine 1,2-dioxides,[11] a number of cis 1,2-*N,N'*-dioxides have been previously described. In the acyclic series both thermally stable aromatic[1] and thermally unstable aliphatic[15,16] examples have been generated from nitroso precursors. The cyclic aliphatic dioxide **11** is prepared similarly.[18] Finally,



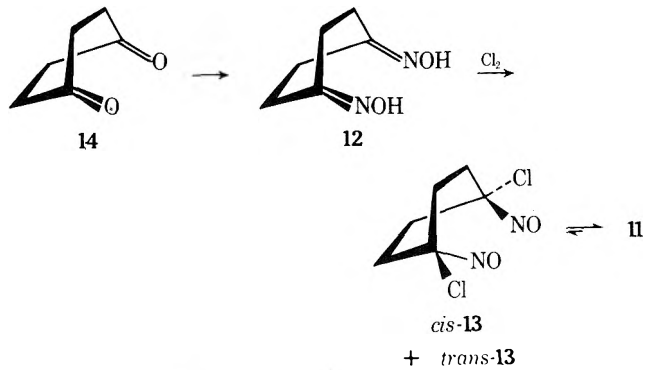
10



11 (X = Cl, Br)

several unsaturated cases arise by cyclization, possibly by means of the intermediacy of the *N*-nitrosonitrone moiety.[19]

Dioxime Chlorination. The bridgehead halogen substituted bicycle **11** is prepared via the bis(nitrosocyclohexane) c-**13** by chlorination of the corresponding dioxime.[18]



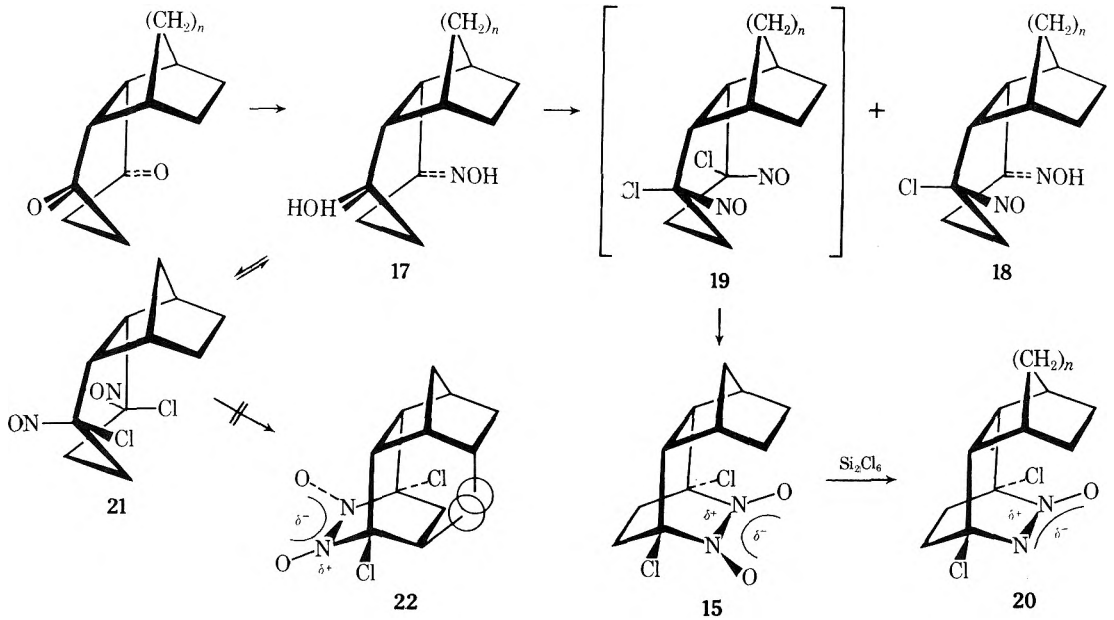
14 12 11

cis-**13** + *trans*-**13**

In order to comparatively evaluate the **11**/**13** equilibrium, we have attempted to exploit the dioxime halogenation route for the preparation of similar systems. Whereas the reaction of dioxime **12** proceeds cleanly in concentrated HCl to give an easily separated mixture of the cis and trans dichlorodinitroso compounds c-**13**/**11** and *t*-**13**, respectively,[18] it is not generally applicable to other cyclic dioximes. Dichloro *N,N'*-dioxides **15** (n = 1) and **16** (n = 1) are, however, accessible in 23 and 42% yields from the latter precursors.

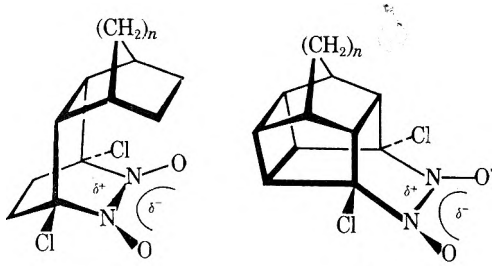
For azodioxy **15**, the transformations are outlined in Scheme I. Dioxime **17** suspended in ethyl acetate leads to two substances when treated with chlorine gas. The first is a thermally labile blue solid. All attempts at further purification led only to the recovery of tarry material. The substance exhibits several characteristic bands in the infrared: λ_{max} (KBr) 3160 (broad, OH, intramolecular H-bonded),

Scheme I[a]



17 19 18 21 22 15 20

[a] n = 1.



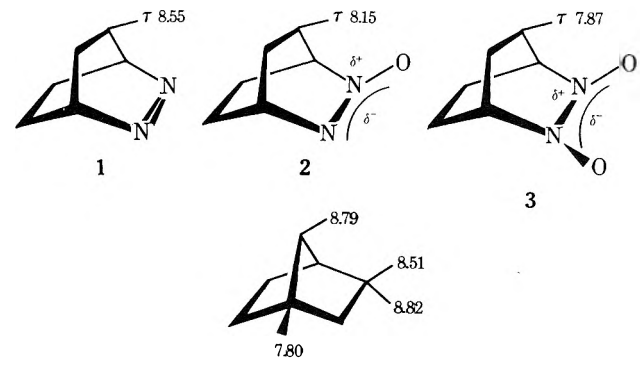
1545 (N=O), 935 cm^{-1} (N–O, oxime). Elemental analysis is in accord with the oxime chloro nitroso structure **18**. The observed lability of the latter was encountered in several other instances to be mentioned below.

A second high-melting material (238° dec) is assigned the azo dioxide structure **15** and is presumed to arise via the intermediacy of dinitroso **19**. Its physical properties conform to those of the cis dioxides described in the previous section (cf. Table I). In addition *N*-oxide **20** is derived by deoxygenation with hexachlorodisilane. Dioxide **11** (X = Cl) is similarly reduced with this reagent to the corresponding monoxide.

The stereochemistry of dioxide **15** has not been unambiguously established. However, molecular models suggest that approach by chlorine on dioxime **17** is least hindered outside the molecular cusp. The resulting bis nitroso species **19** would consequently lead to compound **15**. Conversely, the formation of epimer **21** can in principle deliver azo dioxide **22**, a system which can be anticipated to experience serious nonbonded hydrogen interaction. A van der Waals radius of 1.5 Å implies that a nonrepulsive hydrogen–hydrogen distance as measured from the center of electronic charge would be ≥3.0 Å. The distance estimated for the circled hydrogens of **22** from Dreiding models is 0.4–0.6 Å. Analogous steric congestion is completely absent in structure **15**.[20] We consequently prefer formulation **15** over **22**.

The proton NMR spectra of dioxide **15** and that of azoxy **20** are consistent with the assignment. Consider first the spectra of series **1–3** (n = 2).

While it is known that the azo function in a diazirine ring exerts a considerable shielding effect on a proton above the N=N plane,[22] no comparative correlations have been tabulated for the related oxides. It is, however, evident that N-



oxidation leads to a clear-cut downfield shift for protons lying above the heavy atom plane.[23] Azo dioxide **15** (n = 1) exhibits its highest field absorption as a multiplet centered at τ 8.67 (DMSO-d_6, Me_4Si), while the corresponding value for *N*-oxide **20** is τ 8.56 ($CDCl_3$, Me_4Si). The endo hydrogens for norbornane fall at τ 8.82.[24] Structures **15** and **20** consequently suggest a deshielding of the latter by about 0.2 ppm in accord with the pattern observed for **1–3**.

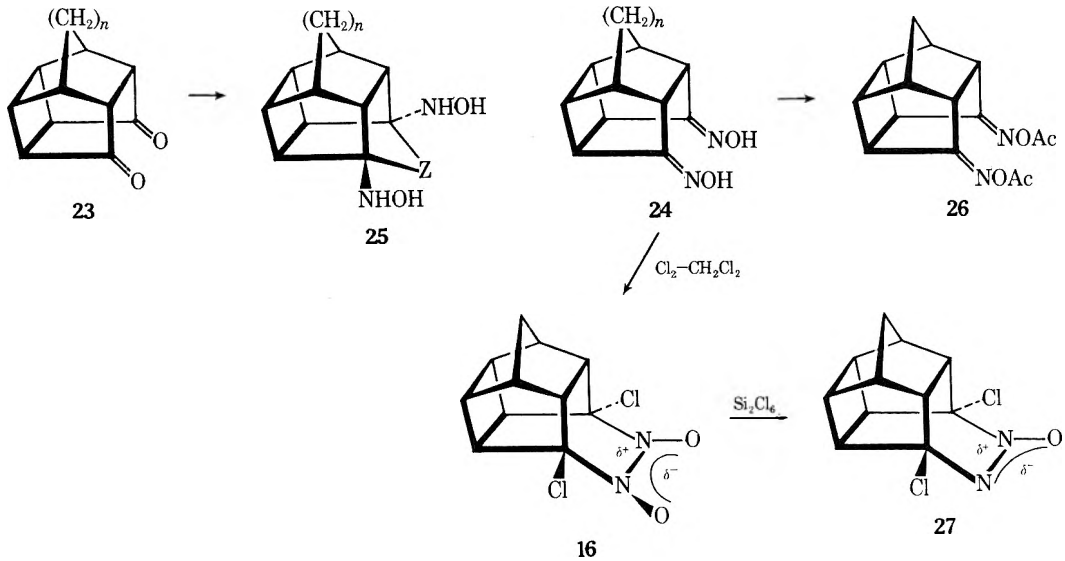
Alternatively, the downfield shifts might be attributed to van der Waals effects in dioxide **22**. However for two bound hydrogens separated by 1.7 Å the deshielding effect is calculated to be >0.5 ppm,[25] a factor which might well be enhanced in the latter considering the H–H separation estimated above.

The polycyclic dioxide **16** can be obtained as outlined in Scheme II. The dihydrochloride of hydrate **25** (Z = O, mp 50°) has been reported as the single product (100% yield) from the reaction of hydroxylamine hydrochloride with diketone **23** in the presence of hydroxide.[26] In our hands the same conditions led to a high-melting, insoluble product (310–320° dec) which contains no chlorine but analyzes for structure **24**. Substitution of pyridine for OH^- caused no change in the product composition. Acetylation results in diacetate **26** in essentially quantitative yield. There is no doubt that oxime **24** has indeed been isolated.

The oxime product suspended in CH_2Cl_2 was treated with chlorine. The resulting blue solution delivers the colorless, crystalline dioxide **16**. The infrared and ultraviolet spectra (Table I) confirm the structure. Accordingly, disilane reduction leads to azoxy **27**.

Several other unsuccessful attempts to generate α,α'-dichloro cis azo dioxides were made. For example, with cyclo-

Scheme II[a]



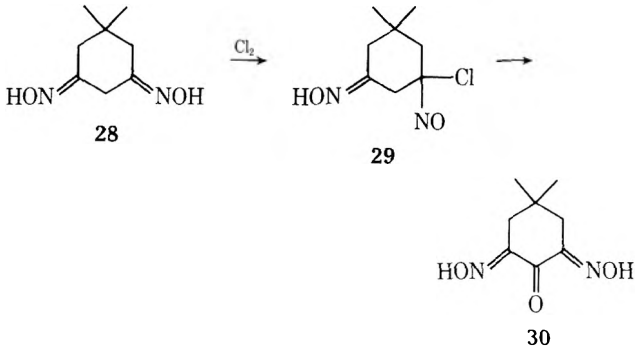
[a] n = 1.

Table II
Thermodynamic Quantities for the Azo Dioxide–Nitroso Equilibrium, 20° [a]

	R	ΔE_{strain} [b]	ΔH, kcal/mol	ΔS, eu	$T\Delta S$, kcal/mol	ΔG, kcal/mol	$K_{eq} \times 10^7$, mol/l.	$K_{eq} \times 10^7$
i	*tert*-Butyl	9–10	11.8[c]	41.5	12.2	−0.38	1.92×10^7	
ii	$CH_3CO(CH_3)_2C$	2–3	18.9[d]	40.9[f]	12.0	6.9	68.6	
iii	c-C_6H_{11}	0.0	20.6[d]	39.2[f]	11.5	9.1	1.55	
			24.8[e]	52.5	15.4	9.4	0.96	
	$C_6H_5CH_2$	0.0	20.4[d]	34.3[f]	10.1	10.4	0.187[g]	
iv	**3**: bicycle a	0.0	22.0	7.5	2.2	19.8		1.6×10^{-8}
	$n = 1$	16.1	5.9	7.5	2.2	3.7		1.7×10^4
	$n = 2$	14.3	7.7	7.5	2.2	5.5		7.8×10^2
	$n = 3$	12.3	9.7	7.5	2.2	7.5		2.5×10^1
	$n = 4$	22.1	−0.1	7.5	2.2	−2.3		5.2×10^8
	9	6.0	16.0	15.0	4.4	11.6		2.2×10^{-2}
	10	30.0	−8.0	5.0	1.4	−9.4		1.1×10^{14}
	10′	19.3	2.7	5.0	1.4	1.3		1.0×10^6

[a] Categories i, ii, and iii list experimental values; category iv includes only estimated values (see text). [b] E_{strain} (azo dioxide) − E_{strain} (nitroso). [c] Reference 3b, solvent CCl_4. [d] Reference 3a, solvent benzene. [e] Reference 4e, solvent decane. [f] Recalculated for dilute solution[36] using the expression $\Delta S = \Delta U/T + R \ln K_c$. [g] Corrected by a factor of 0.1; cf. ref 3a.

hexadiene as ultimate precursor, dioxime **17** ($n = 2$) was prepared. Excess chlorine delivers only the half-converted nitroso oxime **18** ($n = 2$). In the case of the polycyclic diketone **23** ($n = 2$) oximation leads to a high-melting solid which analyzes for **25** ($n = 2$, Z = NOH). Given the propensity for **23** ($n = 2$) to form a hydrate,[20] this result is not surprising. Chlorination of **25** in concentrated HCl as well as in organic solvents results in blue products, none of which provided the desired dioxide. The same conditions were applied to 1,3-cyclohexanedione dioxime **28**. Evidence for the formation of nitroso oxime **29** and its conversion to **30** was gathered. Again no *N,N'*-dioxide could be isolated.

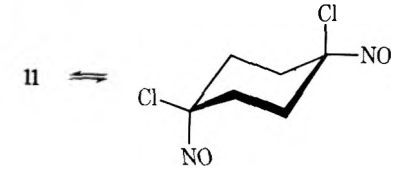


28 **29** **30**

Nitroso Dimerization and Azo Dioxide Dedimerization. The existence of a facile equilibrium between nitroso monomers and the corresponding dimer is well documented. While unhindered aromatic derivatives are monomeric in solution, appropriate ring substitution promotes an ambient equilibrium mixture containing significant quantities of both monomer and dimer.[3] Dissolved alkyl-substituted nitroso compounds, RNO, are generally dimeric at room temperature unless R is either bulky [*t*-BuNO,[3b] $(CH_3)_3CH_2(CH_3)_2CNO$,[3b] $Et(CH_3)_2CNO$[4a]] and/or contains an electronegative substituent [$Cl(CH_3)_2CNO$,[18,27] $F(CF_3)_2CNO$[28]]. Several studies demonstrate nonetheless that simple aliphatic dimers are readily equilibrated with the nitroso monomer. In particular acyclic cis-nitroso dimers are rapidly converted into the trans isomers in solution at room temperature or below.[4g,16,29] The characteristic blue nitroso color is obtained by refluxing organic solutions of either isomer.[4c,f,29] Finally, spectrophotometry in the visible region has been utilized for collection of thermodynamic quantities for the nitrosocyclohexane and related equilibria.[3a,4f]

Attempts to obtain equilibrium data for series **3**, **4b**, **5b**, and **6b** have been frustrated by the complete absence of evidence for the systems' nitroso component. The azo dioxides in boiling organic solvents, be they polar or nonpolar, hydroxylic or aprotic, remain colorless up to the decomposition point (≤250°). Similarly, in the solid state, slow warming leads only to charring in every case without the intermediate development of color.[30]

These observations stimulated our preparation of the dichloro-bridgehead cases **15** and **16**. Azo dioxide **11** on warming in a variety of solvents reversibly develops a deep blue color indicative of ring opening to give dinitroso **31**.[18]



31

The preparation of both **15** and **16** involves preformation of either blue solutions or blue solids which give way upon warming or dissolution to colorless dioxides (see Experimental Section). However, as found for the unchlorinated azo dioxides, once formed neither **15** nor **16** can be coaxed to color either in the solid state or in solution prior to decomposition.[30]

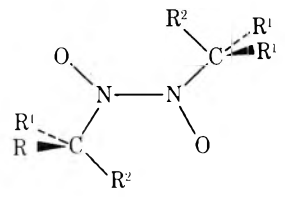
Clues to an understanding of the failure to observe monomer from the polycyclic cis dioxides described above may be gained by inspection of the thermodynamic quantities gathered in Tables II and III. Consider first the equilibrium data of Table II. Of greatest significance is the fact that the first four experimental cases all involve a very large entropy term which contributes 10–16 kcal/mol (i.e., $T\Delta S$) to the free energy of the monomeric equilibrium partner. Since the measurements were taken in nonpolar media (C_6H_6, CCl_4, decane), the bulk of the entropy value is not attributable to solvent orientation effects and must be assigned to substrate reorganization.[31] In spite of this only the *tert*-butyl case exists predominantly as the monomer in solution. Since ΔS is nearly constant for the experimental series, the ΔH contribution to ΔG is the factor responsible for the relative K_{eq} values. Its variation may be rationalized by considering the effect of substituents on the nitroso dimer. The alkyl functions can be classified into three groups according to relative size. Conformation **32** is illustrative.[32] R=: i > ii > iii. Along this series the dimin-

Table III
Activation Parameters for the Nitroso Dimer [(RNO)2]
Dissociation: Dimer → 2 Monomer, 20°

	R	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$T\Delta S^{\ddagger}$, kcal/mol	$\Delta G^{\ddagger}$, kcal/mol	Solvent
i	$CH_3CH_2(CH_3)_2C$	24.3[a]	9.4	2.8	21.5	Benzene
		21.9–23.2[b]				
	$AcOCH_2(CH_3)_2C$	25.8[a]	16.0	4.7	21.1	Benzene
	$(CH_3)_3C$	21.5[b]				Benzene
	$AcCH_2(CH_3)_2C$	23.4[c]				Benzene
ii	$Ac(CH_3)_2C$	29.6[d]	18.6	5.5	24.1	CCl_4
		27.7	13.2	3.9	23.8	c-C_6H_{12}
iii	$C_6H_5CH_2$	35.8[e]	27.8	8.1	27.7	CCl_4
		27.7	11.8	3.5	24.2	c-C_6H_{12}
	c-C_6H_{11}	33.1[f]				Decane
	$(CH_3)_2CHCH_2$	26.0[g]				Gas phase
	CH_3	21.8[g]				Gas phase

[a] Reference 4b. [b] E. Bamberger and R. Seligman, *Chem. Ber.*, 36, 685 (1903), computed in ref 4c. [c] Reference 4a. [d] Reference 4d. [e] Reference 4e. [f] Reference 4f. [g] Reference 4c.

ishing dissociation tendency parallels the increase in ΔH. If grouping iii is taken as "unstrained", the *tert*-butyl derivative is seen to incorporate 9–10 kcal/mol of strain energy.[33]

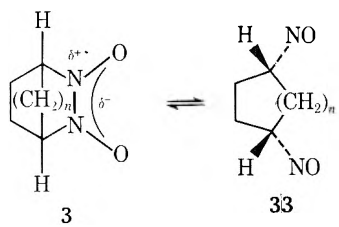


32

	R1	R2
i	CH_3	CH_3
ii	CH_3	$COCH_3$
iii	$-(CH_2)_5-$	H
	C_6H_5, H	H

The influence of molecular crowding is felt in the dissociation rates for the nitroso dimer as well (Table III). The cases tabulated are ones studied either in the gas phase or in nonpolar solvents. Activation energies are somewhat less in polar media[4d] and anomalously high in water.[4e] For groups i, ii, and iii, the $\Delta G^{\ddagger}$ ranges are 21.1–21.5, 23.8–24.1, and 24.2–27.7 kcal/mol, respectively. The entropy contribution is relatively constant, $\Delta H^{\ddagger}$ controlling relative rates.

No thermodynamic values have yet been recorded for polycyclic cis azo dioxides such as **3**. In the discussion to follow both entropy and strain energy values are estimated from literature data. The resulting K_{eq} and k trends are analyzed in terms of the observed cyclic *N,N'*-dioxide behavior. The nitroso azo dioxide equilibrium will be considered first.



3 33

Difference method estimates[35] suggest that ring opening exemplified by **3** → **33** can be associated with ΔS = 5–10 eu. An intermediate value of 7.5 eu will be employed here. Thus for a "strainless" system, bicycle a (**3**, ΔH = 22.0 kcal/mol, the average value of entries 3–5, column 2, Table II), a free-energy difference of 19.8 kcal/mol is calculated. The corresponding equilibrium constant indicates that for a 0.01 *M* solution there would be approximately 10^{12} fewer moles of cyclic dinitrosoalkane in equilibrium with bicycle a at 20° than moles of nitrosocyclohexane in equilibrium with its dimer at the same temperature[37] (cf. Table II). Increased temperature will not ameliorate the situation. Figure 1 exhibits a plot of the decrease in ΔG as a function of temperature for both bicycle a and the cyclohexane derivative.[38] For the latter the free-energy difference drops steadily with temperature until it becomes zero around 200°. Indeed the cyclohexylnitroso dimer has been found to be 42% dissociated at 130°.[4f] On the contrary, ΔG for bicycle a decreases at a much slower rate over the same temperature range.[39] This difference is due almost entirely to the effect of temperature on the $T\Delta S$ term: cyclohexyl, $T\Delta S$ (0 → 300°) = 14.1–30.1 kcal/mol; bicycle a, $T\Delta S$ (0 → 300°) = 2.1–4.3 kcal/mol. It should be noted that the slope of the lines plotted in Figure 1 is a direct measure of ΔS. Figure 2 depicts the situation in another way by illustrating the behavior of ln K_{eq} as a function of the reciprocal of the temperature. Thus for a "strain-free" bicycle **3**, the absence of a considerable equilibrium entropy contribution can be expected to prevent observable nitroso formation even at elevated temperatures.

For most of the substances listed in Table I the strain-free model is not directly applicable. Since the dissociation of trans *tert*-butyl azo dioxide is strongly affected by steric congestion, angle strain in **3** should in principle exert a similar influence on the cyclic azo dioxide–nitroso equilibrium partition. Accordingly, two mechanistically different interpretations, one kinetic and one thermodynamic (i.e., entropy control as outlined above), will accommodate the experimental observations. In order to assess them it is necessary to derive strain energy values for the cyclic and bicyclic azo dioxides.

Strain Energies. For the purpose of estimating the relief of strain in the **3/33** system, we assume a qualitative parallel between the strain energies of azo dioxides **3** (n = 1–4) and those of the corresponding unsaturated hydrocarbons. In order for this assumption to be valid, a knowledge of the force constants associated with the bending of the CNN angle of **3** relative to a corresponding CCC angle would be useful. While azo oxides have yet to be evaluated, several comparisons between trans azo compounds and their isoelectronic carbon counterparts have been made using a common force field. In every case the CNN bond is tighter than the corresponding CCC bond.[40] The consequence of N-oxidation is suggested by a comparative study of acetonitrile (F_{CCN} = 0.265 mdyn-Å/rad^2) and acetonitrile *N*-oxide (F_{CCN} = 0.397 mdyn-Å/rad^2).[41] To a first approximation hydrocarbon strain energies would thus seem to represent at least lower strain limits for the cyclic and bicyclic azo dioxides.

Recent force-field calculations estimate strain energies for norbornene and bicyclo[2.2.2]octene to be 23.6 and 16.0 kcal/mol, respectively.[34] By utilizing data from the tables of Engler et al.[42] and applying Allinger and Sprague's E_{strain} (alkane − alkene) values,[34] 20.3 and 33.6 kcal/mol can be derived for the strain energy content of bicyclo[3.2.2]nonene-2 and bicyclo[4.2.2]decene-2, respectively. Subtracting the strain associated with the simple cycles[34,43] **33**, bicycle **3** is estimated to contain the residual strain energies, ΔE_{strain}, listed in Table II affecting the position of the **3/33** equilibrium.

Similarly, dioxide **9** is estimated to contain 6 kcal/mol strain based on the values for cyclohexene and 3-methylcyclohexene.[34] Finally, the thermally stable four-membered ring azo dioxide **10** must be considered. The strain energy of cyclobutene has recently been placed at 30.6 kcal/mol.[44] However, in addition to the four ring, **10** incorporates two eclipsing interactions between vicinal methyl groups.[45] A reasonable strain estimate might be 30–35 kcal/mol. In view of the congestion in the ring-opened isomer, 2,3-dimethyl-2,3-dinitrosobutane, a ΔS = 5 eu is assigned to the ring opening.

If the strain energy appraisals derived above are meaningful and 22.0 kcal/mol represents a near-strain-free ΔH for the azo dioxide–nitroso equilibrium, then ΔH for the latter can be set from −8.0 to 16.0 kcal/mol for **3, 9,** and **10** as indicated in category iv in Table II. The corresponding ΔG's and ln K_{eq}'s are plotted as a function of temperature in Figures 1 and 2.

Least-Motion vs. Non-Least-Motion Azo Dioxide Fragmentation. Taking the results of Figures 1 and 2 at face value, the incorporation of ring strain in the azo dioxides, a minimal entropy contribution notwithstanding, is predicted to lead to favorable equilibrium constants ($K_{eq} \geq 10^{-3}$)[30] for n = 1, 2 above 100°. Dioxide **3** (n = 4) ought to mimic the room-temperature behavior of the colorless *tert*-butyl nitroso dimer. As mentioned above, dissolving the latter in organic solvents leads to a spontaneous production of the blue monomer (ΔG = −0.38 kcal/mol). The situation for four-ring **10** (ΔG = −9.4 kcal/mol) should be further exaggerated in K_{eq} by nearly 10^6. Furthermore, if the above generalization concerning strain and dissociation rates (Table III) likewise holds in the bicyclic series, activation energies for dedimerization should diminish progressively from bicycle a to compound **10.**

To recapitulate, with the exception of dioxide **11** none of the cis cyclic azo dioxides described in this report,[46] including the bridgehead chlorinated ones, yield nitroso monomer in solution at accessible temperatures (≲250°).[47] The fact that predicted equilibrium properties of cyclic azo dioxides are in conflict with observation suggests a kinetic origin for the lack of ring opening. Unlike the acyclic nitroso dimers the behavior of substances **3** and **10** seems to reflect *enhanced* activation barriers to fragmentation with increased ring strain. A nonlinear decomposition pathway[5] can be anticipated to introduce considerable geometric constraint in the transition state for a rigid system. Were the dissociation to proceed by a linear motion, there is little doubt that ring opening would parallel strain energy.

Inspection of molecular models indicates that for **3** and **16** [and possibly **3** (n = 2) and **15** as well] the computed low-energy pathway is difficult to achieve. On the contrary, models suggest no unambiguous reason why the twisted transition state cannot be attained by **3** (n = 3, 4) and **10.** The chloro-substituted case **11** is interesting and argues that for **3** ($n \geq 2$), if the non-least-motion mechanism is operating, the required transition state can indeed be reached. Alternatively, the introduction of strongly electronegative substituents may in fact alter the stereochemical requirements of the activated complex.

Entropy Control. In view of the above strain estimates, the existence of the four-ring azo dioxide **10** is surprising. It signals that a positive contribution by the N–N bond energy is suppressing ring destruction. Assuming for this compound K_{eq} = 1 and ΔS = 5 eu, a ΔH = 2.7 kcal/mol for ring opening is derived (**10′**, Table II). The latter implies a strain energy of about 20 kcal/mol, 10–15 kcal/mol less than that obtained from the hydrocarbon estimate. If this result were to carry over to all the models listed in Table II (category iv), the conclusion that ring opening is prevented primarily by the absence of an appreciable ΔS is inescapable.

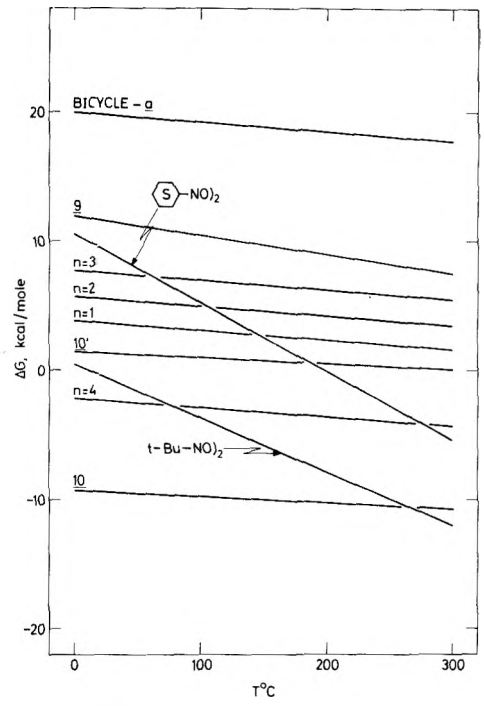


Figure 1. The influence of temperature on the free energy of dissociation for the nitrosocyclohexane and the 2-methyl-2-nitrosopropane dimers and several cyclic azo dioxides (cf. Table II).

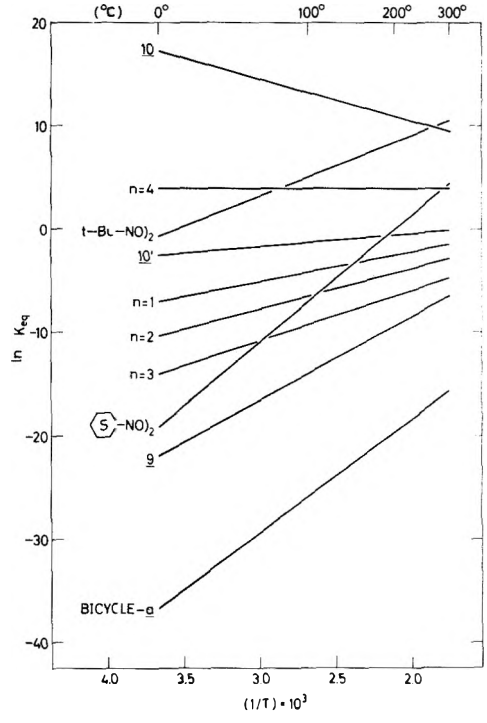


Figure 2. Variation of the equilibrium constant for the azo dioxide–nitroso equilibrium as a function of temperature (K) (cf. Table II).

Conclusion

Entropy plays an important and in some cases a decisive role in suppressing the cleavage of nitroso dimers in the cyclic series. For substances normally considered to be highly strained, entropy effects can in principle be overridden by strain effects. The apparent absence of the influence of the

Table IV

Compd	Mp, °C (recrystn solvent)	Yield, %
2 (n = 2)	158–159 (EtOH)	89
2 (n = 3)	175–176 (hexane)	94
2 (n = 4)	133–134 (hexane)	98
4a	48–49 (Et_2O)	87
5a	131–137 (CCl_4)	70
6a	137–138 (EtOH)	86

latter may be rationalized in kinetic or thermodynamic terms. Either the transition state for azo dioxide dedimerization is even more congested than the ground state (via a non-least-motion pathway) or cyclic cis azo dioxides are far less strained than their unsaturated hydrocarbon counterparts in spite of force constant data to the contrary. The present analysis provides no unambiguous choice between the alternatives but does suggest certain illuminating experiments. Further work is in progress.

Experimental Section

General. Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and The Microanalytical Laboratory, Kemisk Laboratorium II, The H. C. Ørsted Institute, University of Copenhagen. Melting points were measured on a Thomas-Hoover apparatus and a Büchi instrument and are corrected. Infrared (ir) spectra were recorded on Perkin-Elmer Models 257 and 337 grating spectrophotometers. The nuclear magnetic resonance (NMR) spectra were obtained with Varian A-60 and Bruker HX-90E (^{13}C) spectrometers. Ultraviolet spectra were taken on Cary 15 and Unicam SP-1800 recording spectrophotometers. Except where noted solvents were reagent grade and were used as received.

The following is a general procedure for stable azoxy alkanes.

Phosphate Buffer. Stock solutions of 0.2 M $NaHPO_4$ and 0.2 M Na_2HPO_4 were prepared. The phosphate buffer of pH 7.5 was prepared using 31 ml of 0.2 M NaH_2PO_4 and 69 ml of Na_2HPO_4, then diluting to a final volume of 200 ml.

2,3-Diazabicyclo[2.2.2]oct-2-ene *N*-Oxide, 2 (n = 2). A stirred solution of 2,3-diazabicyclo[2.2.2]oct-2-ene[6] (4.3 g, 39 mmol), mp 139–140°, in CH_2Cl_2 (75 ml) cooled to 10° was treated dropwise with MCPBA (98%, 7.6 g, 55 mmol) dissolved in CH_2Cl_2 (175 ml). After one-half of the addition was complete, a white percipitate formed which persisted throughout the reaction. At the end of the addition, which consumed 1.5 hr, 100 ml of a phosphate buffer solution, pH 7.5, was added in one portion and the reaction mixture was stirred for an additional 1.0 hr. The excess oxidant was destroyed with the dropwise addition of 2 M sodium bisulfite solution, and then the pH was adjusted to 9.0 with 2 M Na_2CO_3. The organic layer was separated, washed with 2 × 75 ml of NaCl solution, dried ($MgSO_4$), and the solvent removed in vacuo to yield a white solid (4.6 g). Recrystallization from EtOH afforded white crystals, **2** (n = 2) (4.1 g), mp 158–159°. A second crop was obtained from the mother liquor (0.3 g, total 4.4 g, 35 mmol, 89%).

6,7-Diazatricyclo[3.2.2.$0^{2,4}$]non-6-ene *N*-Oxide, 6b. All operations were carried out below 0°.

The following solutions were prepared and cooled to −10° with a NaCl–ice bath: 500 ml of NaCl solution, 500 ml of CH_2Cl_2, and 150 ml of concentrated NH_4OH. To concentrated NH_4OH (150 ml) at −10° was added 6,7-diazatricyclo[3.2.2.$0^{2,4}$]non-6-ene–cuprous bromide complex[6] (17.4 g, 50.0 mmol) with stirring. The solution became blue, then blue-green, and agitation was required to effect complete solution. The reaction mixture was extracted in a precooled separatory funnel with cold CH_2Cl_2 (2 × 200 ml), and the organic extract was washed with cold NaCl solution (4 × 100 ml), dried ($MgSO_4$), filtered, and added to a 1-l. three-neck flask fitted with an overhead stirrer, a low-temperature thermometer, a dropping funnel, and an external cooling bath (Dry Ice–acetone). Stirring was initiated as the solution was cooled to −30°, and a solution of MCPBA (95%, 10.0 g, 55 mmol) dissolved in CH_2Cl_2 (175 ml) was added dropwise. Addition consumed 1.0 hr and the reaction mixture, which was stirred for an additional 1 hr at 0°, contained excess MCPBA (starch–iodide probe).

Work-up as above afforded an off-white solid (6.25 g), mp 132–133°. Recrystallization from EtOH deposited white needles of **6b** (4.16 g) and a second crop (1.78 g, total 5.94 g, 43.0 mmol, 86%), mp 137–138°.

Compounds **2** (n = 1, 2) and **4a** are likewise obtained from the azo dioxide forming reaction described below (Table IV).

The N-oxides are identical in all respects with those previously reported.[9b]

Synthesis of Azo Dioxides with Peracetic Acid. The following is a general procedure.

2,3-Diazabicyclo[2.2.2]oct-2-ene 2,3-*N,N'*-Dioxide. To a 250-ml flask, fitted with a reflux condenser and an external oil bath, was added 2,3-diazabicyclo[2.2.2]oct-2-ene [1 (n = 2)], 5.5 g, (50 mmol), mp 139–140°, dissolved in reagent grade glacial acetic acid (50 ml), 50% H_2O_2 (50 ml), and concentrated H_3PO_4 (2 drops). The water-white solution was heated at 100° for 6.0 hr, and to ensure an excess of peroxide the solution was periodically tested with starch–iodide paper. If the solution darkened, which was normally a sign of insufficient peroxide, or tested weakly positive to starch–iodide paper, an additional 100 ml of 50% H_2O_2 was added, and the solution was heated until a light yellow color was maintained. At the end of the reaction, the solution was cooled to 35° and the excess oxidant was destroyed with small additions of 1 M sodium bisulfite solution. The acetic acid and the water were removed at low pressure, leaving a white slurry which was dissolved in H_2O (20 ml), and the pH adjusted to 10.0 with 2 M Na_2CO_3. The aqueous phase was extracted with methylene chloride (3 × 75 ml). The organic phase was washed with saturated NaCl (3 × 50 ml), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo, leaving an off-white solid, whose NMR showed two peaks at τ 5.50 (azoxy) and 5.28 (dioxide) in the ratio of 1:3. The crude solid was triturated with ether (3 × 50 ml), removing the azoxy (1.08 g, 8.6 mmol, 17%) and leaving a powdery, white solid. Recrystallization from ethanol, after treatment with charcoal, afforded a white crystalline solid, 2.1 g, and a second crop, 0.8 g (20 mmol total 41%: based on recovered azoxy, 85%), mp 221–222° dec.

Procedural changes where they are necessary for the other azo dioxides are as follows.

Azoxy Alkane 2 (n = 1) and Azo Dioxide 3 (n = 1). After the reaction solution was heated at 100° for 12 hr an additional 35 ml of 50% H_2O_2 was added and the reaction continued for 8 hr. Work-up as above furnished a white solid, the NMR of which showed two peaks at τ 5.40 (azoxy) and 5.23 (dioxide) in the ratio of 5:1. Trituration of the crude product with ether (8 × 50 ml) left a chalky white solid. The ether was dried ($MgSO_4$), filtered, and stripped in vacuo to yield a hygroscopic solid. Recrystallization (dry ether) with rapid filtration of the crystalline product under dry nitrogen afforded a white solid **2** (n = 1), mp 96–97° (70%). The material is hygroscopic and volatile. Drying under vacuum will lead to substantial, if not complete, loss. The N-oxide can be stored at atmospheric pressure under nitrogen.

The ether-insoluble white solid was recrystallized from EtOH, **3** (n = 1) (16%; based on recovered azoxy, 60%).

Azo Dioxide 3 (n = 3, 4). Work-up as above led to crude products which by NMR were completely free of the azoxy intermediate. The ether trituration step can thus be eliminated.

Azo Dioxide 6b. Azoxy **6a** (1.0 g, 7.2 mmol), mp 136–137°, and MCPBA (98%, 2.5 g, 14 mmol) were dissolved in $CHCl_3$ (75 ml) and stirred magnetically at 85° for 5.0 hr. Work-up of the yellow solution proceeded as above, yielding a pale white solid (0.84 g), the NMR of which showed two bands at τ 5.50 (dioxide) and 5.30 (azoxy) in the ratio of 1:3. Trituration of the solid with ether (4 × 50 ml), then warm hexane (4 × 50 ml) led to the soluble azoxy alkane (0.52 g, 57%) and an insoluble white solid. Recrystallization from a minimum amount of ethanol yielded a white solid **6b** (0.32 g, 2.1 mmol, 30%; based on recovered azoxy, 64%). Azo dioxide **6b** may also be obtained in somewhat better yield (51%) by allowing the oxidation to proceed at room temperature for 5 days [MCPBA: azoxy alkane (3:1), $CHCl_3$].

The physical properties of the azo dioxides are tabulated in Table I.

Preparation of 3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N*-Oxide (8). A solution of 2,5-diamino-2,5-dimethylhexane (14.4 g, 100 mmol) and $Na_2WO_4 \cdot 2H_2O$ (0.987 g, 3.0 mmol) in water (20 ml) was cooled in an ice bath to 0°. Initial dropwise addition of H_2O_2 (30%, 45.3 g, 400 mmol) gave a highly exothermic reaction after a 5–10-min induction period. The temperature of the reaction mixture was maintained between 15 and 25° by ice cooling and slow addition. After final addition and stirring at 25° for an additional 1 hr, the reaction mixture was extracted with methylene chloride (2 × 150 ml), and the organic phase was washed with 1 N HCl (2 × 50 ml) and saturated NaCl solution (2 × 50 ml), dried

($MgSO_4$), filtered, and the solvent removed to yield a light brown solid (13.8 g) which showed two main spots on TLC.

PLC chromatography of 1.0 g of the crude product on 20 × 100 mm, 2.5 mm silica gel and elution with ether (once) effected separation of the mixture. The more polar component (R_f 0.3, ether) yielded a white solid, 8 (0.720 g, 64 mmol, 64%): mp 120–121° (ether); NMR ($CDCl_3$, Me_4Si) τ 7.8–8.4 [4 H, complex, $-(CH_2)_2-$], 8.40 (6 H, singlet, CH_3), 8.65 (6 H, CH_3); ir ν_{max} (KBr) 1450, 1470 cm^{-1}; uv λ_{max} (96% EtOH) 233 nm (ϵ 6200).

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9. Found: C, 61.5; H, 10.5; N, 18.4.

The less polar component from 0.7 g of crude product (PLC, ether) yielded a light yellow-green oil with a camphorous odor, 3,3,6,6-tetramethylazocyclohexane (0.15 g, 21 mmol, 21%): NMR ($CDCl_3$, Me_4Si) τ 8.50 [4 H, singlet, $-(CH_2)_2-$], 8.68 (12 H, singlet, CH_3); ir ν_{max} (thin film, NaCl) 1560 cm^{-1}; uv λ_{max} (hexane) 379 nm (ϵ 150).

Anal. Calcd for $C_8H_{16}N_2$: C, 68.5; H, 11.5; N, 20.0. Found: C, 68.0; H, 11.3; N, 19.7.

Preparation of 3,3,6,6-Tetramethylazocyclohexane 1,2-*N,N'*-Dioxide (9). To a stirred solution of azoxy 8 (0.468 g, 3.0 mmol) in methylene chloride (150 ml) cooled to 10° was added dropwise a solution of MCPBA (85%, 1.18 g, 6.0 mmol) in methylene chloride (25 ml). A slight exothermic reaction was noted during addition, and the mixture was stirred for 9.0 hr. The excess peracid was destroyed with careful addition of 1.0 *M* sodium thiosulfate, the pH was adjusted to 7.0 with 2 *M* $NaHCO_3$, and the organic phase was washed with saturated NaCl (3 × 100 ml), dried ($MgSO_4$), filtered, and the solvent removed in vacuo to yield a white, crystalline solid, 9 (0.470 g, 2.7 mmol, 91%). TLC indicated only one spot, R_f 0.0 (Et_2O). See Table I for the physical constants.

Hexachlorodisilane Reduction of Azo Dioxide 3 (n = 2). Azo dioxide 3 (n = 2) (43 mg) dissolved in $CDCl_3$ (400 mg) was treated at intervals with a drop of Si_2Cl_6. Each addition led to an exothermic reaction at room temperature. The mixture was monitored by proton NMR. Characteristic is the change in the bridgehead region. Initially only the dioxide peak at τ 5.25 was present. The first addition of disilane caused an instantaneous appearance of the monoxide at τ 5.50 (**2**, n = 2). With additional reagent the dioxide band disappeared, the monoxide peak grew in intensity, and the azo alkane resonance at τ 4.91 became evident (**1**, n = 2). The changes continued until only azo alkane absorption remained. Corresponding changes in the spectrum between τ 7.5 and 8.9 were likewise observed.

Dichloro Azo Dioxide 15 and Chloro Nitroso Oxime 18 (n = 1). Dry chlorine gas was bubbled into an ethyl acetate (20 ml) suspension of dioxime 17 (n = 1)[49] (1.0 g, 4.8 mmol) at 0° for 30 min. The mixture turned blue within a few minutes as the dioxime dissolved. A blue solid formed gradually during the chlorine treatment. The mixture was filtered and the blue solid (18) was washed with a $NaHCO_3$ buffer (pH 7) and water and then dried on a porous plate (200 mg, 0.82 mmol, 17%), mp 127–128°. Attempted recrystallization and chromatography led to decomposition; ir, see text.

Anal. Calcd for $C_{11}H_{15}N_2O_2Cl$: C, 54.4; H, 6.2; N, 11.5. Found: C, 54.7; H, 6.3; N, 11.6.

The blue-green filtrate was washed with 2 *N* NaOH (2 × 20 ml), then water, dried ($MgSO_4$), and stripped of solvent in vacuo to white crystals (**15**, 300 mg, 1.1 mmol, 23%): mp 237–238° dec; physical data, see Table I. Anal. Calcd for $C_{11}H_{14}N_2O_2Cl_2$: Cl, 25.2. Found: Cl, 25.6.

Dichloroazoxy Alkane 20 (n = 1). Dioxide **15** (100 mg, 0.36 mmol) suspended in CH_2Cl_2 (25 ml) was treated with hexachlorodisilane at 25° (excess), whereupon starting material dissolved completely. After 10 min the mixture was quenched with water, extracted with CH_2Cl_2 (3 × 20 ml), dried ($MgSO_4$), and stripped in vacuo to pale yellow crystals, which were recrystallized twice from methanol and washed once with a small amount of dry ether to obtain white crystals (**20**): mp 165–166° (108 mg, 0.41 mmol, 57%); ir λ_{max} (KBr) 1460 (N–O), 1425, 1286 cm^{-1} (N–O); NMR ($CDCl_3$, Me_4Si) τ 6.9–7.6 (4.5 H, m), 7.7 (3.5 H, broad s), 8.1–9.0 (6 H, m); uv λ_{max} (96% EtOH) 237 nm (ϵ 6300); NMR ($CDCl_3$, Me_4Si) τ 7.29 (4 H, m), 7.67 (4 H, s), 8.56 (6 H, m).

Anal. Calcd for $C_{11}H_{14}N_2OCl_2$: C, 50.6; H, 5.4; N, 10.7. Found: C, 50.4; H, 5.5; N, 10.9.

Deoxygenation of Chloro Dioxide 11. Dioxide **11**[18] (ca. 50 mg) in $CDCl_3$ in an NMR tube was treated with Si_2C_6 (3–4 drops) at room temperature. A multiplet at τ 7.6 characteristic for the *N*-oxide[50] appeared immediately. Additional Si_2Cl_6 caused no further change. The $CDCl_3$ solution was washed with water, extracted with CH_2Cl_2, dried ($MgSO_4$, and stripped in vacuo to white crystals: mp 185–186° (lit.[50] mp 186°); NMR ($CDCl_3$, Me_4Si) τ 7.6 (m) [lit.[50] τ 7.9 (m)].

Dioxime 24 (n = 1). Diketone **23**[26] (3.7 g, 2.1 mmol), hydroxylamine hydrochloride (2.8 g, 40 mmol), and 1 *N* NaOH (40 ml) in absolute ethanol (200 ml) were refluxed for 1 hr. The cooled solution was concentrated to a small volume in vacuo. The resulting white solid was filtered and recrystallized from H_2O–EtOH as white crystals: mp 310–320° dec (3.3 g, 1.6 mmol, 77%); no chlorine (Beilstein test); ir ν_{max} (KBr) 3150 (broad, OH), 1705, 1660, 1425, 900 cm^{-1} (N–O, oxime).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7. Found: C, 64.8; H, 6.0; N, 13.9.

Substitution of pyridine for 1 *N* NaOH (4 *M* excess of NH_2OH·HCl, 2 hr reflux) led to a white solid, mp 304° dec (79%), with the same elemental composition.

Diacetate 26. Dioxime **24** (1.0 g, 4.9 mmol) was suspended in acetic anhydride (20 ml). After several minutes all solid dissolved. The solution was heated on a steam bath (1 hr). Solvent removal in vacuo afforded a white solid (**26**), mp 150° (1.3 g, 4.6 mmol, 94%). Recrystallization from hexane–acetone provided white crystals: mp 159–160° (750 mg); ir ν_{max} (KBr) 1727, 1628, 1339, 1190, 910 cm^{-1}; NMR ($CDCl_3$, Me_4Si) τ 6.0–7.4 (8 H, m), 7.7–8.3 (8 H, m).

Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.5; H, 5.6; N, 9.7. Found: C, 62.2; H, 5.7; N, 9.4.

Dichloro Azo Dioxide 16. Chlorine gas was bubbled into a CH_2Cl_2 (20 ml) suspension of dioxime **24** (450 mg, 2.2 mmol) cooled to 0°. A deep blue color developed over a 5–7 min period as the starting solid dissolved. The reaction was filtered from traces of solid and stripped in vacuo at room temperature. A blue solid (600 mg) was obtained, mp 150°. Washing with ether led to pale blue crystals; recrystallization from acetone delivered white crystals (**16**), mp 241–242° dec (250 mg, 0.92 mmol, 42%). Likewise, suspending the pale blue solid in ethanol caused an immediate disappearance of the blue color: mp 245° dec; physical data, see Table I; chlorine present (Beilstein test).

Dichloroazoxy Alkane 27. Dioxide **16** (200 mg, 0.78 mmol) was treated with Si_2Cl_6 as above to obtain pale yellow crystals, mp 85°, which were recrystallized twice from CH_3OH and washed once with ether to obtain white crystals (**27**): mp 185–186° (159 mg, 0.62 mmol, 79%); ir ν_{max} (KBr) 1459 (N–O), 1275 (N–O), 995 cm^{-1}; uv λ_{max} (96% EtOH) 236 nm (ϵ 6900).

Anal. Calcd for $C_{11}H_{10}N_2OCl_2$: C, 51.4; H, 3.9; N, 10.9. Found: C, 51.5; H, 4.0; N, 10.9.

Dioxime 17 (n = 2). The requisite diketone[51] (Scheme I, n = 2, 1.8 g, 9.4 mmol), hydroxylamine hydrochloride (2.6 g, 37 mmol), pyridine (20 ml), and absolute ethanol (20 ml) were refluxed for 2 hr. The cooled solution was treated with charcoal, filtered, and stripped in vacuo to a white solid. The latter was taken up with water (20 ml), cooled, filtered, and the insoluble white solid (**17**) washed with cold water, mp 240° (1.8 g, 8.1 mmol, 86%). Double recrystallization from H_2O–EtOH afforded a white solid: mp 255° dec; ir ν_{max} (KBr) 3150 (broad, OH, intramolecular H bond), 1422, 928 cm^{-1} (N–O, oxime).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.8; H, 8.2; N, 12.6. Found: C, 65.0; H, 7.9; N, 12.6

Chlorination of Dioxime 17 (n = 2). Chlorine gas was bubbled through a CH_2Cl_2 (15 ml) suspension of dioxime 17 (n = 2) (1.0 g, 4.5 mmol) cooled to 0°. A blue-green solution appeared within a few minutes as the solid dissolved almost completely. The solution was filtered and the blue-green filtrate stripped in vacuo at room temperature. The resulting blue-green solid was washed with ether several times and dried on a porous plate, mp 110° dec (300 mg). Double recrystallization from MeOH (below 50°) led to blue crystals: mp 116–117° dec; ir ν_{max} (KBr) 3175 (broad, OH, intramolecular H bond), 1548 (N=O), 925 cm^{-1} (N–O, oxime).

Anal. Calcd for $C_{12}H_{17}N_2O_2Cl$: C, 56.1; H, 6.7; N, 10.9. Found: C, 55.4; H, 6.6; N, 10.7.

The blue compound is assigned structure **18** (n = 2). Further chlorination under the above conditions does not lead to dioxide **15** (n = 2). As in the case of nitroso **18** (n = 1) the blue material here is thermally sensitive, particularly in solution (CH_2Cl_2). Standing overnight results in tarring. The material may, however, be stored for longer periods as a solid at room temperature or below. In MeOH overnight the blue color gives way to yellow. Evaporation of solvent led to a yellow solid: mp 160° dec; ir ν_{max} (KBr) 3150 (broad, OH), 1535, 1358, 920 cm^{-1}. This material was not investigated further.

Following some runs a chlorine-free white solid, mp 285° dec, with an infrared spectrum nearly superimposable with that of

dioxime 17 (n = 2) was isolated. The latter substance was likewise not characterized further.

Dioxime–Hydroxylamine Adduct 25 (n = 2, Z = NOH). Diketone **23** (n = 2) (2.0 g, 11 mmol), hydroxylamine hydrochloride (4.4 g, 63 mmol), pyridine (20 ml), and absolute ethanol (20 ml) were refluxed for 2 hr. The cooled solution delivered a white solid (**25**) which was washed successively with water, MeOH, and ether: mp 249–250° (2.1 g, 8.4 mmol, 76%); ir ν_{max} (KBr) 3425, 3180, 1309, 1120, 1045, 858, 780 cm^{-1}.

Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.4; H, 6.8; N, 16.7. Found: C, 57.4; H, 6.7; N, 16.7.

Dioxime 28. 5,5-Dimethylcyclohexane-1,3-dione was converted to dioxime as reported[52] and recrystallized from water, giving a white solid (**28**): mp 169–170° (lit.[52] mp 171–173°); ir ν_{max} (KBr) 3150 (broad, OH), 1405, 1250, 945 (N–O, oxime).

Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.3; H, 8.2; N, 16.3. Found: C, 56.5; H, 8.3; N, 16.5.

Chlorination of Dioxime 28. A. Chlorine, Concentrated HCl. Chlorine gas was bubbled into a suspension of dioxime 28 (1.0 g, 5.9 mmol) in concentrated HCl (10 ml) at 0°. A yellow solid formed and was recrystallized from H_2O–EtOH to give a pale yellow solid (**30**): mp 224–225°; ir ν_{max} (KBr) 3150 (broad, OH), 1680 (C=O), 1560, 1385, 1250, 1075, 940 (N–O, oxime), 870 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6, Me_4Si) τ 6.2–6.6 (2 H, broad, OH, D_2O exchange), 7.42 (4 H, broad s), 8.98 (6 H, s); no chlorine (Beilstein test).

Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.2; H, 6.6; N, 15.2. Found: C, 52.1; H, 6.6; N, 15.1.

B. Chlorine, Ethyl Acetate. Chlorine was introduced into an EtOAc (20 ml) suspension of dioxime 28 (500 mg) at 0°. Within 5 min the suspension turned dark blue and the dioxime dissolved. The solvent was stripped in vacuo at room temperature, depositing blue crystals, mp 95°. Attempted chromatography (TLC) on alumina (hexane–EtOAc) led to an immediate loss of blue color. Elution from a silica gel column (hexane), on the other hand, gave blue crystals showing three spots on tlc (silica gel–hexane–EtOAc), ir ν_{max} (KBr) 3180 (broad, OH), 1560 (N=O), 970 cm^{-1} (N–O, oxime). Recrystallization of the blue crystals from hexane afforded an insoluble, pale yellow solid. The latter was recrystallized from H_2O–EtOH to obtain pale yellow crystals (**30**), mp 220° dec, ir (KBr) superimposable on that of the solid obtained from method A.

The labile blue crystals are assigned the oxime chloro nitroso structure **29.** Further chlorination was ineffective in providing the desired dioxide. Chlorination in CH_2Cl_2 or hexane solutions did not cause development of the characteristic nitroso color.

Attempts to Induce Cyclic Azo Dioxides to Ring Open Thermally. All of the new cis azo N,N'-dioxides listed in Table I were melted slowly. Decomposition set in without the development of blue color. For qualitative solution behavior dichloro dioxide **11**[18] was used as a comparative standard. Compound **11** (1–3 mg) was dissolved in the following solvents (1–3 ml, 10^{-2}–10^{-3} M)[30] and the solution was brought to reflux (boiling point indicated): EtOH (78°), acetic acid (118°), ethylene glycol (197°), acetophenone (202°), benzoic acid (249°), and benzophenone (306°). In every case a blue color developed immediately. The process was reversible for all but the latter three high-boiling solvents, for which decomposition occurred following dinitroso formation. Similarly azo dioxides **3** (n = 1–4), **9**, **15** (benzophenone only), and **16** were heated in the indicated solvents. Either no color change took place on prolonged heating or the initially colorless solutions turned yelow and brown.[47] Not unexpectedly, the bicycloheptene system **3** (n = 1) proved to be most labile. It rapidly produced yellow-brown solutions in boiling acetic acid and ethylene glycol, solvents in which the other azo dioxides were inert.

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Registry No.—**1** (n = 1), 2721-32-6; **1** (n = 2), 3310-62-1; **1** (n = 3), 43195-77-3; **1** (n = 4), 32634-64-3; **2** (n = 1), 22509-00-8; **2** (n = 2), 25926-96-9; **2** (n = 3), 26081-83-4; **2** (n = 4), 25926-97-0; **3** (n = 1), 36335-10-1; **3** (n = 2), 36479-80-8; **3** (n = 3), 54143-30-5; **3** (n = 4), 54143-31-6; **4a**, 25927-00-8; **4a** corresponding azo alkene, 16104-45-3; **4b**, 54142-91-5; **5a**, 34098-80-1; **5a** corresponding azo alkene, 24046-80-8; **5b**, 54143-32-7; **6a**, 25926-99-2; **6b**, 54143-33-8; **8**, 54143-34-9; **9**, 54143-35-0; **11** (X = Cl), 54143-36-1; **15** (n = 1), 54142-97-1; **16** (n = 1), 54142-93-7; **17** (n = 1), 54142-96-0; **17** (n = 2), 54143-37-2; **17** (n = 2) diketone analog, 54143-38-3; **18** (n = 1), 54143-39-4; 18 (n = 2), 54143-40-7; **20** (n = 1), 54143-41-8; **23** (n = 2), 712-25-4; **23** (n = 1), 2958-72-7; **24** (n = 1), 54142-92-6; **25** (n = 2, Z = NOH), 54182-33-1; **26**, 54143-42-9; **27**, 54143-43-0; **28**, 37110-24-0; **29**, 54143-44-1; **30**, 54143-45-2; 6,7-diazatricyclo-[3.2.2.$0^{2,4}$]non-6-ene, 25368-34-7; 2,5-diamino-2,5-dimethylhexane, 23578-35-0; 3,3,6,6-tetramethylazocyclohexane, 19403-24-8; 5,5-dimethylcyclohexane-1,3-dione, 126-81-8.

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(30) The lower limit of visual detectability of a cyclic dinitroso alkane can be set at 10^{-3} *M*. For example, under spectrophotometric conditions an absorbance of 0.05, a path length of 5 cm, and an ϵ of 10.5 correspond to this concentration.[4f] Dinitroso *trans*-**13** absorbs in the visible at λ_{max} 645 nm (96% EtOH) with ϵ 53. A 1.2×10^{-3} *M* solution is an unambiguous pale blue, unnoticeable at 1.2×10^{-4} *M*. (cf. Experimental Section for comparisons with dinitroso *cis*-**13**.)
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Convenient Synthesis of Bicyclic and Polycyclic Cis Azo N,N′-Dioxides

Prithipal Singh

Contribution No. 57 from the Syva Research Institute, Palo Alto, California 94304

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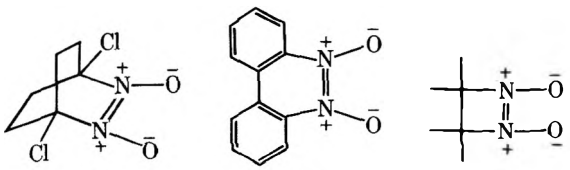
Two methods for the synthesis of bicyclic and polycyclic cis azo N,N′-dioxides are described. Oxidation of azo alkanes with trifluoroperacetic acid afford their corresponding azo N,N′-dioxides, while chlorination of 1,4-dioximes give the α,α′-dichloro azo N,N′-dioxides. Structures of all new compounds are supported by spectral data and elemental analysis.

One of the distinct properties of *C*-nitroso compounds is their tendency to dimerize to form azo *N,N′*-dioxides. The acyclic dimers can exhibit cis–trans configurational isomerism with the trans isomer generally being more stable than the cis isomer. Although many examples of trans azo dioxides are known, there are very few examples reported of cis azo dioxides. Certain cyclic azo *N,N′*-dioxides can only exist in their cis form, e.g., the azo dioxides **1–3**,[1,2] and are

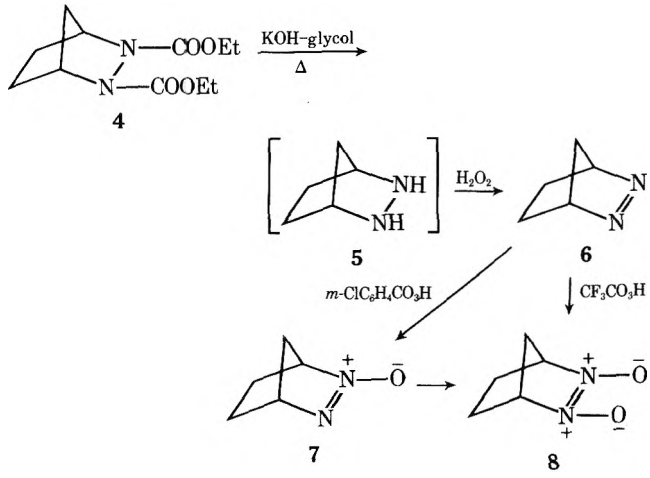


1 **2** **3**

obtained by the ring closure of their corresponding bis nitroso precursors. In connection with other work we needed bicyclic and polycyclic cis azo *N,N′*-dioxides and would like to report convenient synthetic routes to these compounds.[3]

The key intermediate to the synthesis of the azo dioxide **8** is 2,3-diazabicyclo[2.2.1]hept-2-ene (**6**), which was prepared in high yield according to Scheme I. The Diels–Alder adduct of cyclopentadiene and ethyl azodicarboxylate was hydrogenated and the product **4** was hydrolyzed with strong base in ethylene glycol.[4] Oxidation of the crude reaction mixture with 30% hydrogen peroxide gave the bicyclic

Scheme I



azo compound **6** in overall 97% yield from **4**. This observation is in contrast to Snyder's report of the formation of the cis azoxy compound **7** in 73% yield[5] from **5** under similar conditions. The monoxide could, however, be easily obtained in 80% yield by *m*-chloroperbenzoic acid oxidation of the azo compound **6**.[6] The use of hydrogen peroxide for oxidation of hydrazines, such as **5**, has a distinct advantage

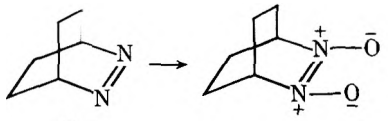
Table I
Physical Data of Bicyclic and Polycyclic Azo *N,N'*-Dioxides

Azo dioxide[a]	Yield,[b] %	Mp, °C (crystn solvent)	Ir,[c] cm^{-1}	Uv,[d] nm (ε)	NMR,[e] δ
8	75, 90[f]	153–154 dec ($CHCl_3$–C_6H_{12})	1485, 1420	265 (7850)	1.97 (d, J = 11 Hz, 1 H) 2.25 (br s, 4 H) 2.53 (d, J = 11 Hz, 1 H) 4.8 (br s, 2 H)
10	71	236–237 dec ($CHCl_3$)	1490, 1420	264 (8800)	1.8–2.4 (m, 8 H) 4.8 (br s, 2 H)
12	72	184–185 ($CHCl_3$–C_6H_6)	1495, 1430	271 (7000)	2.0 (s, 2 H), 2.36 (s, 3 H), 2.98 (br s, 1 H), 4.7 and 4.75 (singlets, 2 H)
16	91[g]	236–238 dec (C_2H_5OH)	1440, 1395	274 (7100)	1.72 and 2.1 (AB quartet, J = 12 Hz, $\Delta\nu_{AB}$ = 23 Hz, 2 H), 3.0–3.4 (m, 8 H)
18	7[g]	234–234.5 dec (CH_3CN)	1445, 1400[h]	273[i]	*i*
1[j]		165 dec (C_2H_5OH)	1445, 1395[h]	270 (7800)	*i*

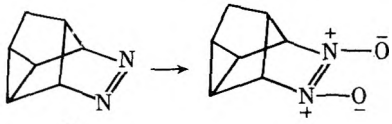
[a] Correct elemental analyses were obtained for all new compounds. [b] Unless stated otherwise the yield are from the corresponding cyclic azo compounds and are unoptimized. [c] Unless indicated otherwise the ir spectra were recorded in $CHCl_3$. [d] In C_2H_5OH. [e] In $CDCl_3$ with Me_4Si as an internal standard. [f] From the azoxy compound 7. [g] By chlorination of the corresponding 1,4-dioxime. [h] In KBr. [i] Not sufficiently soluble. [j] Earlier work, ref 11.

over the cupric chloride and the mercuric oxide methods in that it is less cumbersome and affords the azo compounds in high yield (see Experimental Section).[4,7,8]

Treatment of the azo compound **6** or its monoxide **7** with *m*-chloroperbenzoic and peracetic acid under a variety of conditions failed to give the dioxide **8**.[9] This is presumably due to the fact that the positively charged nitrogen in monoxide **7** considerably decreases the reactivity at the neighboring nitrogen to further oxidation. The oxidations of **6** and **7** to the dioxide **8** were accomplished,[10] however, in 75 and 95% yield, respectively, by use of trifluoroperacetic acid in methylene chloride. That the method of preparation of azo dioxides is general was demonstrated by high-yield conversion of the bicyclic and the quadricyclic azo compounds **9** and **11**[7,8] to the corresponding dioxides **10** and **12**.

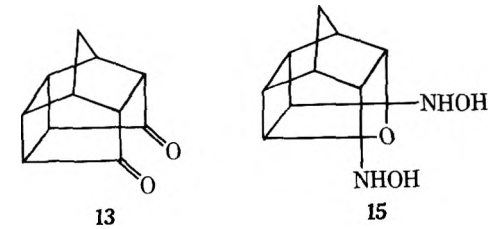


9 **10**

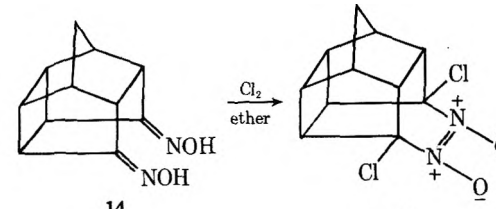


11 **12**

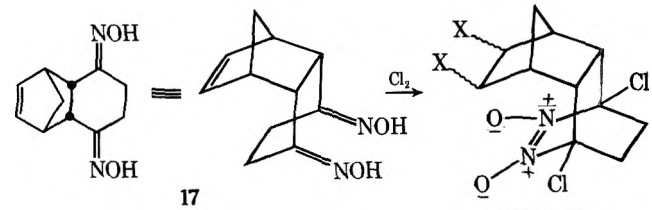
The bridgehead dichloro azo dioxide **1** has been prepared by chlorination of 1,4-cyclohexanedione dioxime.[11] We have now extended the utility of this reaction further in synthesizing polycyclic α,α'-dichloro azo *N,N'*-dioxides **16**, **18** and **21**. Treatment of cage diketone **13** with hydroxylamine gave the bis oxime **14** in 92% yield in contrast to Cookson's report of exclusive formation of oxa bird cage compound **15**.[12,13] A suspension of the dioxime **14** in a solution of excess chlorine in ether at low temperature afforded cleanly the cage azo dioxide **16** in over 90% yield. While the 60-MHz NMR spectrum was able to resolve only the apical proton as an AB quartet, the 300-MHz spectrum[14] afforded complete resolution of all of the different protons, thus supporting the proposed structure **16** (see Experimental Section). Similarly, chlorination of suspensions of tricyclic



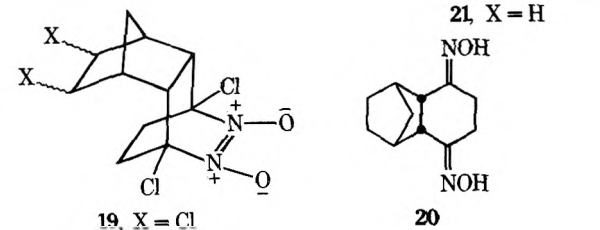
13 **15**



14 **16**



17 **18**, X = Cl; **21**, X = H



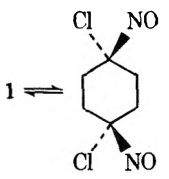
19, X = Cl; **22**, X = H **20**

bis oximes **17**[15] and **20**[16] gave high-melting azo dioxides **18** and **21** in poor yields, along with blue liquids which decomposed to a complex mixure during isolation. The stereochemistry of the azo dioxides **18** and **22** has not been rigorously established but is preferred over the alternative structures **19** and **22** on the basis of steric approach of chlorine from the least hindered side.[17,18]

The structures proposed for all of the azo *N,N'*-dioxides prepared are in accord with their analytical and spectral

properties (Table I). They are characterized by a pair of strong infrared bands between 1350 and 1500 cm^{-1} and strong $\pi-\pi^*$ ultraviolet absorption between 260 and 275 nm.

The bicyclic azo dioxide **1** on heating in a variety of solvents develops a deep blue color (characteristic of nitroso compounds). Color formation is reversible and is dependent on temperature and solvent, indicating its equilibrium with bis nitroso isomer **23**. In contrast to this observation



23

other bicyclic and polycyclic azo dioxides showed no color when they were heated in a variety of solvents.[19] Slow heating of the azo dioxides, in solid state, resulted in charring at their melting point.[20]

Although direct irradiation of the azo dioxides **8**, **10**, and **12** gave complex mixtures, these compounds have been found to be remarkably stable to sensitized photolysis. Like 3,3,4,4-tetramethyldiazatine 1,2-dioxide (**3**), the cis azo *N,N'*-dioxides are expected to have very low energy triplet states. Their efficiency as low energy triplet quenchers will be described elsewhere.[2,21]

Experimental Section[22]

2,3-Diazabicyclo[2.2.1]hept-2-ene (6). This azo compound was obtained as a white, crystalline solid by a modified procedure of Gassman and Mansfield.[4]

A slow stream of nitrogen was bubbled for 30 min through 50 ml of warm ethylene glycol in a 500-ml three-necked flask fitted with a constant-pressure dropping funnel and a reflux condenser equipped with a Drierite tube to protect from atmospheric moisture. The solution was stirred with a magnetic stirrer and potassium hydroxide (17 g) was added. When the potassium hydroxide had dissolved the solution was heated to 125°, and the diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate (**4**,[4] 13.5 g) was dropped in rapidly, maintaining the reaction temperature between 125 and 130°. The reaction mixture was stirred at ca. 125° for 1.5 hr and then diluted with 100 ml of water. The resulting solution was cooled and to the stirring solution was added dropwise 30% hydrogen peroxide solution (100 ml, excess) at room temperature. The reaction mixture was stirred for 2 hr,[23] diluted with water, and extracted with methylene chloride. The extract was washed with saturated aqueous sodium sulfite solution and water and dried. Removal of the solvent afforded the azo compound **6** as a dirty white solid (5.2 g, 97%). Recrystallization from pentane afforded white crystals: mp 98–99° (lit.[4] mp 99.5–100°); δ ($CDCl_3$) 0.7–1.8 (m, 6 H), 4.49 (broad s, 2 H).

2,3-Diazabicyclo[2.2.2]oct-2-ene (9). The 4-phenyl-2,4,6-triazatricyclo[5.2.2.$0^{2,6}$]undeca-3,5-dione[24] (2.2 g) in a 1:1 mixture of ethylene glycol–water (100 ml) was refluxed with potassium hydroxide pellets (3.3 g) under a slow stream of nitrogen. After 5 hr the reaction mixture was cooled and 30% hydrogen peroxide (20 ml) was adde carefully. The solution was stirred for 30 min and then refluxed for 1 hr. The aniline formed during the reaction was removed by steam distillation. The resulting product was diluted with water and extracted with chloroform. The organic layer was dried and removal of the solvent, under reduced pressure, at room temperature gave the bicyclic diazo compound **9** as a light brown solid (700 mg, 76%). The product was purified by preparative tlc (silica, chloroform–methanol, 9:1) and crystallization from *n*-hexane gave colorless needles: mp 145–146° (lit.[7] mp 146–147°); δ ($CDCl_3$) 1.2–2.1 (m, 8 H), 5.1 (broad s, 2 H).

6,7-Diazaquadricyclo[3.2.1.$1^{3,8}$.$0^{2,4}$]non-6-ene (11). The homoconjugate Diels–Alder adduct of ethyl azodicarboxylate to norbornadiene was hydrolyzed with potassium hydroxide according to Moriarty's method.[8a] The product was oxidized with 30% hydrogen peroxide as above and there was obtained the tetracyclic azo compound **11** as a thick oil which solidified on standing (1.06 g, 87%). This was homogenous on TLC (silica) in a variety of solvent systems and its spectral data were identical with that reported in the literature.[8]

Oxidation of the Cyclic Azo Compounds to Azo *N,N'*-Dioxides with Trifluoroperacetic Acid. A general method for the formation of cyclic azo dioxides from the azo compounds is given below.

Trifluoroperacetic acid was prepared from trifluoroacetic anhydride (46.2 g, 0.22 mol) in methylene chloride (50 ml) and 98% hydrogen peroxide (5.4 ml) according to Hart's[25] method. The crude 2,3-diazabicyclic compound **6** (9.6 g, 0.1 mol) in methylene chloride (21 ml) was added dropwise to an ice-cooled, stirring methylene chloride solution of trifluoroperacetic acid. The reaction mixture was stirred in the ice bath for 3 hr and at room temperature for an additional day. The oxidized reaction mixture was taken in a 1-l. beaker, cooled to 0°, and stirred with aqueous sodium bisulfite solution until it gave a negative test to potassium iodide–starch paper. The solution was neutralized carefully with saturated aqueous sodium bicarbonate and filtered. Continuous extraction of the filtrate with chloroform for 2 days furnished TLC-pure azo dioxide **8** (10.2 g, 80%) as a dirty white, crystalline solid. Decolorization with Norit A and recrystallization from chloroform–hexane afforded **8** as shining white microcrystals (9.5 g, 75%), mp 153–154° dec.

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.87; mol wt, 128. Found: C, 46.81; H, 6.39; N, 21.96; mol wt, 125.3.[26]

All azo dioxides are white, crystalline solids.

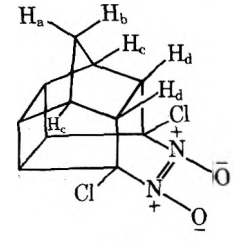
2,3-Diazabicyclo[2.2.1]hept-2-ene 2-Oxide (7). A solution of the diazo compound **6** (200 mg) in chloroform (20 ml) was stirred at room temperature with *m*-chloroperbenzoic acid (1.4 g) for 2 hr, and was then refluxed for 1 day. The reaction mixture was cooled and the excess peracid destroyed with 10% aqueous sodium sulfite. The organic layer was washed with 10% aqueous sodium bicarbonate and water and dried. Removal of the solvent under reduced pressure afforded a semisolid residue which by TLC and GLC was found to be only one compound. The product was purified by preparative tlc (silica, chloroform–methanol, 9:1) and there was obtained **7** (180 mg 80%) as easily sublimable white crystals: mp 93–95° (lit.[6] mp 93–95°); ν_{max} (CCl_4) 1515 cm^{-1}; λ_{max} (MeOH) 228 nm; δ ($CDCl_3$) 4.7 (broad s, 2 H), 1.5–2.4 (m, 6 H).

The azoxy compound **7** was oxidized in 90% yield to the azo dioxide **8** with trifluoroperacetic acid in methylene chloride.

Treatment of Cage Diketone 13 with Hydroxylamine Hydrochloride. Formation of Dioxime 14. A solution of the diketone **13** (20 g) and hydroxylamine hydrochloride (60 g) in ethanol (400 ml) and pyridine (200 ml) was heated under reflux for 4 hr, during which time most of the product crystallized out. The reaction mixture was cooled, stripped of the solvents under vacuum, and diluted with excess of water. The dioxime **14** was filtered, washed with water, and dried, mp 302–304° dec (lit.[13a] mp 302° dec). The yield of the dioxime was 24.3 g (92%). Sublimation at 120° (0.03 mm) afforded the analytical sample, mp 303–305° dec.

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.59; H, 5.82; N, 14.03.

Reaction of Cage Dioxime 14 with Chlorine. Formation of Dichloro Azo Dioxide 16. The dioxime **14** (20.4 g) was suspended in dry ether (1 l.) in a 2-l., three-necked flask equipped with a gas bubbler, a thermometer, and a drying tube. The reaction mixture was cooled in a Dry Ice–acetone bath and chlorine gas (ca. 20 g) was gently bubbled through the stirring suspension in the dark. The reaction mixture was warmed slowly to 10–15° and further stirred for 1.5 hr at this temperature. The white crystalline azo dioxide **16** was filtered and washed with ether, cold 5% aqueous sodium hydroxide, and water. The dried product weighed 22 g (91%, TLC pure). Recrystallization from ethanol gave **16** as white needles (19 g), mp 236–238° dec. The 60-MHz NMR ($CDCl_3$) spectrum showed apical protons as an AB quartet at δ 2.72 (H_a) and 2.10 (H_b) (J = 12 Hz, $\Delta\nu_{AB}$ = 23 Hz, 2 H) and a multiplet between δ 3.0 and 3.4 (8 H)



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The 300-MHz NMR spectrum ($CDCl_3$) exhibited signals at δ 1.70 (d, J = 12 Hz, 1 H, H_a), 2.08 (d, J = 12 Hz, 1 H, H_b), 3.07 (s, 2 H, bridgehead protons H_c), 3.1–3.2 (m, 4 H, cyclobutyl protons), and 3.24–3.30 (m, 2 H, H_d).

Anal. Calcd for $C_{11}H_{10}Cl_2N_2O_2$: C, 48.40; H, 3.66; Cl, 26.00; N, 10.23. Found: C, 48.32; H, 3.60; Cl, 25.71; N, 10.33.

Chlorination of 1,4-Dioxime 17. Formation of Tetrachloro Azo Dioxide 18. The tricyclic dioxime **17** (5 g) was suspended in dry ether (150 ml) in a three-necked flask equipped with a gas bubbler, a thermometer, and a drying tube. The reaction mixture was cooled to −40° and chlorine gas was bubbled through it. The contents of the flask were stirred for 90 min and then allowed to warm to room temperature. The solid was filtered. The greenish-blue filtrate was neutralized with solid sodium bicarbonate and washed with water. The organic layer was dried and evaporation of the solvent gave a blue semisolid residue which decomposed on standing for a few hours.

The solid obtained above, containing unreacted dioxime **17** and the azo dioxide **18**, was stirred with 5% sodium hydroxide in the cold. After 1.5 hr the solution was filtered and the filtrate was acidified (pH 6) with glacial acetic acid to furnish 1.8 g of recovered dioxime, mp 191–192° dec. The solid residue was washed with water and dried to give crude azo dioxide **17** (ca. 300 mg, 7%). The product was decolorized with Norit A and recrystallized from acetonitrile to afford colorless microcrystals of **17**, mp 234–234.5° dec.

Anal. Calcd for $C_{11}H_{12}Cl_4N_2O_2$: C, 38.15; H, 3.47; Cl, 41.10; N, 8.10. Found: C, 38.34; H, 3.57; Cl, 40.93; N, 8.00.

Chlorination of Dioxime 20. Formation of Azo Dioxide 21. A suspension of dioxime **20** (500 mg) in ether at −40° was treated with chlorine gas. Work-up as above afforded the azo dioxide **21** as a white solid: mp 226–230° dec (10 mg); λ_{max} (EtOH) 273 nm; mass spectrum (70 eV) m/e 278, 276 (M^+), 248, (M − NO), 218, 216 (M − 2NO), 183, 181 (M − 2NO − Cl).

Acknowledgments. The author is thankful to Dr. E. F. Ullman for helpful discussions.

Registry No.—**4**, 18860-71-4; **6**, 2721-32-6; **7**, 22509-00-8; **8**, 36335-10-1; **9**, 3310-62-1; **10**, 36479-80-8; **11**, 16104-45-3; **12**, 54142-91-5; **13**, 2958-72-7; **14**, 54142-92-6; **16**, 54142-93-7; **17**, 54142-94-8; **18**, 54142-95-9; **20**, 54142-96-0; **21**, 54142-97-1; 4-phenyl-2,4,6-triazatricyclo[5.2.2.0^{26}]undeca-3,5-dione, 30169-55-2; trifluoroperacetic acid, 359-48-8; hydroylamine hydrochloride, 5470-11-1; chlorine, 7782-50-5.

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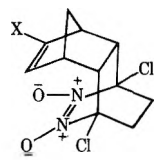
(14) I am thankful to Professor M. Anteunis, Organic Chemistry Department, State University of Gent, Gent, Belgium, for recording the 300-MHz nmr spectrum.

(15) (a) W. Albrecht, *Justus Liebigs Ann. Chem.*, **348**, 31 (1906); (b) A. Wassermann, *J. Chem. Soc.*, 1511 (1935).

(16) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 108 (1928).

(17) For a similar argument on stereochemistry of the azo dioxide **21** see ref 13b.

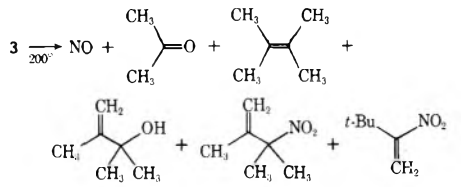
(18) We are yet unable to dehalogenate or dehydrohalogenate the compound **18** to unsaturated azo dioxide **24**, which should be capable of exhibiting an interesting through-space interaction of the two chromophores.



24a, X = H
b, X = Cl

(19) Ethanol solution of **1** (2×10^{-3} *M*) at 25° contains, at equilibrium, ca. 1% of the dinitroso compound **23**. Solutions of other azo dioxides are estimated to contain <0.05% of their open dinitroso isomers under similar conditions: P. Singh and E. F. Ullman, to be submitted for publication.

(20) The greenish-blue color obtained by heating 3,3,4,4-tetramethyldiazetine 1,2-dioxide (**3**) at its melting point is considered due to dissolved oxides of nitrogen. Thermolysis of **3** gives a complex mixture of which six compounds have been tentatively identified: P. Singh and E. F. Ullman, unpublished observations.



(21) P. Singh and E. F. Ullman, presented at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974, Abstract ORGN 78.

(22) Melting points were determined in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Solutions in organic solvents were dried over anhydrous magnessium sulfate. Uv spectra were recorded on a Cary 15 spectrophotometer and ir spectra were run on a Perkin-Elmer spectrophotomer. The NMR spectra were recorded on a Varian T-60 machine and the values are given in δ parts per million downfield from tetramethylsilane as internal standard.

(23) Further heating of the reaction mixture for 2 hr did not give any azoxy compound **7** (TLC and GLPC analysis); cf. ref 5.

(24) A. B. Evnin, D. R. Arnold, L. A. Karnischky, and E. Strom, *J. Am. Chem. Soc.*, **92**, 6219 (1970).

(25) H. Hart, R. M. Lange, and P. M. Collins, "Organic Syntheses", Collect. Vol. V, H. E. Baumgarten, Ed., Wiley, New York, N.Y., 1973, p 593.

(26) Determined in benzene with a Macrolab vapor pressure osmometer.

Cyclic Azo Dioxides. Preparation, Properties, and Consideration of Azo Dioxide–Nitrosoalkane Equilibria[1a,b]

Frederick D. Greene* and Kevin E. Gilbert[1c]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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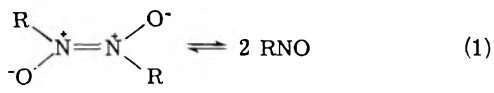
The cyclic azo dioxides, 3,3,6,6-tetramethyl-1,2-diazacyclohex-1-ene *N,N'*-dioxide (**1**), 1,4,4-trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-dioxide (**2**), and 3,3,4,4-tetramethyldiazetine *N,N'*-dioxide (**3**), have been prepared and examined. Azo dioxides **1** and **3** are resistant to oxidation but may be reduced to azoxy and/or azo, leading in the case of azo dioxide **3** to the novel four-membered-ring azo compound **10**, 3,3,4,4-tetramethyldiazetine. Photolysis of azo dioxides **1** and **2** affords the corresponding cyclic nitroxyl radicals (overall loss of NO). In solution, azo dioxide **2** is in equilibrium with the dinitroso compound; azo dioxides **1** and **3** give no evidence for the corresponding dinitroso forms. The equilibrium with azo dioxide **2** is solvent dependent, polar solvents favoring the azo dioxide form. In ethyl acetate, $\Delta H^\circ = 7 \pm 0.7$ kcal/mol; $\Delta S^\circ = 21 \pm 3$ gibbs/mol. Thermodynamic and kinetic considerations of azo dioxide dissociation are discussed. The results with **1**, **2**, and **3** are consistent with dissociation of azo dioxides via a "twisted" transition state, in general accord with orbital symmetry considerations. Attention is directed to the marked differences in properties, physical and chemical, of azo dioxides and nitroso species, and the potential control over the properties exhibited in a specific case by proper design to select the position of equilibrium desired.

Azo dioxides have been known for many years, including both cis and trans forms of which the latter are the more stable.[2] The functional group, possessing partial positive charges on adjacent nitrogens, has many aspects of interest, including (in a formal sense) the thermal cleavage of a double bond under mild conditions—dissociation of the azo dioxide to the corresponding nitroso compound (eq 1).



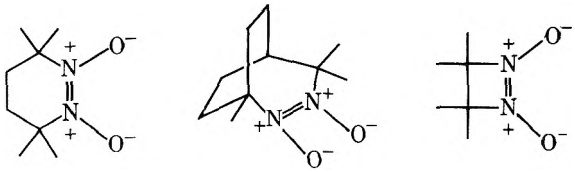
(1)

Both rates and equilibria have been studied for a number of acyclic systems.[2,3] The azo dioxide would appear to be a rather polar functional group; and the studies show considerable dependence on the nature of the solvent.[4] A theoretical study on the mechanism of dissociation and dimerization has appeared indicating a "non-least motion" path.[5] A few cyclic azo dioxides[1b,6] have been reported, including a compound to which a four-membered ring azo dioxide[7] structure was assigned.

The objective of the present study was to prepare some aliphatic cyclic azo dioxides and to examine the nature of this functional group, with special emphasis on the question of ring–chain isomerism.

Results

The three systems of interest in this study are **1**, **2**, and **3**.



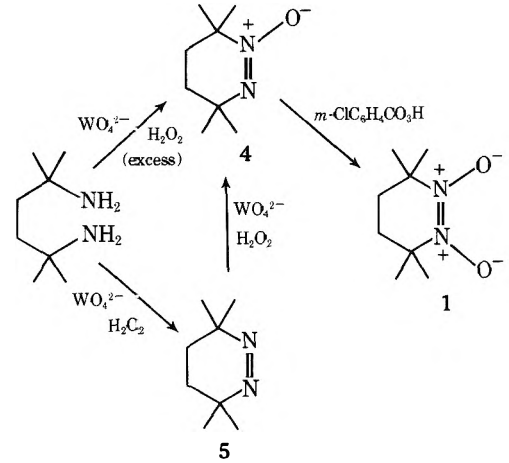
1 **2** **3**

Compound **1**, 3,3,6,6-tetramethyl-1,2-diazacyclohex-1-ene *N,N'*-dioxide, was prepared by peracid oxidation of the corresponding azoxy compound, **4**, in turn prepared by oxidative cyclization of the diamine by tungstate, hydrogen peroxide. This latter step, patterned after a method for the oxidation of amines to nitroso compounds,[3a] represents a new route to a nitrogen–nitrogen bond in cyclic systems. Cyclization takes place at an early point in the reaction, since the cyclic azo compound may be isolated by use of a limited amount of oxidant. The results are summarized in eq 2 and physical data in Table I.

Table I
Physical Data for Azo Dioxides 1–3

Compd	Ir, cm^{-1}	Uv,[a] nm (ε)	NMR	ESCA[b]
1	1460, 1420, 1335	273 (8100)	1.62 (12 H, s) 2.20 (4 H, s)	401.3
2	1480, 1390, 1325	277 (8100)	See text	
3	1540	255 (10,000)	1.59 (s)	401.4

[a] *trans*-$(CH_3NO)_2$, 276 nm (ε 10,700), *cis*-$(CH_3NO)_2$, 265 nm (ε 10,000); *trans*-(*i*-PrNO)$_2$, 280 nm (ε 10,000), *cis*-(*i*-PrNO)$_2$, 267 nm (ε 10,000), B. G. Gowenlock and J. Trotman, *J. Chem. Soc.*, 1670 (1956); *trans*-(*c*-$C_6H_{11}NO)_2$, 292, *cis*-(*c*-$C_6H_{11}NO)_2$, 278 (ref 2a). [b] E_b (N 1s) in electron volts, relative to E_b (N 1s) for $NaNO_3$ at 407.4 eV and for $NaNO_2$ at 404.3 (ref 13).



(2)

Compound **1** is assigned the intramolecular azo dioxide structure on the basis of its NMR, uv, mode of preparation, and reduction to the corresponding azoxy compound **4**.

Compound **1** is a stable, colorless solid. It melts with decomposition at 188–190°, giving no indication of a blue color (usually associated with the nitroso group). Various reagents effect reduction to azoxy, **4**, and to azo compound, **5** (e.g., Si_2Cl_6).[8] Compound **1** is resistant to further oxidation by aqueous permanganate or ceric ammonium nitrate.

Some reactions and nonreactions of **1** are summarized in eq 3–6.[9]

$$\mathbf{1} \xrightarrow[CHCl_3]{Si_2Cl_6} \mathbf{5} \quad (3)$$

$$\xrightarrow{LiAlH_4} \mathbf{4} \text{ and } \mathbf{5} \quad (4)$$

$$\underset{CHCl_3}{\overset{TCNE}{\rightleftharpoons}} \text{1:1 complex (red solution)} \quad (5)$$

$$p\text{-}(CH_3)_2NC_6H_4N(CH_3)_2, CHCl_3, 25^\circ \text{ NR} \quad (6a)$$

$$\text{galvinoxyl,}^9 C_6H_6, 25^\circ \text{ NR} \quad (6b)$$

$$SO_2, CHCl_3, 25^\circ \text{ NR} \quad (6c)$$

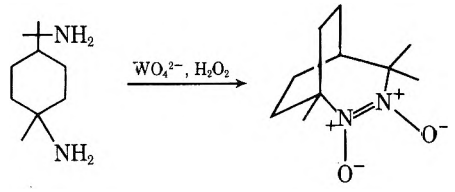
$$i\text{-PrNC, octane, } \Delta \text{ NR} \quad (6d)$$

$$\text{1,3-cyclohexadiene, } 150^\circ \text{ NR} \quad (6e)$$

$$Ce(NH_4)_2(NO_3)_6, CH_3CN\text{–}H_2O, \Delta \text{ NR} \quad (6f)$$

$$KMnO_4, H_2O, \Delta \text{ 12 hr NR} \quad (6g)$$

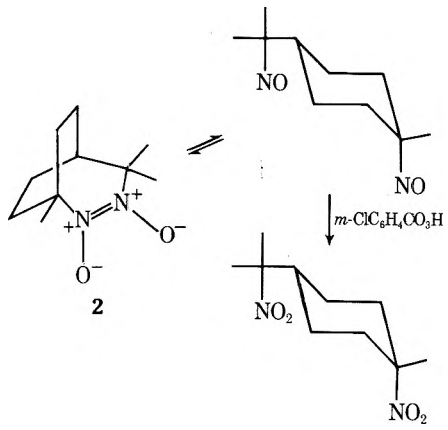
Compound **2**, 1,4,4-trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-dioxide, first reported by Rassat and Ray,[10] was prepared here in low yield by the oxidation of a cis–trans mixture of the diamine (eq 7). Compound **2** melts at



(7)

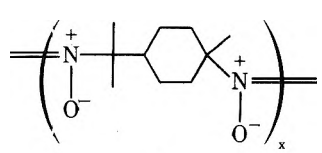
2

135–137° to a green liquid. Assignment of structure to **2** is based on the physical data (Table I), on equilibria data (eq 8 and Table II), and on oxidation in high yield to the corresponding dinitro compound (eq 9). Assignment of **2**, a well-



(8) (9)

defined crystalline solid, as an intramolecular cis azo dioxide rather than a polymeric azo dioxide, **6**, is based on the



6

volatility of the compound (sublimes unchanged) and on the independence of K (azo dioxide ⇌ dinitroso) on concentration. Detailed consideration of this equilibrium is taken up later in this paper.

Compound **3**, 3,3,4,4-tetramethyl-1,2-diazetine *N,N'*-dioxide was recently reported by Ullman and Singh as the product of oxidation of bis hydroxylamine **7** with bromine (eq 10).[7] Physical data are summarized in Table I. Com-

Table II
Equilibrium between 1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-Dioxide (2) and 1,8-Dinitroso-*p*-menthane (eq 8)

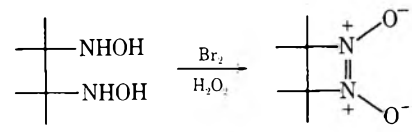
A. Effect of Solvent

Solvent	K_{eq} (39°)
Ethanol	~0.04
Chloroform	~0.07
Ethyl acetate	~0.3
Benzene	~0.3

B. Effect of Temperature on K in EtOAc

Temp, °C	K_{eq}
12	0.10
15	0.12
20	0.15
25	0.18
29	0.22
33	0.26
38	0.31
42	0.36

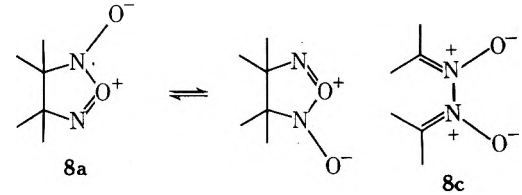
$\Delta H^\circ \simeq +7 \pm 0.7$ kcal/mol
$\Delta S^\circ \simeq +21 \pm 3$ gibbs/mol



(10)

7 **3**

pound **3**, a colorless solid, melts with decomposition at 190–192°. Solutions of **3** remain colorless on warming. The stability of **3** toward ring opening to a dinitroso species (in contrast to **2**) and the differences in uv and ir led us to consider other possible structures such as **8**. Rapid equilibra-

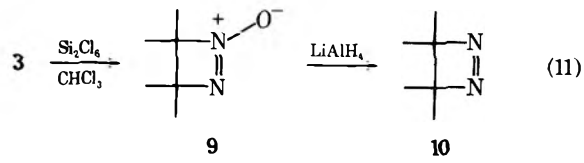


8a **8b** **8c**

tion between **8a** and **8b**[11a] could account for the observed sharp singlet in the proton NMR, which remained sharp to −100° (lowest temperature measured). For **8a** ⇌ **8b**, the formal charge on each nitrogen may be near zero. Consequently, ^{13}C NMR data were examined. The results (C_α 80.6, C_β 19.0 ppm downfield from Me_4Si in $CHCl_3$ solution) indicate that **3** is much closer to nitro alkanes than to amines[11b] and are supportive of the azo dioxide structure **3**.

ESCA data for **1** and **3** are included in Table I.[12] The single maximum in each spectrum and the similarity of the results for **1** and **3** are consistent with the azo dioxide structure assigned. The potential charge system (two adjacent, partially positively charged nitrogen atoms) makes detailed interpretation difficult. Work with suitable model systems may lead to good estimates of the amount of charge on the nitrogen atoms.

Compound **3** is reduced by Si_2Cl_6[8] to the corresponding azoxy compound. Further reduction (with $LiAlH_4$) affords the diazetine **10** (eq 11). (Under comparable conditions, azo dioxide **1** is reduced by Si_2Cl_6 to the azo compound, eq 3.) One other monocyclic Δ^1-1,2-diazetine (the 3,3,4,4-tetraflu-

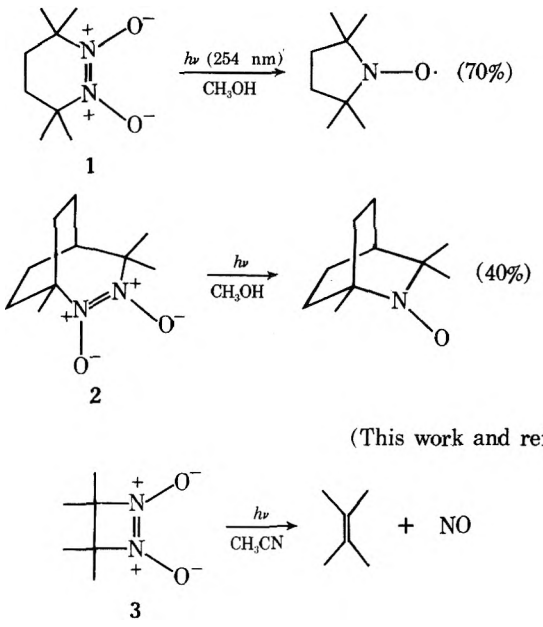


(11)

oro derivative)[13a] and three bicyclic derivatives[13b,c] have been reported. All of these diazetines, including **10**, are thermally rather stable. Pyrolysis of **10** at 130° in decane gives 2,3-dimethyl-2-butene and no acetone azine.

Photochemistry of Azo Dioxides 1, 2, and 3. Ullman and Singh observed a low-energy triplet state for azo dioxide **3** and described the products of photolysis in methanol.[7] We have briefly examined the photolysis of **1** and **2** (also examined by Rassat and Ray).[10] The results are summarized in Scheme I.

Scheme I



Complex Formation.[14] Azo dioxides **1** and **3** give red solutions with tetracyanoethylene in chloroform. The absorbing species for **1** has λ_{max} 490 nm and is a 1:1 complex of azo dioxide and TCNE. Ultraviolet and NMR evidence indicate that the equilibrium lies heavily on the side of the reactants, and azo dioxide can be recovered in high yield from the solution.

Azo Dioxide–Nitroso Equilibrium. As indicated above, the bicyclic azo dioxide **2** gives a blue solution on warming in benzene. Color formation is reversible and is dependent on temperature and solvent. The blue color (associated with the nitroso group) is observed on warming of solutions of **2** in solvents of E_T[15] less than 39. With more polar solvents ($E_T > 40$) the solutions remained colorless evennon heating to reflux, in general accordizith expectations that polar solvents should favor the azo dioxide form (eq 8).

The azo dioxide chromophore, λ_{max} 277 nm (ϵ 8100), has been used to measure the equilibrium. The small extinction coefficient for a nitroso group, coupled with the low solubility of **2** in nonpolar media and the one-sidedness of the equilibrium (favoring azo dioxide) in polar solvents, has prevented direct measurement of nitroso concentration. Qualitative values for K in several solvents are reported in Table IIA. In ethyl acetate the degree of ring opening to the dinitroso form was sufficient to determine K with greater confidence, and measurements were made over a 30° range in temperature. The results are summarized in Table IIB.

Table III
Thermodynamic Data for Azo Dioxide–Nitroso Equilibria
$R—N_2O_2—R \rightleftharpoons 2RNO$

R	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$ (20), kcal/mol	Solvent
tert-Butyl[a,b]	11.8	41.5	−0.4	CCl_4
Cyclohexyl[a,c]	20.6	41	8.6	C_6H_6
Cyclohexyl[a,d]	19.8	37	9.0	CH_3CN
Cyclohexyl[d,e]	17.4	37	6.6	CH_3CN
Benzyl[a,c]	20.4	36	9.9	C_6H_6

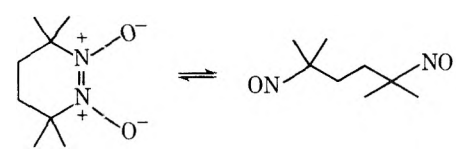
[a] Trans azo dioxide. [b] Reference 3a. [c] Reference 3b. [d] Reference 2a. [e] Cis azo dioxide.

In perdeuteriobenzene, a qualitative[16] indication of the position of equilibrium was obtained by Fourier transform proton NMR (solvent absorbance precluded the uv method). At 25° the major peaks are those for **2** at 1.28 (s, 6 H) and 1.37 (s, 3 H), with small peaks at 0.53 (s, 3 H) and 0.62 (s, 6 H) associated with the methyl groups of the dinitroso form. Upon warming to 70° the peaks for **2** decrease and those for the dinitroso form increase to an approximate[16] ratio of azo dioxide/dinitroso of 1.3:1. No indication of coalescence is observed. At high temperatures some decomposition occurs.

In contrast to **2**, the six-membered and four-membered azo dioxides **1** and **3** give no indication of formation of blue color on heating.

Discussion

Thermodynamic Considerations. Thermodynamic data for the dissociation of several acyclic azo dioxides to nitroso compounds are summarized in Table III. The enthalpy term favors the azo dioxide form, and the entropy term favors the nitroso form; both terms make important contributions to the free energy. What estimates are appropriate for equilibrium between cyclic azo dioxides and the corresponding dinitroso species? The ΔS^0 for a ring–chain isomerism should be considerably smaller than for a monomer–dimer interconversion. The ΔH^0 might be approximated by selecting a base value for the conversion of azo dioxide to nitroso and applying correction terms, as needed, for factors such as strain release. Thus, by extrapolation of the results of Table III, nonstrained cyclic azo dioxides should heavily favor the cyclic azo dioxide form over the dinitroso form. A highly strained system might be expected to favor the dinitroso form (or an "intermolecular azo dioxide" form). How well do these notions fit to available data on **1**, **2**, and **3**? A base value for ΔH^0 may be taken as +20 kcal/mol for the conversion of trans azo dioxide to nitroso in nonstrained cases (Table III) (the lower value for the *tert*-butyl case is attributed to strain from methyl–O^- interactions). The ΔH^0 for eq 12 might be expected to be a



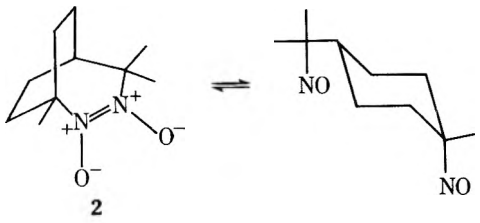
(12)

1

	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$, kcal/mol
estimated, gas phase, 20°	+18	+20	+12

little smaller than the ΔH^0 for the nonstrained azo dioxide cases (e.g., for the nitrosocyclohexane dimers of Table III the cis azo dioxide is 2.4 kcal/mol less stable than the trans isomer, acetonitrile solvent). A rough estimate of ΔS^0 for eq 12 is +20 gibbs/mol.[17] These considerations lead to the estimates for 1 shown in eq 12; compound 1 should be the more stable form and should remain so even at elevated temperatures (e.g., at 200°, $\Delta G^0 \sim >9$).

What would be appropriate estimates for equilibrium between azo dioxide 2 and the dinitroso species? A value for ΔH^0 may be obtained by combination of the above-derived value of ΔH^0 of +18 kcal/mol along with an assessment of the difference in strain energy between azo dioxide and the dinitroso species. The strain energy in 2 is estimated to be ~15 kcal/mol, using the corresponding olefin as a model for the azo dioxide.[18,19] An estimate of ΔH^0 for the ring opening of 2 is then +3 kcal/mol. The ΔS^0 should be positive, and somewhat smaller than for ring opening of 1, perhaps 10–15 gibbs/mol,[17] leading to the estimates for ring opening of 2 in eq 13.

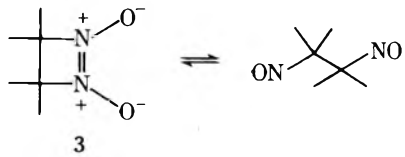


2 (13)

	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$, kcal/mol
estimated, gas phase, 20°	+3	10–15	~0
observed, EtOAc, soln, 20°	+7	+21	+1

The agreement, considering the rough nature of the estimates and the phase change, may be largely fortuitous. The principal point, however, is that the considerable strain in azo dioxide 2 which is relieved in the dinitroso species provides an adequate basis for the observation that the dinitroso species related to 2 *is* observed while that related to azo dioxide 1 *is not*.

Analysis of the four-membered ring azo dioxide 3 is made in the same way. For estimation of ΔH^0 for eq 14, the



3 (14)

	$\Delta H°$, kcal/mol	$\Delta S°$, gibbs/mol	$\Delta G°$, kcal/mol
estimated, gas phase, 20°	−12	positive	>−12

strain in 3 is approximated from the strain in cyclobutene (~30 kcal/mol).[19] The eclipsing interactions of the methyl groups in 3 (several kilocalories/mole) is considered to be largely balanced by strain remaining in the dinitroso species. The ΔS^0 should still be positive but smaller than ΔS^0 for 2. The estimated values indicate that ΔG^0 at 20° is at least −12 kcal/mol. The experimental observation, however, is that 3 exists in the azo dioxide form, is quite stable to heat, and gives no indication of ring opening to the dinitroso form even at elevated temperatures.[20]

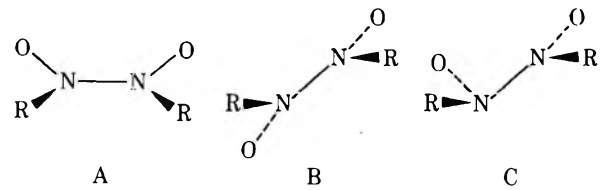
The apparent existence of 3 in the azo dioxide form might be explained in two different ways: (a) equilibrium control, with azo dioxide 3 more stable than the dinitroso form, associated with a much lower value for the strain energy in the four-membered ring azo dioxide than estimated above, or (b) rate control, with azo dioxide 3 less stable than the dinitroso form but with a substantially greater activation barrier to ring opening than that associated with the opening of, e.g., 2. Although we do not feel that the first explanation, a, can be summarily dismissed at this point, we think that the strain energy estimate for 3 is reasonable and also think that there is good reason mechanistically for explanation b, as indicated below.

Kinetic Considerations. Free energies of activation for dissociation of acyclic azo dioxides are in the range 21–28 kcal/mol.[3c] For bicyclic azo dioxide 2, we can make some estimates in the following way. Peaks for both the azo dioxide 2 and the dinitroso species are seen in the NMR (separation, 50 Hz) in benzene and give no indication of coalescing up to 70°. Thus the rate constants for ring opening and closing must be no faster than 30 sec^{-1} at room temperature. Rapid mixing of a solution of 2 in ethyl acetate, cooled to 10°, with an equal volume of solvent at 40° afforded the final equilibrium value before measurement was started (~5 sec), setting a lower limit of 0.3 sec^{-1} on the rate of ring opening. These limits indicate a ΔG^0 for ring opening of 2 in the range 16–19 kcal/mol at 25°.

Azo dioxide 3 is stable up to 150°. A minimum estimate of ΔG^0 for ring opening at 150° is 35 kcal/mol (with the assumption that 3 is less stable than the dinitroso form).

To summarize: Compound 1 exists in the azo dioxide form and gives no indication of ring opening to the dinitroso form; these findings are consistent with estimates for ΔG^0, ΔH^0, and ΔS^0. Compound 2 is isolated in the azo dioxide form; in solution it is in equilibrium with the ring-opened dinitroso form; these findings also are consistent with estimates for ΔG^0, ΔH^0, and ΔS^0. Compound 2 differs from 1 in ring strain (~15 kcal/mol) which is relieved on going from azo dioxide to dinitroso; compound 2 uses this driving force to surmount the activation barrier at a total cost of 16–19 kcal/mol instead of the usual 21–28 kcal/mol. Compound 3 is isolated in the azo dioxide form, would appear to have considerably greater strain than 2, but gives no indication of ring opening, appears unable to use the strain to aid in ring opening.

These findings, at first sight anomalous, appear well fitted to the considerations of Hoffmann, Gleiter, and Mallory[5] on "non-least motion" modes of dissociation of an azo dioxide group. Dissociation by stretching of the nitrogen–nitrogen bond while retaining coplanarity of the N_2O_2 moiety is "symmetry forbidden".[21] Allowed paths involve twisting about the nitrogen–nitrogen bond. Many variants are possible, involving the different locations for the two oxygen atoms relative to the R's and the N's, e.g., B and C.

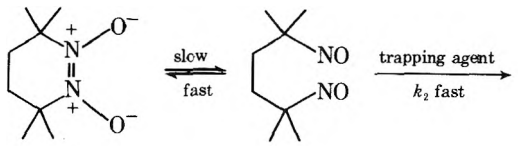


A B C

Although both 2 and 3 are strained systems, they are of different types. Examination of models suggests that the strain in 2 is in part a torsional strain, relieved by twisting about the nitrogen–nitrogen bond; i.e., the type of strain in 2 *decreases* the barrier between reactant and an "orbital symmetry allowed" transition state. In compound 3, however, the small angles force the system to be planar; twisting about the nitrogen–nitrogen bond would produce an increase in angle strain elsewhere in the system; i.e., the type of strain in 3 may *increase* the barrier between reactants and the proposed transition state.

In compound 1, a "twisted" transition state should be ac-

cessible, and perhaps at not much greater cost than the activation barriers for other strain-free cases. The lack of observation of any dinitroso form for this case may be due simply to a high rate of ring closure. Establishment of the barrier to ring opening might be possible by a sequence as shown in eq 15. Efforts to date to find reagents sufficiently



(15)

1

reactive to trap an intermediate dinitroso species have been unsuccessful (e.g., see eq 6): refluxing 1 in aqueous permanganate for 12 hr led only to recovery of **1**, indicating both the need for a more effective trapping agent and the high stability of the azo dioxide to further oxidation.

The likelihood that **3** is less stable than the corresponding dinitroso species has prompted attempts to synthesize the latter and to examine the reaction by which **3** is formed from the bis hydroxylamine **7** (eq 10): (a) oxidation of **7** with tungstate–hydrogen peroxide gave acetone oxime in low yield and no **3**; (b) the azoxy compound, prepared separately, is not the precursor of **3**; (c) use of a large excess of bromine in the oxidation of **7** still afforded **3** in high yield, suggesting that the iminoxyl radical $(CH_3)_2C{=}NO\cdot$ is not the precursor of **3**. Thus, the actual precursors of **3** are not known (probably are *N*-bromo species) but the dinitroso compound is not a required intermediate.

The few examples described here point to many additional aspects for investigation in the azo dioxide–nitroso species equilibria, and more generally in the little-investigated area of ring–chain isomerism in aprotic systems. Of particular interest are the marked differences in properties (solubility, reactivity) of azo dioxides and nitroso species, and potential control over the properties exhibited by a specific system by proper design to select the position of equilibrium desired.

Experimental

3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N*-Oxide (4). 2,5-Diamino-2,5-dimethylhexane (30 g, 0.208 mol) (Aldrich) and sodium tungstate dihydrate (3 g, 9.1 mmol) were dissolved in 200 ml of distilled water and cooled while hydrogen peroxide (95 g of a 30% solution, 0.832 mol) was added slowly. The rate of peroxide addition was such that the temperature of the reaction never rose above 30°. The solution was stirred for 1 hr and then extracted with 3 × 100 ml of 2 *N* HCl and 2 × 100 ml of distilled water and dried ($MgSO_4$), and the chloroform was removed under reduced pressure. The residue was recrystallized from pentane: yield 23.5 g (72.5%); mp 119–121°; uv (pentane) λ_{max} 234 nm (ϵ 9350); ir ($CHCl_3$) 2960 (s), 1470 (s), 1395 (w), 1370 (m), 1345 (w), 1310 (m), 1215 (s), 1180 (w), 1130 cm^{-1} (w); NMR ($CDCl_3$) 1.35 (s, 6 H), 1.61 (s, 6 H), 1.90 ppm (m, 4 H); mass spectrum *m/e* (rel intensity) 156 (69), 141 (20), 111 (48), 96 (24), 87 (48), 69 (56), 57 (84), 56 (100), 55 (50).

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.51; H, 10.32. Found: C, 61.42; H, 10.49.

3,3,6,6-Tetramethyl-1,2-diazacyclohexene (5). 2,5-Diamino-2,5-dimethylhexane (10 g, 0.069 mol), sodium tungstate dihydrate (0.5 g, 1.5 mmol), and hydrogen peroxide (15.7 g of a 30% solution, 0.139 mol) were allowed to react as above. After the chloroform was removed under reduced pressure, the solution was filtered to remove the 3,3,6,6-tetramethyl-1,2-diazacyclohexene *N*-oxide (4), 1.65 g (15.5%). The residue was distilled, giving 4.0 g, bp 48–50° (4.2 mm), of a mixture of the starting material and 3,3,6,6-tetramethyl-1,2-diazacyclohexene (5). Analysis of this mixture by NMR indicated that 72% was compound **5**, which corresponds to a 33% yield. Compound **5** may be obtained in pure form by washing the mixture with 2 *N* HCl, drying ($MgSO_4$), and removing all solvents under reduced pressure: ir (CCl_4) 2960 (s), 1565 (m), 1475 (s), 1460 (s), 1380 (s), 1360 (s), and 1340 cm^{-1} (s) [lit.[22] ir (CCl_4) 1565 cm^{-1}]; NMR (CCl_4) 1.28 (s, 12 H) and 1.48 ppm (s, 4 H) [lit.[22] NMR (CCl_4) 1.25 (s, 12 H) and 1.45 ppm (s, 4 H)].

3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N,N'*-Dioxide (1). 3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N*-oxide (4, 5 g, 0.032 mol) and *m*-chloroperbenzoic acid (6.5 g, 85% peracid, 0.032 mol) were dissolved in 100 ml of methylene chloride and stirred for 2 days. The solution was filtered, saturated with dry NH_3, and filtered again.[23] The solvent was removed under reduced pressure to give a white, crystalline solid, **1**, recrystallized from a mixture of $CHCl_3$ and CCl_4: yield 4.0 g (72%); mp 188–190° dec; uv (CH_3OH) λ_{max} 273 nm (ϵ 8160); ir ($CHCl_3$) 2980 (s), 1470 (sh), 1460 (m), 1410 (m), 1370 (m), 1335 (s), 1250 (m), 1125 cm^{-1} (m); NMR ($CDCl_3$) 1.62 (s, 12 H), 2.20 ppm (s, 4 H); mass spectrum *m/e* (rel intensity) 172 (16), 142 (24), 112 (5), 86 (8), 74 (46), 69 (43), 57 (19), 56 (100), 55 (26), 41 (54).

Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.78; H, 9.37. Found: C, 55.61; H, 9.48.

1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-Dioxide (2). *cis*- and *trans*-1-Methyl-4-(1-amino-1-methylethyl)-cyclohexylamine (10 g, 0.058 mol, technical grade) and sodium tungstate dihydrate (0.5 g, 1.5 mmol) were dissolved in 50 ml of H_2O and cooled while hydrogen peroxide (26.7 g of a 30% solution, 0.236 mol) was added slowly. The reaction mixture was stirred for 2 hr while slowly warming to room temperature and then extracted into $CHCl_3$. The $CHCl_3$ was washed with H_2O and dried ($MgSO_4$) and the solvent was removed under reduced pressure. Diethyl ether was added to the residue, at which point the cis azo dioxide **2** crystallized from solution. The cis azo dioxide can be recrystallized from tetrahydrofuran, and it sublimes unchanged at 115° (0.17 mm): yield 0.90 g (8%); mp 135–137° (to a green liquid that resolidifies to a greenish material) (lit.[10] mp 161°; in spite of this difference in melting point, the compounds are thought to be the same, based on the available physical and chemical data); ir ($CHCl_3$) 2980 (m), 1470 (m), 1450 (sh), 1380 (m), 1350 (m), 1340 (m), and 1325 cm^{-1} (m); NMR ($CDCl_3$) 1.60 (s, 3 H), 1.66 (s, 6 H), 2.04 ppm (m, 9 H); uv (EtOH) λ_{max} 277 nm (ϵ 8100).

Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.57; H, 9.15. Found: C, 60.57; H, 9.14.

3,3,4,4-Tetramethyldiazetine *N,N'*-Dioxide (3). 2,3-Dihydroxylamino-2,3-dimethylbutane[24] (2.40 g, 0.016 mol) and sodium carbonate (3.36 g, 0.032 mol) were dissolved in 20 ml of H_2O and stirred while bromine (5.1 g, 0.032 mol) was added dropwise. After 10 min the solution was extracted into $CHCl_3$, washed with H_2O, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 1.78 g (77%) of the diazetine dioxide: mp 190–192° dec (lit.[7] mp 190–192° dec); ir ($CHCl_3$) 2980 (m), 1560 (m), 1465 (s), 1380 cm^{-1} (m); NMR ($CDCl_3$) 1.59 ppm (s); mass spectrum *m/e* (rel intensity) 144 (6.5), 114 (16), 84 (69), 69 (100), 41 (58).

Reduction of 3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N,N'*-Dioxide (1). A. With Hexachlorodisilane.[8] Compound **1** (0.10 g, 0.58 mmol) was stirred in 5 ml of dry $CHCl_3$ under a nitrogen atmosphere while hexachlorodisilane (0.20 ml, 1.2 mmol) was added. The solution was stirred for 1 hr and then quenched with 1 *N* NaOH, washed with H_2O, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 0.083 g (99%) of a yellow oil whose ir spectra were identical with the ir spectra of 3,3,6,6-tetramethyl-1,2-diazacyclohexene (5).

B. With Lithium Aluminum Hydride. Compound **1** (0.2 g, 1.16 mmol) and lithium aluminum hydride (excess) were stirred in 20 ml of anhydrous diethyl ether for 1 hr. Work-up afforded 0.1 g of an oil; NMR analysis indicated azo, azoxy, and azodioxy compounds **5**, **4**, and **1** in the ratio 4:2:1.

Attempted Reactions of Azo Dioxide 1. Several unsuccessful attempts were made to react 3,3,6,6-tetramethyl-1,2-diazacyclohexene *N,N'*-dioxide (**1**) with different reagents. The results are summarized in eq 6.

Reaction of 1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-Dioxide (2) with *m*-Chloroperbenzoic Acid. Compound **2** (0.124 g, 0.626 mmol) and *m*-chloroperbenzoic acid (0.27 g, 87% peracid, 1.33 mmol) were dissolved in 10 ml of benzene, refluxed for 2 hr, and then stirred at room temperature overnight. Dry NH_3 was bubbled through the solution and the precipitate was filtered.[23] The solvent was removed under reduced pressure to give 0.129 g (89%) of 1,8-dinitro-*p*-menthane [1-(1-methyl-1-nitroethyl)-4-*t*-methyl-4-*c*-nitrocyclohexane]: mp 103–104° (lit.[25] mp 104–106° from oxidation of a cis–trans mixture of diamines); ir ($CHCl_3$) 2940 (m) 1535 (s), 1450 (m), 1400 (m), 1375 (m), 1350 (m), and 1210 cm^{-1} (br); NMR ($CDCl_3$) 1.48 (s, 6 H) and 1.53 ppm (s, 3 H).

Reaction of 3,3,4,4-Tetramethyl-1,2-diazetine *N,N'*-Dioxide (3) with Hexachlorodisilane. Compound 3 (0.6852 g, 4.75 mmol) and hexachlorodisilane[8] (0.9 ml, 4.8 mmol) were dissolved in 25 ml of dry $CHCl_3$ under a nitrogen atmosphere. The solution was stirred at room temperature for several hours and then quenched with 5 ml of 1 *M* NaOH. The $CHCl_3$ layer was separated, washed with H_2O, dried (K_2CO_3), and the solvent removed under reduced pressure to give 0.6068 g (99%) of 3,3,4,4-tetramethyldiazetine *N*-oxide (9): mp 168–169° (lit.[7] mp 170°); ir ($CHCl_3$) 2990 (s), 1555 (s), 1470 (m), 1465 (m), 1400 (m), 1390 (s), 1380 (s), 1265 (m), and 1215 cm^{-1} (br); NMR ($CDCl_3$) 1.47 (s, 6 H) and 1.52 ppm (s, 6 H).

3,3,4,4-Tetramethyl-Δ^1-1,2-diazetine (10). 3,3,4,4-Tetramethyldiazetine *N*-oxide (0.1006 g, 0.853 mmol) and an excess of $LiAlH_4$ were dissolved in 15 ml of anhydrous ether and stirred at reflux under a nitrogen atmosphere for 1 hr. The remaining hydride was quenched with wet ether, the solution was extracted with H_2O, and the ether phase was dried (K_2CO_3). The ether was removed by distillation through a Vigreux column with a total reflux stillhead and the residue was recrystallized from diethyl ether at −78° to give 0.0208 g (22%) of 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine, a volatile solid: mp 83–85°; ir ($CHCl_3$) 2970 (s), 1480 (m), 1450 (w), 1390 (w), 1375 (s), 1220 (br), and 1140 cm^{-1} (m); NMR ($CDCl_3$) 1.15 ppm (s); uv (pentane) highly structured 325 nm (ϵ 57), 333 (86), 340 (121), 347.5 (136), 356 (103); mass spectrum *m/e* (rel intensity) 112 (2), 97 (2), 84 (39), 69 (100), 55 (18), 41 (100). Pyrolysis of **10** at 130° in decane afforded 2,3-dimethyl-2-butene (>80% yield), identified by comparison with authentic material. No other products were seen in the VPC trace of the reaction mixture. An authentic sample of acetone azine was prepared, and shown not to be a product of thermolysis of diazetine **10**.

ESCA Spectra of 3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N,N'*-Dioxide (1) and 3,3,4,4-Tetramethyldiazetine Dioxide (3). The photoelectron spectra of the nitrogen 1s electrons of the azo dioxides were obtained on a Hewlett-Packard 5958 ESCA spectrometer using Al Kα irradiation. The samples were prepared by grinding up weighed amounts of azo dioxide and a standard, either $NaNO_3$ or $NaNO_2$, adding graphite, and pressing into a pellet.[26] Each azo dioxide was run with both standards to determine the peak positions. The graphite pellets were placed in a sample holder in the instrument, and the entire system was pumped down to 10^{-8} Torr. The spectra were obtained at 10^{-8} Torr and ambient temperature. Results are summarized in Table I.

Photolysis of Azo Dioxides in Methanol at 254 nm. A. Compound 1 (0.2047 g, 1.19 mmol) was dissolved in 50 ml of MeOH and purged with dry nitrogen for 30 min. The solution was irradiated for 2.5 hr in a Rayonet reactor at 254 nm in a quartz vessel. The MeOH was removed by distillation through a Vigreux column with a total reflux stillhead and the residue was analyzed by VPC on 15% SE-30 (temperature programmed at 80° and 2°/min), showing one major peak corresponding to an 80% yield of the nitroxyl radical, 2,2,5,5-tetramethylpyrrolidine-*N*-oxyl: ir ($CHCl_3$) 2960 (s), 1460 (m), 1370 (m), 1330 (w), and 1210 cm^{-1} (m); uv (EtOH) λ_{max} 232 nm (ϵ 2850), 400 (14) [lit.[27] uv (MeOH) λ_{max} 233 nm (ϵ 2500), 410 (6)]; ESR (cyclohexane) triplet a_N 13.5 G.

B. Compound 2 (0.100 g, 0.503 mmol) was dissolved in 50 ml of MeOH, irradiated, and worked up as described above. VPC on 15% SE-30 showed only one major product, in 41% yield, identified as the nitroxyl radical, 1,3,3-trimethyl-2-azabicyclo[2.2.2]octane-*N*-oxyl: ir ($CHCl_3$) 2920 (s), 1465 (m), 1455 (s), 1375 (m), and 1355 cm^{-1} (m); uv (MeOH) λ_{max} 246 nm (ϵ 2020) and 418 (12) [lit.[10] uv λ_{max} 238 nm (ϵ 2480) and 450 (10.4)]; ESR (cyclohexane) triplet, a_N 15.0 G.

3,3,6,6-Tetramethyl-1,2-diazacyclohexene *N,N'*-Dioxide (1) and Tetracyanoethylene. Compound 1 (8.6 mg, 0.05 mmol) and tetracyanoethyene (6.4 mg, 0.05 mmol) were mixed as solids and a red color soon developed. When the mixture was dissolved in 2 ml of $CDCl_3$ the solution was bright red, and the NMR of the solution was identical with the NMR of pure 1: NMR ($CDCl_3$) 1.62 (s, 12 H) and 2.20 ppm (s, 4 H). The uv and visible spectrum showed absorptions due to 1, TCNE, and a new band at 490 nm. The dependence of the intensity of the band at 490 nm on the concentration of the TCNE and azo dioxide 1 indicated a 1:1 complex.[28] The NMR results (above) indicate that $K \ll 1$. 3,3,4,4-Tetramethyldiazetine dioxide (3) and TCNE react to give an orange-colored solution in chloroform with λ_{max} 452 nm.

Study of the Equilibrium between 1,4,4-Trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-Dioxide (2) and 1,8-Dinitrosomenthane. The equilibrium constant for this system was determined in a variety of solvents by measuring the concentration of azo dioxide as a function of temperature by ultraviolet or NMR spectroscopy.

A weighed amount of azo dioxideiwas dissolved in a pure solvent and diluted to the proper concentration at ambient temperature. The ultraviolet spectrum was determinednon a Guilford Model 222 spectrometer equipped with a thermostatted cell, a nitrogen inlet to purge the cell compartment, and a copper–constantan thermocouple to measure the temperature of the cell. The temperature of the cell was regulated by a Haake constant-temperature circulating bath in the temperature range of 5–45°. Below 0° a Cary instrument with low-temperature cell compartment was used; dry nitrogen was passed through a heat exchanger cooled by liquid nitrogen and then into the thermostatting section of the cell compartment. The sample was placed in a glass-stoppered quartz uv cell and several determinations of the absorbance over the temperature range were recorded. All work was done at the wavelength of maximum absorption. The results are summarized in Table III and in the microfilm edition.[28]

A 7.3×10^{-2} *M* solution of 2 in $CHCl_3$ was studied by variable temperature visible spectrometry. The change in the absorbance at 700 nm (nitroso) was from 0.012 to 0.016 when the temperature was changed from 20 to 40°, not large enough to give reliable results.

Estimation of Rates of Ring Opening and Closing. A. From NMR Evidence. The NMR spectrum of 1,4,4-trimethyl-2,3-diazabicyclo[3.2.2]non-2-ene *N,N'*-dioxide (2) in benzene shows methyl peaks assignable to azo dioxide and to nitroso approximately 50 Hz apart. No broadening is seen with increasing temperature up to 70°, at which point decomposition of sample begins indicating an upper limit of 30 sec^{-1} for the rate of ring opening at room temperature.

B. Modified "Temperature Jump." A solution of 2 in ethyl acetate at 10° was rapidly mixed with an equal volume of pure ethyl acetate at 40° in a uv cell thermostatted at 25°. No change in the absorbance of the solution as a function of time was observed, i.e., equilibrium was established upon mixing, indicating a τ of less than 2 sec. The expected change in the absorbance was from 0.494 to 0.445. From these results a lower limit to the rate of ring opening and ring closing is 0.3 sec^{-1}.

Control Experiments on the Oxidation of 2,3-Dihydroxylamino-2,3-dimethylbutane with Bromine. A. Use of 1 Equiv of Bromine. To a solution of 2,3-dihydroxylamino-2,3-dimethylbutane (0.20 g, 1.35 mmol) and sodium carbonate (0.5 g, 4.8 mmol) in 10 ml of H_2O was slowly added a solution of bromine (0.216 g, 1.35 mmol) in 10 ml of H_2O. The solution was stirred for 30 min, extracted into $CHCl_3$, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 0.10 g (51%) of 3,3,4,4-tetramethyldiazetine dioxide (3), mp 190–192° (lit.[7] mp 190–192°).

B. Use of 10 Equiv of Bromine. To a solution of 2,3-dihydroxylamino-2,3-dimethylbutane (0.20 g, 1.35 mmol) and sodium carbonate (0.50 g, 4.8 mmol) in 10 ml of H_2O was added bromine (2.1 g, 13.5 mmol). The solution was stirred for 30 min, extracted into $CHCl_3$, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 0.193 g (99%) of 3,3,4,4-tetramethyldiazetine dioxide (3), mp 190–192° (lit.[7] mp 190–192°).

C. Reaction of 3,3,4,4-Tetramethyldiazetine *N*-Oxide (9) with Bromine. Compound 9 (0.10 g, 0.78 mmol) and sodium carbonate (0.50 g, 4.8 mmol) were dissolved in approximately 50 ml of warm water. The water solution was warmed slightly to ensure the dissolution of all the azoxy. Bromine (0.50 g, 3.12 mmol) was added and the solution was stirred for 3 hr, extracted into $CHCl_3$, and dried ($MgSO_4$). The solvent was removed under reduced pressure, giving 90% recovery of the starting material: mp 166–168°; ir identical with ir of starting material.

Registry No.—**1**, 54143-35-0; **2**, 34122-40-2; **3**, 34493-89-5; **4**, 54143-34-9; **5**, 19403-24-8; **7**, 14384-45-3; **9**, 40543-89-3; **10**, 54166-22-2; 1,8-dinitroso-*p*-menthane, 54166-23-3; 2,5-diamino-2,5-dimethylhexane, 23578-35-0; *cis*-1-methyl-4-(1-amino-1-methylethyl)cyclohexylamine, 54166-24-4; *trans*-1-methyl-4-(1-amino-1-methylethyl)cyclohexylamine, 54166-25-5; 1,8-dinitro-*p*-menthane, 54166-26-6; 1,3,3-trimethyl-2-azabicyclo[2.2.2]octane-*N*-oxyl, 34122-41-3; 2,2,5,5-tetramethylpyrrolidine-*N*-oxyl, 3229-53-6.

Supplementary Material Available. Supporting data for the TCNE–azo dioxide 1:1 complex and for determination of position of equilibrium with azo dioxide 2 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 $2.50 for microfiche, referring to code number JOC-75-1409.

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(16) Methylene protons of both **2** and 1,8-dinitroso-*p*-menthane fell underneath the methyl groups of **2**. However, it was possible to estimate the relative amounts of **2** and 1,8-dinitroso-*p*-menthane by measuring the height and the width at half height of the signals due to the methyl groups of the two compounds.
(17) Associated primarily with rotations in dinitroso that are "frozen out" in azo dioxide; see S. W. Benson, "Thermochemical Kinetics", Wiley, New York, N.Y., 1968, Chapter 2.
(18) The strain energy in bicyclo[3.2.2]nonane is ~15 kcal/mol [E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, 95, 8005 (1973)]; the *difference* in strain energy between *cis*-cycloheptene and cycloheptane is ~0 (see ref 19), on which grounds an estimate of ~15 kcal/mol is obtained for the strain in bicyclo[3.2.2]non-2-ene. Methyl interactions in reactant and product are not included in this estimate.
(19) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Am. Chem. Soc.*, **92**, 2377 (1970).
(20) Whether the dinitroso form would exist as such, close to **8a**, or dissociate to the iminoxyl radical $(CH_3)_2C{=}NO\cdot$ is not known.
(21) This point was also recognized by Gowenlock and Luttke (see ref 2b and ref 5, 1461).
(22) N. A. Porter, Ph.D. Thesis, Harvard University, 1969.
(23) Weiwish to thank Dr. Peter Chao for this suggestion, constituting a usefulizay to work up peracid reactions.
(24) M. Lamchen and T. W. Mittag, *J. Chem. Soc. C*, 2300 (1966). For preparation of the precursor, 2,3-dinitro-2,3-dimethylbutane, see S. Limatibul and J. W. Watson, *J. Org. Chem.*, **37**, 4491 (1972).
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(27) H. Dupeyre, H. Lemaire, and A. Rassat, *Tetrahedron Lett.*, 1781 (1964).
(28) Supporting data are reported in the microfilm edition; see paragraph at end of paper. Additional tables are reported in the thesis of K.G. (ref 1b).

Synthesis of Metabolites of Prostaglandin $F_{2\alpha}$ Resulting from β-Oxidation of the Carboxylic Acid Side Chain

Eldon G. Nidy and Roy A. Johnson*

Experimental Chemistry Research, The Upjohn Company, Kalamazoo, Michigan 49001

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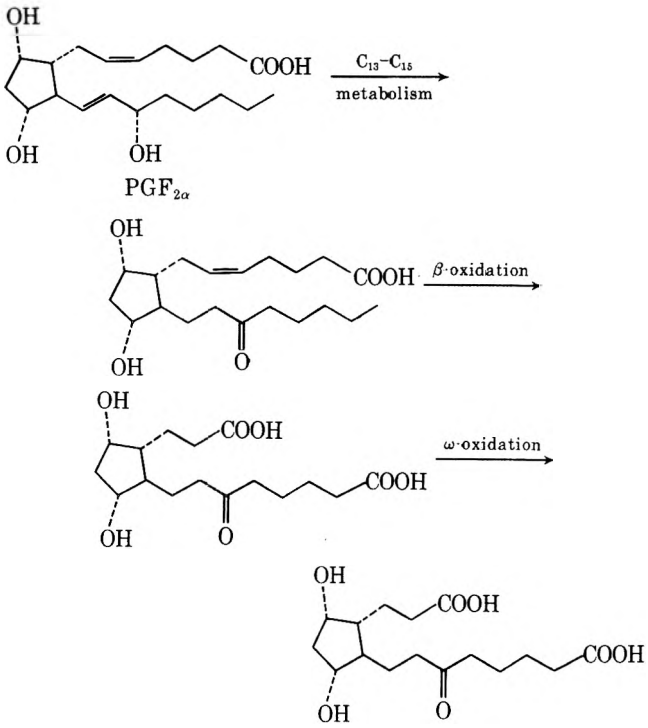
A synthetic sequence has been developed that leads to metabolites of $PGF_{2\alpha}$ having the carboxylic acid side chain shortened by four carbons. The readily available lactol **2** is treated with (methoxymethyl)triphenylphosphorane, giving enol ethers **3** and **4**. Acid-catalyzed hydrolysis and cyclization in aqueous methanol gives the acetal **5**. Hydrogenation of **5** gives **6** while oxidation of **5** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gives **10**. Hydrogenation of **10** gives **11**. The methyl acetals of **6** and **11** may be hydrolyzed, giving **7** and **12**, respectively. Oxidation of **7** and **12** with silver oxide results in formation of 9α,11α,15α-trihydroxy-2,3,4,5-tetranorprostanoic acid (**8**), a metabolite of $PGF_{2\alpha}$ found in urine of the rabbit, and 9α,11α-dihydroxy-15-oxo-2,3,4,5-tetranorprostanoic acid (**14**), a metabolite of $PGF_{2\alpha}$ found in urine of the rat, the rabbit, the guinea pig, and the monkey, respectively. Compounds **8** and **14** were isolated and characterized as the corresponding lactones **9** and **13**. Compound **9** was converted via the sodium salt of its ditetrahydropyranyl ether derivative (**15**) to 11α,15α-dihydroxy-9-oxo-2,3,4,5-tetranorprostanoic acid (**16**), a metabolite of PGE_1 found during in vitro metabolism studies that used rat liver mitochondria.

The prostaglandins are a class of C-20 fatty acids found distributed throughout most mammalian systems and having potent physiological effects in many of these systems. Although widespread throughout the body, the quantity of prostaglandins found in any single tissue is exceedingly small and may fluctuate considerably. As a consequence of this situation, it has been difficult to develop methods for the assay of prostaglandins at physiological concentrations. One approach to this problem has been to develop assays based on the urinary excretion of prostaglandin metabolites.[1]

The metabolism of the prostaglandins has been studied in a number of mammalian systems and the details have been described in several review articles.[2,3] To summarize, for the purposes of this discussion, it may be noted that three portions of the prostaglandin nucleus appear to be the most susceptible to the generally oxidative processes of metabolism. The first of these is the allylic alcohol system at C_{13}–C_{15}, which undergoes oxidation of the alcohol and reduction of the double bond, resulting in a series of "primary" metabolites.[3] The second is the carboxylic acid side chain, which is susceptible to β-oxidation. The third is the

aliphatic side chain, which suffers hydroxylation and subsequent further oxidation of the carbinol function. These overall steps are shown in the accompanying structural formulas, illustrating the metabolism of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$).



We have undertaken the synthesis of metabolites resulting from a combination of the first two modes of attack described above in order to (a) develop a synthetic route to the carboxylic acid side chain shortened by four carbons, (b) provide further characterization of such metabolites, and (c) provide samples of metabolites for use in the development of assays for prostaglandin levels. Our approach to the preparation of these metabolites has been to carry out an homologation of the carboxylate function present in the optically active lactone, 3α,5α-dihydroxy-2β-[(3*R*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1α-acetaldehyde γ-lactol 3-tetrahydropyranyl ether (**2**), readily available as an intermediate in several synthetic routes[4,5] to the natural prostaglandins. Such an homologation would provide the desired three-carbon acid side chain present in the metabolites.

The synthetic sequence that has led to the desired metabolites is outlined in Chart I.[6] The structures shown in Chart I are drawn so that they indicate correct stereochemistry and absolute configuration. The sequence began with a reaction between the lactol **2** and the ylide prepared from methoxymethyltriphenylphosphonium chloride and dimethylsulfinyl carbanion. The products of this reaction are the cis and trans enol ethers, **3** and **4**, in the ratio of about 2:3. These isomers are sufficiently different in polarity so that they partially separate during chromatography of the reaction mixture on silica gel. In this way samples of each have been isolated and characterized.

Assignment of the olefinic geometry of isomers **3** and **4** has been made on the basis of the nuclear magnetic resonance (NMR) signals for the vinyl protons. The isomer (**3**) having the smaller coupling constant (J = 6.5 Hz) for the vinyl proton next to the ether oxygen (δ 5.98) is assigned the cis configuration. The other isomer (**4**) has J = 12.5 Hz (δ 6.35) and is assigned the trans configuration.

Hydrolysis of **3** or **4** in acidic aqueous methanol results both in the removal of the THP groups and in the formation of a six-membered acetal (**5**). The presence of the epimeric methoxyl groups is easily observed in the NMR spectrum of the product. Whether the acetal arises from immediate cyclization of the protonated enol ether or from acetalization following initial hydrolysis of the enol ether to an aldehyde and cyclization to the lactol is not clear. Approximately the same epimeric mixture of **5** is obtained whether pure **3** or pure **4** are used in the hydrolysis reaction, consistent with a mobile equilibrium for this acetal group.

Retention of the methoxyl group in **5**, a consequence of the reaction conditions employed, is advantageous, since now the reactivity of the lactol is diminished. Reactions such as oxidation with dichlorodicyanoquinone, described below, can now be approached without fear of involving the lactol group.

The catalytic hydrogenation of the double bond of **5** was examined next. Initial experiments resulted in the formation of considerable by-product, presumably the result of hydrogenolysis of the allylic alcohol. This hydrogenolysis was effectively suppressed by the addition of sodium nitrite to the hydrogenation, according to the procedure of Dart and Henbest,[7] and resulted in formation of **6**.

Hydrolysis of **6** in acidic aqueous tetrahydrofuran served to remove the methoxyl group, giving lactol **7** as the product. Loss of the methoxyl group was easily detected in the NMR spectrum of **7**.

The selective oxidation of the lactol to a lactone was now studied. A number of conditions for this conversion were examined, including the use of manganese dioxide, Caros acid,[8] Fehling's and Collins' reagent, and (on the acetal) ozone,[9] before it was found that silver oxide[10] was very effective in this reaction. Examination of the reaction mixture by tlc showed that both acid **8** and lactone **9** were present. Treatment of the mixture with *p*-toluenesulfonic acid in an organic solvent served to lactonize the acid so that the product could be isolated entirely as the lactone **9**. The identity of the lactone was confirmed by a carbonyl absorption band at 1725 cm^{-1} in the infrared spectrum of **9**, as well as by consistent elemental and mass spectral analyses. Peak positions in the mass spectrum[11] of the di-TMS derivative of **9** were found to be identical with those reported for the same derivative of the metabolite isolated from rabbit urine.[12]

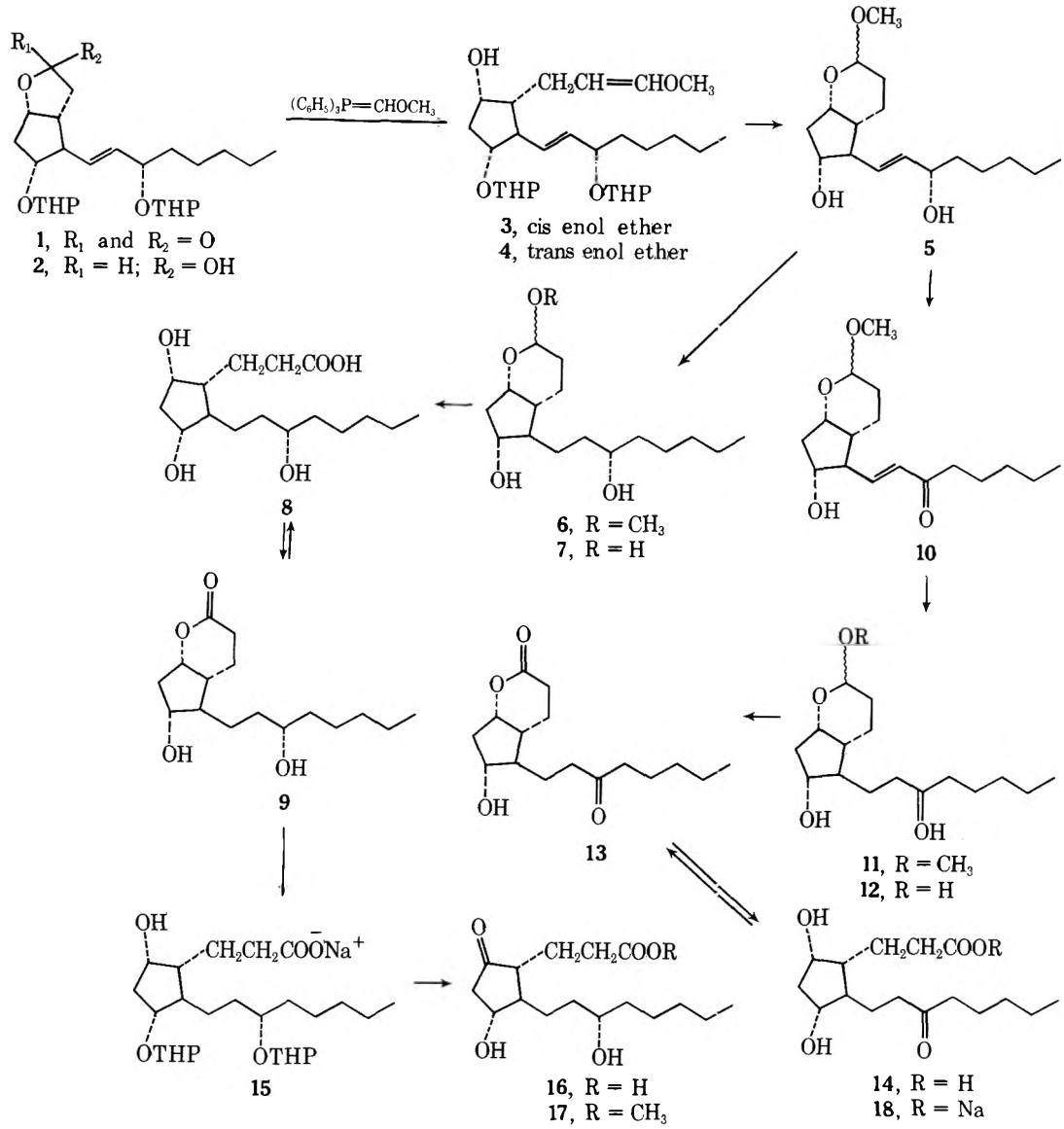
More commonly found as metabolites of the prostaglandins are compounds in which the hydroxyl group in the alkyl side chain has been oxidized to a ketone. To prepare such a compound, the allylic alcohol function of intermediate **5** was first oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), giving the α,β-unsaturated ketone **10**. The presence of the unsaturated ketone function was detected by the infrared spectrum (1690 and 1675 cm^{-1}), the ultraviolet spectrum [λ_{max} 232 mμ (ε = 14,100)], and the NMR spectrum (doublet of doublets at δ 6.75 and doublet at δ 6.16) of **10**.

Reduction of the double bond of **10** with palladium on carbon was carried out as above in the presence of sodium nitrite. The carbonyl absorption band was now found at 1710 cm^{-1} in the spectrum of the product **11**.

Hydrolysis of the acetal of **11** gave the lactol **12**, which, as above, was oxidized with silver oxide to produce a mixture of lactone **13** and acid **14**. Again, the acid **14** was lactonized so that the product was obtained entirely as the lactone **13**. Both forms of the metabolite have been isolated from the urine of the guinea pig,[13] the rat,[14,15] the rabbit,[12] and the monkey[15b] and have their origin in $PGF_{2\alpha}$.

In order to prepare corresponding metabolites of the PGE series, the following sequence of reactions was applied

Chart I



to lactone **9**. The hydroxyl groups of **9** were protected by formation of THP ethers and the lactone was then opened by addition of a stoichiometric quantity of sodium hydroxide in water. The free hydroxyl group of the resulting sodium salt **15** was then oxidized with Jones reagent. Subsequent work-up under acidic conditions served to remove the protecting THP groups and gave the metabolite **16**. Purification of acid **16** was difficult, so the methyl ester **17** was prepared by the careful addition of diazomethane to **16**. Acid **16** has been observed as a metabolite of PGE_1 in incubations of rat liver mitochondria.[16]

The stoichiometric addition of sodium hydroxide to **14** has also been carried out in order to provide a convenient form (**18**) in which to use **14** in physiological systems.

Experimental Section[17]

3β-[(3*S*)-Hydroxy-*trans*-1-octenyl]-2α-(3-methoxy-*cis*-2-propenyl)-1α,4α-cyclopentanediol (3) and 3β-[(3*S*)-3-Hydroxy-*trans*-1-octenyl]-2α-(3-methoxy-*trans*-2-propenyl)-1α,4α-cyclopentanediol (4). A dry 1-l., three-necked flask equipped with an efficient stirrer, dropping funnel, drying tube, and nitrogen inlet was maintained under a dry N_2 atmosphere. The flask was charged with 59% sodium hydride dispersion in oil (2.77 g, 0.068 mol) (washed with dry hexane to remove the mineral oil) and DMSO (40 ml) which had been stored over 4A molecular sieves. The mixture was heated at 65–70° (oil bath temperature) with gentle stirring until a clear, gray-colored solution was obtained (almost 2 hr). The mixture was cooled to about 15° with a cold-water bath and (methoxymethyl)triphenylphosphonium chloride (23.2 g, 0.068 mol) (dried previously over P_2O_5 in a vacuum desiccator) was added with vigorous stirring. The mixture became a dark red-orange color. Cooling was continued and within 10 min the lactol **2** (15 g, 0.034 mol) was added dropwise in DMSO (30 ml). The lactol was rinsed in with some fresh DMSO. The reaction mixture was allowed to warm to room temperature with continued stirring overnight. The reaction mixture was chilled with an ice–water bath while 600 ml of water was added. The mixture was stirred for an additional 0.5 hr and then extracted with diethyl ether (4 × 300 ml). The combined ether layers were washed with water (2 × 100 ml), dried (anhydrous $MgSO_4$), and filtered, and the ether was removed under reduced pressure to give 28.83 g of a dark red oil. The material was chromatographed on 2.5 kg of silica gel using 14.5 l. of 10% acetone in CH_2Cl_2 followed by 8.9 l. of 15% acetone in CH_2Cl_2. Fractions with a volume of 350 ml each were collected. Pure **3** (3.07 g) was found in fractions 26–35, a mixture of **3** and **4** (3.11 g) was found in fractions 36–42, and pure **4** (3.31 g) was found in fractions 43–57. In addition, **4** plus two slightly more polar impurities were found in fractions 58–65. Total yield of **3** and **4** was 9.8 g (0.021 mol, 61%).

An analytical sample of **3** was prepared by chromatography of 222 mg on a preparative 2-mm thick silica gel plate. The plate was developed by running twice in acetone–methylene chloride (10:90). The area of silica gel containing **3** was removed from the plate and **3** was recovered by leaching with ethyl acetate (five times). The ethyl acetate was filtered, washed with brine, and dried. Removal of the ethyl acetate gave 82 mg of **3** as a pale yellow oil: ir ν_{OH} 3500, $\nu_{C=C}$ 1665, $\nu_{transC=C}$ 980 cm^{-1} (neat); NMR ($CDCl_3$) δ 5.98 (d, 1 H,

J = 6.5 Hz, =CHOCH$_3$), 5.52 (m, 2 H, -CH=CH-), 4.71 (m, 2 H, 2 -OCHO-), 4.45 (m, 1 H, -CH=CHOCH$_3$), 3.62 (3, 3 H, -OCH$_3$), 0.89 (t, 3 H, J = 5 Hz, -CH$_3$); ORD plain positive curve but all rotations between 300 and 240 mμ were negative in sign, $[\phi]_{260}$ −90 in methanol; mass spectrum of TMS derivative, theory for $C_{30}H_{54}SiO_6$; 538.3689; found, 538.3661; other peaks at 506, 453, 436, 381.

Anal. Calcd for $C_{27}H_{46}O_6$: C, 69.49; H, 9.94. Found: C, 69.17; H, 9.89.

An analytical sample of 4 was prepared by first carrying out preparative TLC, using a 247-mg sample, as described above for 3. This gave 153 mg of an oil which was further purified on a silica gel column using 1:1 ethyl acetate–Skellysolve B to elute. A total of 73 mg of pure 4 was obtained as a pale yellow oil: ir ν_{OH} 3460, $\nu_{C=C}$ 1670 sh, $\nu_{transCH=CH}$ 975 cm^{-1} (neat); NMR ($CDCl_3$) δ 6.35 (d, 1 H, J = 12.5 Hz, =CHOCH$_3$), 5.52 (m, 2 H, -CH=CH-), 4.68 (m, 3 H, -CH=CHOCH$_3$, 2 OCHO), 3.50 (s, 3 H, -OCH$_3$), 0.88 (t, 3 H, J = 5 Hz, -CH$_3$); ORD plain positive curve, $[\phi]_{260}$ +660 in methanol; mass spectrum of Me$_3$Si derivative, theory for $C_{30}H_{54}SiO_6$, 538.3689; found, 538.3672; other peaks at 506, 453, 436, 71.

Anal. Calcd for $C_{27}H_{46}O_6$: C, 69.49; H, 9.94. Found: C, 69.67; H, 10.14.

3α,5α-Dihydroxy-2β-[(3*S*)-3-hydroxy-1-*trans*-octenyl]cyclopentane-1α-propionaldehyde δ-Lactol Methyl Ether (5). A solution of the enol ethers 3 and 4 (1.0 g, 2.15 mmol) in methanol (50 ml) was treated with 20 ml of a pH 2.0 buffer solution (prepared with 25 ml of 0.2 *M* KCl and 6.5 ml of 0.2 *M* HCl) and stirred at room temperature for approximately 52 hr. The methanol was partially removed under reduced pressure (30°). Saturated NaCl solution was added (~15 ml) and the mixture was then extracted with chloroform four times. The combined chloroform extracts were washed twice with saturated NaCl solution, dried ($MgSO_4$), and filtered and the chloroform was evaporated under reduced pressure to give 605 mg (94%) of a pale yellow oil. A 277-mg sample of 5 was chromatographed on 30 g of silica gel using $CHCl_3$–methanol (95:5) to elute the column. Fractions with a volume of 20 ml each were collected. The major portions of the desired product were obtained in fractions 5 and 6 to give 210 mg of an oil. A 188-mg portion of the material obtained from the above column was chromatographed again on silica gel using ethyl acetate–Skelly B (3:1) to elute. Fractions with a volume of 15 ml each were collected. A total of 136 mg of pure 5 was found in fraction 5–8 as a very pale yellow oil: ir ν_{OH} 3390, $\nu_{C=C}$ 1665, $\nu_{transCH=CH}$ 970 cm^{-1} (neat); NMR ($CDCl_3$) δ 5.52 (m, 2 H, -CH=CH-); 4.70 (m, ~0.6 H, -OCHO); 4.43–3.17 (m, 5.4 H, -OCH-, -OCHO, -OH); 3.47, 3.39 (2 s, 3 H, -OCH$_3$); 0.88 (t, 3 H, J = 5 Hz, -CH$_3$); ORD negative Cotton effect, $[\phi]_{260}$ −500 mμ in methanol; mass spectrum of di-Me$_3$Si derivative, theory for $C_{23}H_{46}O_4Si_2$, 442.2932; found, 442.2931.

3α,5α-Dihydroxy-2β-[(3*S*)-3-hydroxyoctyl]cyclopentane-1α-propionaldehyde δ-Lactol Methyl Ether (6). A solution of the olefin 5 (2.885 g, 9.7 mmol) in 95% ethanol (200 ml) with 5% palladium on carbon (300 mg) and $NaNO_2$ (30 mg) was hydrogenated on the Parr apparatus for 1.5 hr. The amount of hydrogen consumed was 13 lb (theory 9.7 mmol × 1.28 lb/mmol = 12.4 lb). The reaction was purged with nitrogen, removed from the apparatus, and filtered and the solvent was removed to give an amber oil. A 854-mg sample of the oil was chromatographed on 100 g of silica gel using ethyl acetate–Skelly B (3:1) to elute the column. Fractions with a volume of 40 ml each were collected. The compound was obtained in fractions 15–20 (218 mg), 21–28 (244 mg), and 29–42 (108 mg). The material in fractions 15–20 (218 mg) was then chromatographed on silica gel (30 g) using chloroform–methanol to elute the column. Fractions of 15 ml each were collected. There was obtained 142 mg in fractions 8–9 (A) and 82 mg in fractions 10 and 11 (B). The material called A (142 mg) above was then chromatographed on 10 g of silica using ethyl acetate–Skelly B (3:1) to elute the column, collecting fractions of 10 ml each. The material used for analysis was collected in fractions 4–9 (94 mg): ir ν_{OH} 3400 cm^{-1} (liquid film); NMR ($CDCl_3$) δ 4.71 (m, ~0.6 H, -OCHO); 4.37–3.29 (m, 3.4 H, 2 -OCH-, -OCHO-); 3.47, 3.39 (2 s, 3 H, OCH$_3$); 0.89 (t, 3 H, J = 5 Hz, -CH$_3$); ORD plain negative curve, $[\phi]_{260}$ −700 mμ in methanol; mass spectrum of di-Me$_3$Si derivative, theory for $C_{23}H_{48}Si_2O_4$, 444.3091; found, 444.3071; other peaks at 429, 413, 412, 373, 173.

Anal. Calcd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74. Found: C, 68.04; H, 10.55.

3α,5α-Dihydroxy-2β-[(3*S*)-3-hydroxyoctyl]cyclopentane-1α-propionaldehyde δ-Lactol (7). A solution of the lactol ether 6 (3.17 g, 0.0106 mol) in tetrahydrofuran (125 ml) was treated with a pH 1 buffer solution (60 ml) (from 25 ml of 0.2 *M* KCl plus 67 ml of 0.2 *M* HCl) and stirred at room temperature for 72 hr. The reaction was monitored by TLC on silica gel in $CHCl_3$–methanol (9:1). The reaction mixture was worked up by adding 200 ml of saturated NaCl solution plus solid NaCl and extracting with CH_2Cl_2 (4 × 150 ml). The combined CH_2Cl_2 extracts were washed with saturated NaCl solution, dried ($MgSO_4$), and filtered and the CH_2Cl_2 was removed under reduced pressure to give 2.912 g (96%) of a yellow oil. An analytical sample was obtained by chromatographing a portion (800 mg) of the oil on a silica gel column (100 g) using acetone–methylene chloride (1:1) to elute. Fractions with a volume of 50 ml were collected, changing to 150 ml at fraction 17. Fraction 17, containing 221 mg, was used for analysis: ir ν_{OH} 3360 cm^{-1} (liquid film); NMR ($CDCl_3$) δ 0.90 (t, 3 H, $J \simeq$ 5 Hz, -CH$_3$), no signal for methoxyl protons; ORD, plain negative curve, $[\phi]_{260}$ −70 mμ in methanol; mass spectrum of tri-Me$_3$Si derivative, theory for $C_{25}H_{54}Si_3O_4$, 502.3330; found, 502.3324; other peaks at 487, 484, 431, 356, 341, 173.

Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.09; H, 10.56. Found: C, 67.07; H, 10.74.

3α,5α-Dihydroxy-2β-[(3*S*)-3-hydroxyoctyl]cyclopentane-1α-propionic Acid δ-Lactone (9). Silver oxide was prepared by adding a solution of silver nitrate (2.84, 16.7 mmol) in water (4 ml) to 16.5 ml of 2 *N* NaOH (0.033 mol) with vigorous stirring. A brown semisolid mixture resulted. To this mixture, contained in an ice bath, was added the lactol 7 (2.05 g, 7.17 mmol) dropwise in tetrahydrofuran (Burdick and Jackson) (8.5 ml). The mixture was stirred at ice-bath temperature for 0.5 hr and then the ice bath was removed. The mixture was stirred at ambient temperature for 1.5 hr. A silver mirror formed on the sides of the flask. The black silver suspension was removed by filtration and washed with several portions of water. The combined filtrate and washings were extracted with CH_2Cl_2 followed by diethyl ether. The CH_2Cl_2 and ether extracts were discarded. The aqueous layer was acidified with concentrated hydrochloric acid, sodium chloride was added, and then it was extracted well with methylene chloride. The combined CH_2Cl_2 extracts were washed with saturated NaCl solution and dried ($MgSO_4$). The solution was filtered and the CH_2Cl_2 was removed under reduced pressure to give 1.662 g (80%) of the lactone 9 plus traces of the acid 8. A 1.572-g sample of the above material was dissolved in CH_2Cl_2 (100 ml) and treated with *p*-toluenesulfonic acid (80 mg) to convert 8 to 9. The reaction was complete in 2 hr by TLC evidence in $CHCl_3$–methanol (9:1) on silica gel. The CH_2Cl_2 solution was washed twice with 10% $NaHCO_3$ followed by saturated NaCl solution. The CH_2Cl_2 layer was dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure to give 1.159 g. For analytical data a 580-mg sample of 9 was chromatographed on silica gel (50 g) using CH_2Cl_2–acetone (1:1) to elute the column collecting fractions of 40 ml each. The lactone 9 was collected in fractions 4–8 (481 mg). The material obtained crystallized and was recrystallized from diethyl ether–methylene chloride–Skelly B to give 282 mg of 9: mp 75–76.5°; ir ν_{OH} 3470, 3360, 3300, $\nu_{C=O}$ 1725 cm^{-1} (Nujol); NMR ($CDCl_3$) δ 4.69 [m, 1 H, -C(=O)OCH-], 4.81 (m, 2 H, -OCH-), 3.65 (m, 2 H, OH), 2.42 [m, 2 H, -C(=O)CH$_2$-], 0.89 (t, 3 H, J = 5 Hz, -CH$_3$); ORD negative cotton curve, $[\phi]_{228m\mu}$ (min) −5100, $[\phi]_{260}$ −1900 (methanol); mass spectrum of di-Me$_3$Si derivative, theory for $C_{22}H_{44}O_4Si_2$, 428.2778; found, 428.2807; other peaks at 413, 399, 357, 328, 173.

Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.69; H, 9.81.

Sodium 9α,11α,15α-Trihydroxy-2,3,4,5-tetranorprostanoate 11,15-Ditetrahydropyranyl Ether (15). A solution of the lactone 9 (578 mg, 2.04 mmol) in methylene chloride (10 ml) with a catalytic amount of *p*-toluenesulfonic acid was treated with dihydropyran (360 mg, 4.5 mmol). The reaction was complete by TLC evidence after 0.5 hr [TLC in $CHCl_3$–methanol (9:1)]. The R_f for the lactone dialcohol was 0.32 and for the lactone ditetrahydropyranyl ether was 0.72. The reaction mixture was washed with 10% $NaHCO_3$ (2 × 20 ml) followed by saturated NaCl solution (20 ml). The combined aqueous layers were extracted with CH_2Cl_2. The CH_2Cl_2 layers were combined and dried ($MgSO_4$), and the solvent was removed to give 857 mg (95%) of an oil.

The lactone ditetrahydropyranyl ether (857 mg, 1.9 mmol) was treated with a mixture of 1 ml of methanol and 1.05 ml of 2 *N* NaOH solution (2.1 mmol) at room temperature for 2.5 hr. The reaction was monitored by TLC in ethyl acetate–Skelly B (3:1) with a R_f of 0.54 for the lactone ditetrahydropyranyl ether and R_f 0.00–0.26 (streaking) for the salt 15. The water and methanol were removed under reduced pressure. The residue was stored in a vac-

uum desiccator overnight in the presence of NaOH pellets. Obtained was 1.015 g (108%) of a gum which eventually crystallized after standing in the desiccator to give a yellow solid.

11α,15α-Dihydroxy-9-oxo-2,3,4,5-tetranorprostanoic Acid (16). A solution of the sodium salt ditetrahydropyranyl ether (15) (534 mg, 1.29 mmol) in acetone (50 ml) was chilled with an ice–methanol bath and treated with 0.61 ml of 2.67 *M* Jones reagent (1.64 mmol) which was added dropwise over a 5-min period. The reaction was monitored by TLC in CH_2Cl_2–acetone–methanol (85:10:5) with an R_f of 0.00–0.21 (streaking) for the starting material and a R_f of 0.31–0.51 (streaking) for the keto acid ditetrahydropyranyl ether. After 40 min, another 0.1 ml of Jones reagent was added which produced very little noticeable change by TLC. After 45 min, the reaction was quenched with isopropyl alcohol. Water was added (~20 ml) followed by ether. The ether layer was separated and the aqueous layer was extracted with more ether. The ether layers were combined and washed with saturated sodium chloride solution (2 × 10 ml), dried ($MgSO_4$), and filtered, and the solvent was removed. The oil obtained was treated with 6 ml of an acetic acid–water–THF (50:25:7.5) mixture and heated at 37–39° for 4 hr. The solution was cooled and 6 ml of water was added. The solution was frozen in a Dry Ice–acetone bath and placed on the freeze dryer. A total of 517 mg as an amber oil was obtained.

Methyl 11α,15α-Dihydroxy-9-oxo-2,3,4,5-tetranorprostanoate (17). A solution of 90 mg of 16 in ether (5 ml) was treated by the addition of an ether solution of diazomethane (dropwise) until the yellow color was persistent (magnetic stirring and ice-bath cooling). The reaction was monitored by TLC on silica gel in $CHCl_3$–methanol (9:1) [R_f methyl ester 0.33, R_f acid 0–0.20 (streaking)]. When the reaction was complete by TLC evidence, it was allowed to warm to room temperature and the ether was removed under reduced pressure. The residue was chromatographed on 10 g of silica gel. The column was prepared as a slurry with CH_2Cl_2–hexane–acetone (1:1:1) and eluted with the same. Fractions with a volume of 4 ml each were collected; R_f of ester on TLC in CH_2Cl_2–hexane–acetone (1:1:1) is 0.23. Pure 17 (42 mg) was obtained in fractions 14–19: ir ν_{OH} 3400, $\nu_{C=O}$ 1740 cm^{-1} (microsmear on KBr); NMR ($CDCl_3$) δ 3.67 (s, 3 H, methyl ester), 2.45 (m, protons α to carbonyls), 0.89 (t, 3 H, J = 5 Hz, $-CH_3$); CD, negative Cotton curve $[\theta]_{300}$ −5750 in dioxane; mass spectrum of di-Me_3Si, theory for $M^+ - CH_3$, 443.2617; found, 443.264.

Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.99; H, 9.80.

(2*R*)-3α,5α-Dihydroxy-2-(3-oxo-1-*trans*-octenyl)cyclopentane-1α-propionaldehyde δ-Lactol Methyl Ether (10). A solution of 5 (1.0 g, 0.00336 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.914 g, 0.00403 mol) in dioxane (80 ml) was heated to 50° for 18 hr under a nitrogen atmosphere. The reaction mixture was then cooled, filtered through Celite, and washed with dioxane. The filtrate was concentrated under reduced pressure and the residue (1.67 g) was chromatographed on a column of silica gel (200 g) packed as a slurry in 50% ethyl acetate–Skellysolve B. Elution with 50% ethyl acetate–Skellysolve B (1 l.) removes nonpolar impurities. Elution with 75% ethyl acetate–Skellysolve B (2 l.) removes the product (0.609 g, 0.00206 mol, 60%). The epimeric methyl acetals of the product mixture were partially separated during the chromatography and in this way some of the less polar epimer was obtained pure and was crystalline. Two recrystallizations from Skellysolve F gave white solid: mp 61–63.5°; ir ν_{OH} 3450, $\nu_{C=O}$ 1690, 1675, $\nu_{C=C}$ 1630, 1620 cm^{-1} (Nujol); NMR ($CDCl_3$), δ 6.75 (doublet of doublets, 1 H, J_H = 8, $J_{trans\ H}$ = 16 Hz, H-13), 6.16 (d, 1 H, $J_{trans\ H}$ = 16 Hz, H-14), 4.70 (m, 1 H, –OCHO), 3.39 (s, 3 H, $-OCH_3$), 2.54 [t, 2 H, J = 7 Hz, $-C(=O)CH_2-$], 0.89 (t, 3 H, J = 5.5 Hz, $-CH_3$), a sample consisting of approximately a 1:1 ratio of the two epimers gave singlets at δ 3.47 and 3.39 for the protons of the methoxyl groups; uv λ_{max} 232 mμ (ε 14,100); mass spectrum of Me_3Si derivative, theory for $C_{20}H_{36}SiO_4$, 368.2383; found, 368.2429, other peaks at 353, 350, 327, 326, 321, 318, 297, 278, 99.

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.50; H, 9.83.

(2*R*)-3α,5α-Dihydroxy-2-(3-oxooctyl)cyclopentane-1α-propionaldehyde δ-Lactol Methyl Ether (11). A solution of the olefin 10 (1.206 g, 4.07 mmol) in 95% ethanol (200 ml) with sodium nitrite (70 mg) and 5% palladium on carbon (350 mg) was hydrogenated on the Parr apparatus for 70 min. The reaction mixture was then filtered and the solvent was removed under reduced pressure to give 1.148 g (94%) of an oil. For analytical data a 112-mg sample of the oil was chromatographed twice on silica gel (10 g) packed as a slurry in 1:1 ethyl acetate–Skellysolve B. Elution was with 3:1 ethyl acetate–Skellysolve B and fractions of 4 ml were collected. The compound was eluted in fractions 8–25 and in this way 26 mg of 11 in fractions 9–10 of the second column were used for analysis: ir ν_{OH} 3460, $\nu_{C=O}$ 1710 cm^{-1} (liquid film); NMR ($CDCl_3$), δ 4.67 (m, ~0.5 H, –OCHO–), 4.38–3.58 (m, 2.5 H, 2 –OCH–, –OCHO–), 3.45, 3.37 (2 s, 3 H, $-OCH_3$), 0.89 (t, 3 H, J = 5.5 Hz, $-CH_3$); CD $[\theta]_{279}$ −400 mμ (methanol); mass spectrum of Me_3Si derivative, theory, 370.2538; found, 370.2524; other peaks at 355, 352, 338, 323, 254, 99.

(2*R*)-3α,5α-Dihydroxy-2-(3-oxooctyl)cyclopentane-1α-propionaldehyde δ-Lactol (12). A solution of the ketone 11 (1.036 g, 3.47 mmol) in THF (38 ml) was treated with 19 ml of pH 1 buffer solution (from 25 ml of 0.2 *M* KCl plus 67 ml of 0.2 *M* HCl) and stirred at room temperature for 30 hr. The reaction was monitored by TLC on silica gel in $CHCl_3$–methanol (9:1). The reaction was worked up by adding saturated sodium chloride solution and extracting well with methylene chloride. The combined methylene chloride extracts were washed with brine and dried (Na_2SO_4) and the solvent was removed under reduced pressure to give 944 mg (97%) of a pale yellow oil. The material (944 mg) was chromatographed on 100 g of silica gel. The column was packed as a slurry with CH_2Cl_2–acetone (2:1). The column was eluted with 850 ml of CH_2Cl_2–acetone (2:1) followed by a 1:1 mixture. Fractions with a volume of 40 ml each were collected. The lactol 12 was obtained in fractions 13–14 (249 mg), 15–16 (247 mg), and 17–24 (220 mg). The analytical sample was obtained by chromatographing fractions 13–14 (249 mg) again on 20 g of silica gel. The column was packed as a slurry with CH_2Cl_2–acetone (2:1). The column was eluted with CH_2Cl_2–acetone (1:1) collecting fractions of 4 ml each. The material collected in fractions 16–25 (112 mg) was used for analysis: ir ν_{OH} 3400, $\nu_{C=O}$ 1705 cm^{-1} (liquid film); NMR ($CDCl_3$), δ 0.89 (t, 3 H, J = 5.5 Hz, $-CH_3$), no signal for methoxyl protons; CD $[\theta]_{280}$ −442 ± 18 mμ (methanol); mass spectrum of di-Me_3Si derivative, theory, 428.2778; found, 428.2747; other peaks at 413, 410, 395, 357, 338, 323, 320, 99.

Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.11; H, 9.97.

(2*R*)-3α,5α-Dihydroxy-2-(3-oxooctyl)cyclopentane-1α-propionic Acid δ-Lactone (13). Silver oxide was prepared by adding 773 mg (4.57 mmol) of silver nitrate in 3 ml of water dropwise to 4.5 ml of 2 *N* NaOH with stirring. A brown semisolid mixture was obtained. To this mixture, contained in an ice bath, was added the lactol 12 (619 mg, 2.18 mmol) in THF (4.5 ml). The ice bath was removed after 0.5 hr. The reaction was monitored by TLC on silica gel in $CHCl_3$–methanol (9:1). After 3 hr, more silver oxide was prepared as above with 84.5 mg (0.5 mmol) of $AgNO_3$ and 0.5 ml of 2 *N* NaOH. The resulting brown semisolid was added to the reaction. After another 0.75 hr, the reaction mixture was again treated with another 0.5 mmol of silver oxide. After a total of 5 hr reaction time, the reaction was worked up by removing the black silver suspension by filtration and washing the suspension with several portions of water. The combined filtrate and washings were acidified to pH 1 with concentrated HCl at ice-bath temperature. Solid NaCl was added and the solution was then extracted well with methylene chloride. The methylene chloride extracts were combined, washed with saturated NaCl solution and dried ($MgSO_4$) and the solvent was removed to give 610 mg (99% of theory) of an oil. The product was a mixture of the lactone 13 and the acid 14. The above material was dissolved in CH_2Cl_2 (40 ml) and treated with a catalytic amount of *p*-toluenesulfonic acid to convert the acid to lactone. The reaction was complete in 15 min by TLC evidence in $CHCl_3$–methanol (9:1) on silica gel. The reaction mixture was then diluted to 100 ml with CH_2Cl_2 and washed with ice-cold $NaHCO_3$ solution followed by 1 *N* HCl and saturated NaCl solution. All aqueous layers were back extracted with CH_2Cl_2. The CH_2Cl_2 layers were then combined and dried ($MgSO_4$), and the CH_2Cl_2 was evaporated under reduced pressure to give 486 mg (79%) of an oil. This product was combined with some additional material (80 mg) obtained from a previous experiment and chromatographed on silica gel (60 g). The column was packed as a slurry with acetone–CH_2Cl_2–Skelly B (1:1:1) and eluted with the same. Fractions with a volume of 30 ml each were collected; the lactone 13 was collected in fractions 8–12 (488 mg). A 45-mg sample of the material obtained was recrystallized from Skelly F–diethyl ether twice to give 25 mg of 13: mp 35.5–36.5°; ir ν_{OH} 3510, $\nu_{C=O}$ 1710 cm^{-1} (Nujol); NMR ($CDCl_3$), δ 4.68 [m, 1 H, $-C(=O)OCH-$], 3.80 (m, 1 H, –OCH–), 0.89 (t, 3 H, J = 5.5 Hz, $-CH_3$); mass spectrum of Me_3Si derivative, theory, 354.2226; found, 354.2248; other peaks at 339, 336, 321, 299, 293, 281, 264, 208, 99.

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.16; H, 9.53.

9α,11α-Dihydroxy-15-oxo-2,3,4,5-tetranorprostanoic Acid Sodium Salt (18). The lactone **13** (100 mg, 0.355 mmol) was treated with 3.55 ml of 0.1 *N* NaOH. After 45 min, it was necessary to add 10 ml of water to keep the reaction homogeneous. The reaction was complete by TLC evidence on silica gel in chloroform–methanol (9:1) after a total reaction time of 1.5 hr. The reaction was then frozen in a Dry Ice–acetone bath. A white solid was obtained after lyophilization.

Registry No.—**2**, 37435-65-7; **3**, **4**, 50889-15-1; **5** α epimer, 54517-81-6; **5** β epimer, 54548-87-7; **6** α epimer, 54517-82-7; **6** β epimer, 54548-88-8; **7** α epimer, 54517-83-8; **7** β epimer, 54548-89-9; **9**, 54139-68-3; **9** ditetrahydropyranyl ether, 54517-79-2; **10** α epimer, 54517-84-9; **10** β epimer, 54548-90-2; **11** α epimer, 54517-85-0; **11** β epimer, 54548-91-3; **12** α epimer, 54517-86-1; **12** β epimer, 54548-92-4; **13**, 54164-67-9; **14**, 24379-94-0; **15**, 54517-80-5; **16**, 21641-89-4; **17**, 54517-87-2; **18**, 54548-93-5; (methoxymethyl)triphenylphosphonium chloride, 4009-98-7.

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(11) Mass spectra were recorded on an instrument coupled with a vapor phase chromatograph; consequently, relative peak heights are not exactly reproduced from one spectrum to another.
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(15) (a) F. F. Sun, *Biochim. Biophys. Acta*, **348**, 249 (1974); (b) F. F. Sun and J. E. Stafford, *ibid.*, **369**, 95 (1974).
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(17) Melting points were determined with a Thomas capillary melting apparatus and are uncorrected. Infrared spectra were determined with a Digilab Model FTS-14D spectrophotometer. The NMR spectra were determined at 60 MHz with a Varian A-60D spectrometer, using tetramethylsilane as an internal standard. First-order analyses of the NMR spectra are given. High-resolution mass spectra were obtained with a CEC-110 spectrometer. Gas chromatography–mass spectrometry was with a Model LKB instrument. ORD and CD spectra were obtained with a Cary 60 spectrophotometer. In general solvents used for reactions were distilled in glass and purchased from the Burdick and Jackson Laboratories, Muskegon, Mich. Skellysolve B is the trade name for a petroleum hydrocarbon fraction, bp 60–70°, of the Skelly Oil Co.

Preparation and Transformations of Steroidal Butadiynes[1]

P. K. Gupta,[2a] J. G. Ll. Jones,[2b] and E. Caspi*

The Worcester Foundation for Experimental Biology, Inc., Shrewsbury, Massachusetts 01545

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Steroidal ketones were treated with monosodiodibutyne to yield the corresponding tertiary hydroxy butadiynes. The diynes were hydrated with 10% sulfuric acid and mercuric sulfate. Predominantly, the obtained products were not the expected mono- and diketones, but were conjugated spiro methylfurenones. Chemical and spectroscopic evidence for the assigned structures is given. Spiro furenone derivatives attached at C-3, -7, -17, and -20 were prepared from the appropriate ketones. Several unusual transformation products were obtained from ozonolysis of the C-3 analog.

For the elaboration of steroid systems we required a method by which a multiple-carbon moiety could be introduced into the molecule, preferably in one operation. The added moiety had to contain certain functional groupings, and be amenable to further transformations. The reaction of ketones with monosodiobutadiyne[3,4] (Na^+ $^-C{\equiv}C{-}C{\equiv}CH$) suggests itself as a reasonable method for a "one-step" addition of four carbon atoms.

$$R_1R_2CO\ (a) \rightarrow R_1R_2C(OH){\cdot}C{\equiv}C{-}C{\equiv}CH\ (b)$$

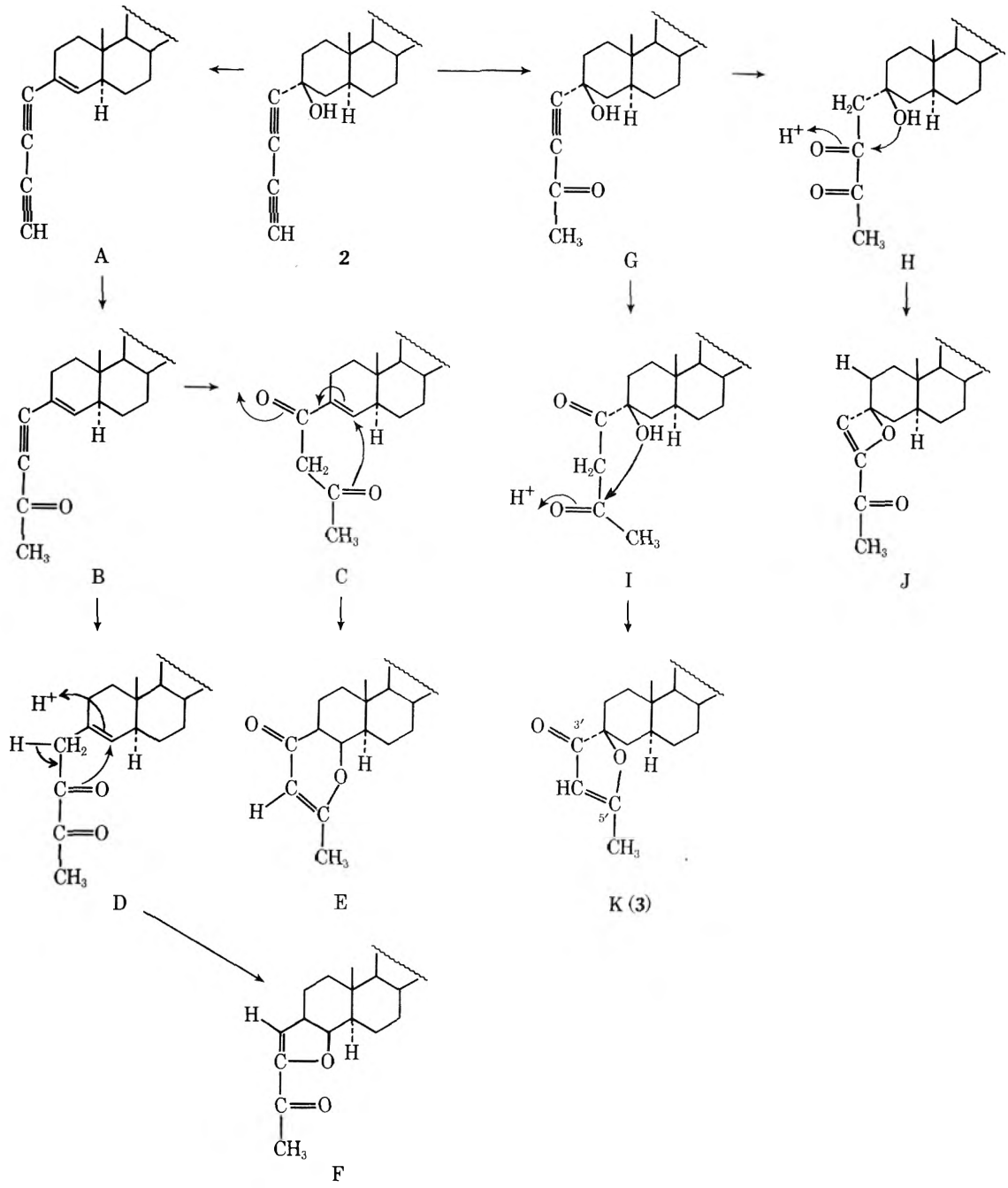
The diacetylene (b) thus formed could be processed as needed. Preliminary model studies with 17β-hydroxy-5α-androstan-3-one resulted in a residue from which the diyne could be recovered, with difficulty and in poor yield. The obtained hydroxydiacetylene (b) was labile, difficult to handle, and easily decomposed on warming or crystallization. This characteristic severely limited the synthetic utility of the procedure and a method of bypassing the need for the isolation and purification of diacetylene was indicated. Direct acid-catalyzed hydration[3] of the crude diacetylenes appeared a plausible operational alternative. Unfortunately, this short cut was not devoid of pitfalls, particularly because the pathway of hydration of the hydroxydiacetylenes of type b was not previously well defined. Indeed the reaction took an unexpected course and is the subject of this paper.

Treatment of 17β-hydroxy-5α-androstan-3-one (**1a**) with monosodiodibutyne in liquid ammonia resulted in a gummy powder, from which a small amount of solid (**2**) was isolated. The recrystallized product had an ill-defined melting point, but its ir and NMR spectra were in agreement with the proposed structure. The elemental analysis was only passable for the expected composition. The mass spectrum of **2** was devoid of a peak for the molecular ion (M^+, *m/e* 340) but had fragments at *m/e* 290 (M − C_4H_2), 246 (290 − 44), and 231 (246 − CH_3).

In view of the poor recovery of **2**, an aliquot (8 g) of the crude product was hydrated by boiling with 10% aqueous methanolic sulfuric acid in the presence of mercuric sulfate. After processing the reaction mixture, a compound (5.5 g) later identified as **3a** was obtained. The unknown **3a** absorbed uv light [263 nm (ε 3.98)] and had bands in the ir at 1675 and 1598 cm^{-1}, indicating the presence of a conjugated carbonyl. The NMR spectrum (all spectra were recorded at 60 MHz) had, inter alia, signals at 312.5 Hz for one vinylic proton and a narrow doublet at 130 Hz (*J* = ca. 1 Hz) equivalent to three hydrogens.

The mass spectrum had the most prominent peak at *m/e* 358 (M^+, 100%) and lesser fragments at *m/e* 343 (M − 15), 340 (M − 18), 325 (343 − 18), 301 (M − 57, C_3H_5O), 298 (M − 60), 297 (M − 61). Both the mass spectrum and the elemental analysis indicated a $C_{23}H_{34}O_3$ composition.

Scheme I



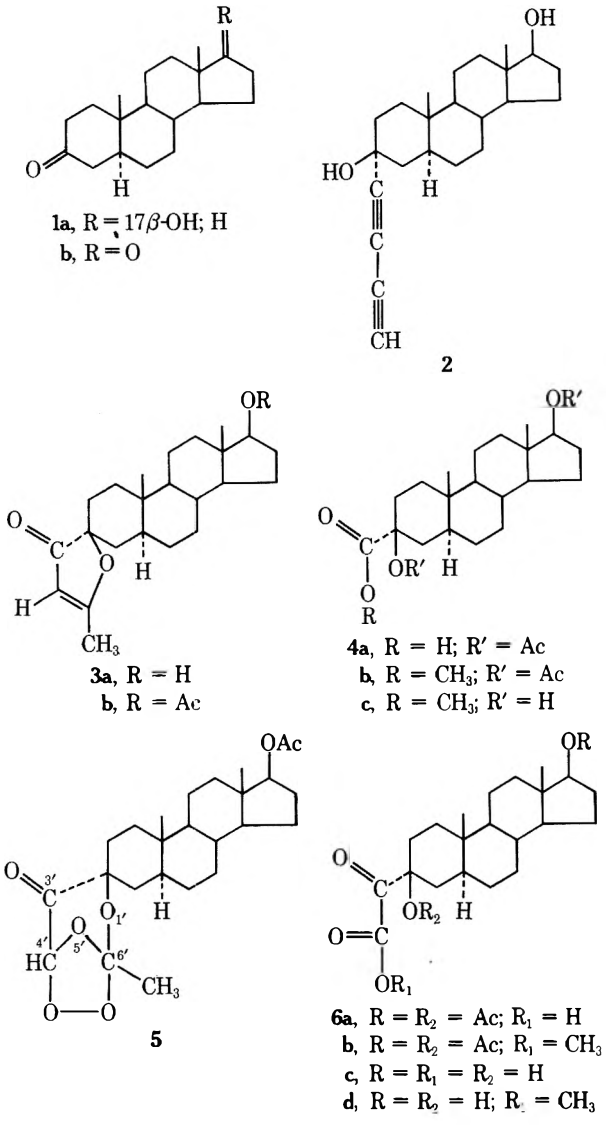
In discussing the structure of the unknown, it might be helpful to consider certain of the possible hydration pathways of the diacetylene **2** and some of their reactions outlined in Scheme I.

The assumption that dehydration of the tertiary hydroxyl will occur in the early stages of exposure of **2** to mineral acid proved incorrect, as evident from the sequel. However, the hypothesis that the terminal triple bond will be hydrated first was confirmed.

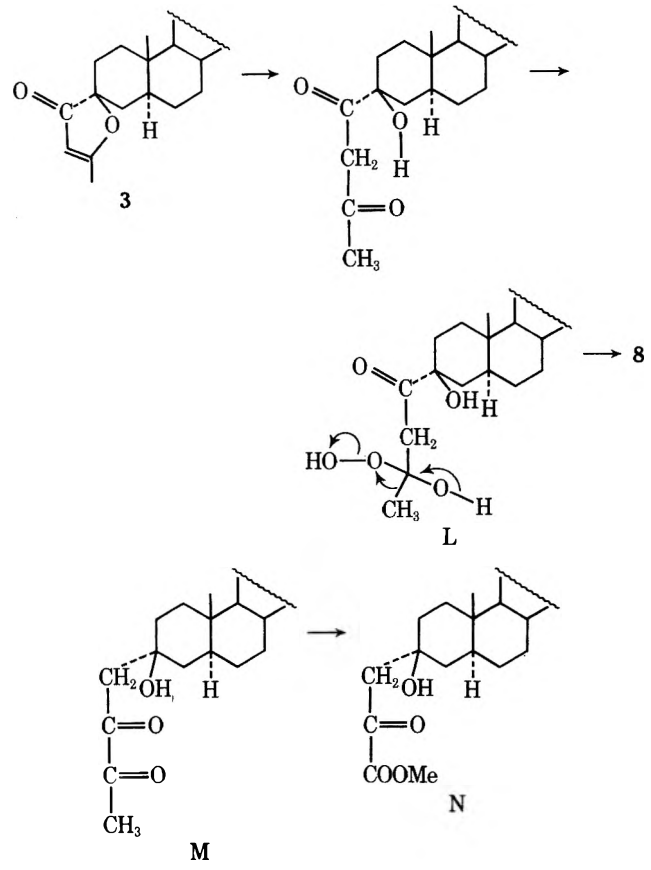
Structures A, B, C, D, G, H, and I (Scheme I) were excluded on the basis of the above given spectroscopic and analytical data. In addition, the product was resistant to periodic acid oxidation under conditions in which α- and β-diketones would be attacked by this reagent. Hence, the choice was narrowed to the cyclic enol ether structures E, F, K, and J. The fact that **3** had a signal only for the C-17 proton attached to a carbon bearing an oxygen function excluded structures E and F, in which a second hydrogen of this type would be present at C-4. This, therefore, left K and J as the two possible structures for **3**. The uv spectrum (λ_{max} 263 nm) favored structure K because it could be anticipated that conjugation of the acetyl carbonyl and the oxeten double bond in J would be strained and the uv maximum would probably be at a shorter wavelength. Also, the presence of a split methyl signal at 130 Hz (J = ca. 1 Hz), characteristic for a vinylic methyl bearing a proton on the β carbon, provided added support for the unknown **3** having structure K.

In view of these considerations, structure **3** was accepted as a working hypothesis and its confirmation by chemical means was undertaken. An obvious point for a degradative attack on the molecule was the conjugated double bond. It was believed that ozonization of the 17-acetate **3b** and an oxidative work-up of the ozonide would yield the diacetoxy acid **4a** (Chart I). The hypothesis was based on results obtained with steroidal Δ^4-3-ketones.[5] However, when **3b** was ozonized, and then the mixture treated for 16 hr with hydrogen peroxide, a neutral product, the ozonide **5**, and an

Chart I



Scheme II



acidic product (**6a**) were isolated. Compound **5** showed a singlet for one hydrogen at 328 Hz (H-4′) and a sharp singlet for a methyl group at 108.5 Hz (CH_3-6′). The dry ozonide was relatively stable and could be rapidly recrystallized from cold methanol. However, when left in methanol for some time it rearranged to several products (see below). The acid **6a** was characterized as the methyl ester **6b.** Combustion analysis and the mass spectrum indicated a $C_{26}H_{38}O_7$ composition; the NMR showed, among others, signals for two acetate groups and one carbomethoxy group.

Removal of solvent from the crude mother liquor of crystallization of the ozonide **5** yielded a noncrystalline residue. This residue was resolved chromatographically (TLC) and two products were isolated. The less mobile substance was identified as acid **4a** and on treatment with diazomethane gave the ester **4b.** The more mobile compound resisted crystallization and was probably a hydroperoxide. The peroxide structure is suggested by the 3450-cm^{-1} band present in the infrared spectrum. Instability of the product prevented its characterization.

Alternatively, when the crude mother liquor of ozonide crystallization was treated with diazomethane and then the solvent removed, a brown solid was formed. The solid, on recrystallization from methanol, yielded the α-keto ester **6b.** The acid **6a,** on treatment with lead tetraacetate, gave the acid **4a.** Lithium aluminum hydride reduction of the methyl ester **6b** (obtained from **6a**) gave the tetraol **7a,** which was characterized as the triacetate **7b.** The tetraol **7a** was also obtained by treatment of the ozonide **5** (vide infra) with $LiAlH_4$.

An interesting product was obtained when the mother liquor of crystallization of the ozonide was treated with methanolic potassium hydroxide. Work-up of the reaction mixture gave an acid which has been *tentatively* assigned the structure **8a.** The conditional assignment of structure **8a** to the product is based upon spectroscopic data obtained for its methyl ester derivative, formed on treatment of **8a** with diazomethane. The latter was also converted to the 17β-acetoxymethyl ester **8c.** The infrared spectrum of **8b** showed two hydroxyl bands at 3502 and 3480 cm^{-1} while the spectrum of **8c** exhibited a single sharp band at 3500 cm^{-1} and an acetoxy band at 1730 cm^{-1} indicating the presence of a secondary hydroxyl group and a tertiary hydroxyl group in **8a.** Both spectra also exhibited a sharp band at 1720 cm^{-1}. The NMR spectrum of **8b** in deuterated dimethyl sulfoxide exhibited an AB quartet centered at 172.9 Hz indicating the presence of an isolated methylene group. The observed geminal coupling (J_{AB} = 5 Hz) is somewhat smaller than usually found. The spectrum also showed a singlet at 217.5 Hz assigned to the methyl of the carbomethoxy group, a doublet located at 261 Hz (J = 5.0 Hz) for the 17α-H coupled with the 17β-OH, and a sharp singlet (equivalent to one proton) at 282.5 Hz due to the hydrogen of the tertiary hydroxyl. On exchange with D_2O all the signals for the OH protons disappeared, confirming the presence of a secondary and tertiary hydroxyl group. The NMR spectrum of the 17β-acetoxymethyl ester **8c** in deuteriochloroform was similar to that of **8b,** and exhibited a C-17 methine multiplet at 274 Hz.

The nature of the moiety at C-3 was deduced mainly from the high-resolution mass spectra of **8c** and **8b** (Tables I and II). The base peak at *m/e* 333 ($C_{21}H_{33}O_3$; see Table I)

Table I
Summary of High-Resolution Mass Spectral Data of Compound 8c

Base peak		Other ions			Metastable Peaks	
m/e	Formula	m/e	Formula (calcd mass)	Relative abundance, %	m/e	Transition
333.2427	$C_{21}H_{33}O_3$ 333.2430	416.2563	$C_{25}H_{36}O_5$ (416.2563)	17.6	398.7 (weak)	434–416
		398.2462	$C_{25}H_{34}O_4$ (398.2457)	8.1	382	416–398
		356.2383	$C_{23}H_{32}O_3$ (356.2357)	8.6	255	434–333
		334.2479	$C_{21}H_{34}O_3$ (334.2508)	25	223.8	333–273
		273.2238	$C_{19}H_{29}O_1$ (273.2218)	10.6	238	255–273
		255.2097	$C_{19}H_{27}$ (255.2113)	35.7		

Table II
Summary of High-Resolution Mass Spectral Data of Compound 8b

Base peak		Other ions			Metastable peaks	
m/e	Formula	m/e	Formula (calcd mass)	Relative abundance, %	m/e	Transition
291.2324	$C_{19}H_{31}O_2$ (291.2324)	374.2456	$C_{23}H_{34}O_4$ (374.2457)	19.1	338.8	392–374
		359		10.1	356.8	374–356
		356.2376	$C_{23}H_{32}O_3$ (356.2351)	12.5	256	291–273
		341		10.1	238	273–255
		315		24.8	223.5	291–255
		273.2245	$C_{19}H_{29}O$ (273.2218)	9.1		
		255.2113	$C_{19}H_{27}$ (255.2113)	18.7		
		231.1771	$C_{16}H_{26}O_1$ (231.1749)	9.5		
		215.1826	$C_{16}H_{23}$ (215.1800)	17.2		

in the spectrum of **8c** cannot be rationalized as arising from the ion *m/e* 416 ($C_{25}H_{36}O_5$) because this would require the loss of a $C_4H_3O_2$ (*m/e* 83) fragment. This suggests that the mass spectrum of **8c** (Table I) does not exhibit a molecular ion peak, and the base peak *m/e* 333 could be due to the loss of $C_4H_5O_3$ from an absent molecular ion at *m/e* 434. This fragmentation is confirmed by the presence of a weak metastable ion at *m/e* 255 for the transition *m/e* 434–333, and another at *m/e* 398.7 for the transition *m/e* 434–416. Hence, the fragment ion *m/e* 416 corresponds to the loss of water from the absent molecular ion *m/e* 434. The subsequent loss of acetate (*m/e* 273) and water (*m/e* 255) from the fragment *m/e* 333 (base peak) is in accord with the view that a $C_4H_5O_3$ moiety was first lost from C-3. A similar fragmentation pattern can be noted in the high-resolution mass spectrum of the 3,17β-dihydroxy **8b** (Table II). In this instance, in addition to the $C_4H_5O_3$ fragment two molecules of water were lost.

The presented evidence appears to be consistent with the β-keto ester structure **8c**. It is unlikely that 8 is derived from the ozonide **5** because **5** on treatment first with methanolic potassium hydroxide and then with diazomethane gave the 17β-hydroxy ester **4c**. The formation of 8 could be rationalized as proceeding by attack of peroxide on the β-diketone derived from the opening of the spiro enol ether **3** (Scheme II). The resulting hydroperoxide intermediate L in turn could undergo a Baeyer–Villiger type process giving **8c**, which on treatment with base gave **8a**. The β-keto acid **8a** thus formed would be expected to be cleaved under the basic conditions, and this may well account for the low yield obtained.

It should be pointed out that the structure of the α-keto ester N (Scheme II) would also be consistent with the presented spectroscopic data. The α-keto ester N could be obtained via a Baeyer–Villiger type reaction of a peroxide derived from the α-diketone M in a manner similar to that described for L. However, in view of the starting material **3** used and the method of processing the reaction mixture, this product seems less likely.

The described oxidative work-up of the ozonide provided a host of significant and interesting information; however, the overall picture was rather complex, particularly because of the multitude of rearrangements taking place. In an attempt to simplify the process and eliminate the oxidative rearrangements, a reductive work-up of the ozonide was undertaken. The ozonide **5**, on treatment with lithium aluminum hydride, gave a tetraol **7a** (Chart II) which was converted (acetic anhydride–pyridine) to the hydroxy triacetate **7b**. The NMR spectrum of **7b** showed a typical ABX pattern. The two methylene protons at C-4′ and the single proton at C-3′ form an isolated ABX three-proton system. The proton at C-3′, being adjacent to both the ace-

Chart II

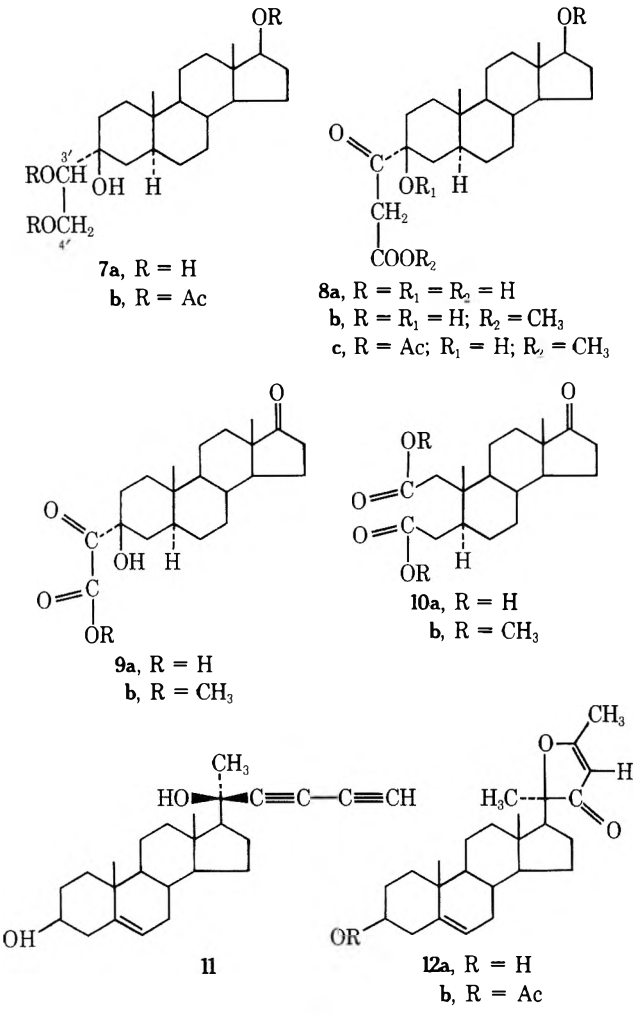
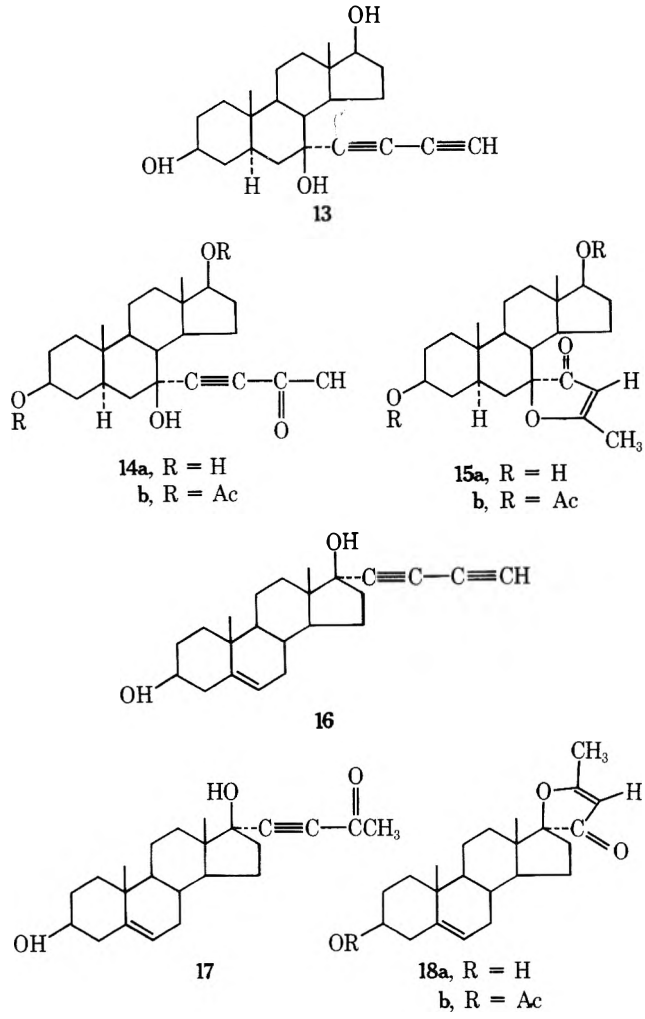


Chart III



tate and the hydroxy group, resonates in the downfield portion of the spectrum at 327.9 Hz and is the X portion of the ABX system. This hydrogen is coupled vicinally to both hydrogens at C-4′ (A and B) (J_{AX} = 2.8 Hz) giving rise to a quartet. The eight lines due to C-4′ protons which are coupled geminally as well as vicinally are centered at 273.5 and 248.6 Hz, respectively, the geminal coupling constant being 12 Hz. The chemical shifts and coupling constants were computed using the program[6] LAOCOON II.

Although the evidence assembled until now was consistent with the spiro structure **3,** we wished to provide more tangible proof for it. For this purpose the dihydroxy keto acid **6c** was submitted to mild oxidation with Jones reagent (2 min, 0°). Rather surprisingly, the C-3 moiety was not cleaved and only the 17β-hydroxyl was converted to a 17-ketone, yielding **9a,** which was identified as its methyl ester **9b.** The oxidation was then repeated at room temperature for 10 min, and in this instance both **9a** and 5α-androstane-3,17-dione (**1b**) were obtained. Rigorous oxidation of **6c** with chromium trioxide in acetic acid at 60° gave the dione **1b** and the dicarboxylic acid **10.** Finally, lead tetraacetate oxidation of **6c** gave 17β-hydroxy-5α-androstan-3-one (**1a**). These results constitute full proof of the spiro structure **3.**

No effort was made to determine the stereochemistry of the C-3 spiro moiety. However, based on the generally greater accessibility of the α side of the steroid molecule, and the linearity of the butadiyne anion, it seems reasonable to assume that the stereochemistry of the condensation product is as shown in **2.** Some support for this view is provided by the fact that the acetylene anion reacts with steroidal ketones to yield products with an axial ethinyl group.[7] Hence, barring inversion at C-3 during hydration and the subsequent enol ether formation, the stereochemistry of the spiro ring system is *tentatively assigned the configuration shown in* **3.**

We now turned our attention to other steroidal ketones. The reaction with pregnenolone proceeded uneventfully, except for the fact that in addition to **11,** a considerable amount of pregnenolone and of an insoluble (polymeric?) material was obtained. If it is assumed that the dibutyne anion reacted with the C-20 ketone in a manner analogous to other nucleophiles, then **11** should have the 20*R* configuration. Hydration and cyclization of **11** were carried out as before, and the resulting spiro product **12a** was characterized as the 3-acetate **12b.**

Treatment of 3β,17β-dihydroxy-5α-androstan-7-one with the reagent gave **13** (Chart III). The stereochemical assignment of the 7β-hydroxy-7α-diacetylene structure rests on the assumption that the attack of the reagent occurred from the less hindered α side of the substrate. The hydration–cyclization of **13** proceeded sluggishly and resulted in a mixture of products which was acetylated and then resolved by TLC (ethyl acetate); the more mobile compound proved to be the acetylenic ketone **14.** This indicates that hydration of the diyne does not proceed with the elimination of the tertiary hydroxyl and that the *terminal triple bond* is converted first to a ketone. The major product of the reaction was **15.**

Finally, the reaction of 3β-hydroxyandrost-5-en-17-one gave the 17β-hydroxydiyne **16.** Hydration of the 17β-hydroxydiyne **16** gave again two products, the keto acetylene **17** and the spiro analog **18.**

It may be concluded that saturated steroidal ketones react readily with the butadiyne anion to yield hydroxy diacetylenes. Hydration of the diacetylene proceeded without dehydration of the tertiary hydroxyl, as evidenced by the isolation of **14** and **17**. It is noteworthy that no evidence was obtained for the formation of α-diketones, and presumably in the instances investigated the β-diketones were formed. The facile enol cyclization of the terminal carbonyl with the tertiary hydroxyl is of considerable interest and has not been previously reported. Apparently in the case of the C-7 (**13**) and C-17 (**16**) analogs the hydration of the second acetylene group was slower and it was possible, therefore, to isolate the ketonic intermediates.

Experimental Section

Melting points were taken on a hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer in KBr micropellets. NMR spectra were recorded on a Varian DA-60 spectrometer at 60 MHz using $CDCl_3$ solutions, unless otherwise stated. Peaks are quoted in hertz downfield from a Me_4Si internal standard. Low-resolution mass spectra were recorded on a Varian Associates M-66 instrument and a Du Pont Model 21-491 instrument. The high-resolution mass spectra were recorded through the courtesy of Professor J. Meinwald of the Department of Chemistry of Cornell University, Ithaca, N.Y. Analyses were done by I. Betz, Kronach, Germany.

Preparation of 1,4-Dichloro-2-butyne.[8] 2-Butyne-1,4-diol (3.44 g) was placed in a three-necked flask fitted with a condenser, a dropping funnel, and a drying tube. The flask was immersed in a cooling bath, and thionyl chloride (12 g, 7.5 ml) was added dropwise (10 min) with constant stirring. When the evolution of gas ceased (30 min), the ice bath was removed and the contents were left at room temperature for 18 hr. The flask was slowly warmed on a water bath up to 80° and the temperature was maintained until there was no more evolution of gas. Excess thionyl chloride was removed on a water aspirator and the residual dark liquid was transferred to a vacuum distillation unit. The product, bp 61–65° (14–18 mm) [reported[3] bp 65–66° (16 mm)], weighed 2.6–3.0 g.

General Procedure for the Preparation of Butadiynyl Derivatives.[3] Sodium (2.3 g) and $Fe(NO_3)_3$ (50 mg) were added to liquid ammonia (135 ml) and the mixture was stirred under reflux until the blue color changed to light gray. 1,4-Dichlorobut-2-yne (4.1 g) was added dropwise and after 5 min a solution of the keto steroid (0.033 mol) in anhydrous tetrahydrofuran (65 ml, or enough to dissolve) was added. The mixture was stirred under reflux for 2.5 hr. Solid NH_4Cl was added, and the ammonia was allowed to evaporate overnight. Water was then added and the product was recovered with ether or chloroform. Purification by recrystallization was rather difficult. Stability of the butadiynyl derivatives was, in general, low and most of them decomposed when heated to moderate temperatures so that melting points were often ill defined. During recrystallization it was necessary to avoid lengthy heating of solution. In particular, satisfactory analyses could not be obtained for butadiynyl derivatives of 7-keto and 20-keto steroids. All the butadiynyl derivatives described herein were characterized mainly by the absence in the ir spectra of carbonyl peaks and the appearance of small bands at or near 2200 and/or 2050 cm^{-1}. The presence of a tertiary hydroxyl was established by its resistance to acetylation with acetic anhydride in pyridine. The NMR spectra of all these compounds showed a characteristic signal at 133–134 Hz for an acetylenic (–C≡CH) proton.

3α-Butadiynyl-3β,17β-dihydroxy-5α-androstane (2). Treatment of **1a** (18.8 g) with the reagent gave 13.8 g of crude **2**. The product was crystallized from ether–methanol, and showed an ill-defined melting point at about 240° dec: ν_{max} (KBr) 3300, 3400, 2210, 2050 cm^{-1}; NMR triplet 219 (J = 7 Hz, 17α-H), singlet 133 (–C≡CH), 49 (19-Me), 44 Hz (18-Me).

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.45. Found: C, 80.48; H, 9.47.

(20*R*)-20-Butadiynyl-3β,20-dihydroxypregn-5-ene (11). From the reaction of pregnenolone (5.2 g) with the butadiyne reagent there was obtained **11** (1.05 g), starting material (2.05 g), and an insoluble residue (1.8 g). The product **11** was not fully purified (ν_{max} 3590, 3400 cm^{-1}).

7α-Butadiynyl-3β,7β,17β-trihydroxy-5α-androstane (13). The reaction of 3β,17β-dihydroxy-5α-androstan-7-one (15.3 g) with the diyne reagent gave 13.0 g of crude **13**: ν_{max} 3325, 3400, 2225, 2060 cm^{-1}; NMR 134 Hz (s, –C≡CH). The product was not fully purified.

17α-Butadiynyl-3β,17β-dihydroxyandrost-5-ene (16). Treatment of 3β-hydroxyandrost-5-en-17-one (4.2 g) gave **16** (3.5 g). The crude product was crystallized from methanol: mp 206–208°; ν_{max} (KBr) 3595, 3345, 3200, 2240, 2060 cm^{-1}; NMR 322 (C-6 H), 134 (s, –C≡CH), 61 (19-Me), and 51 Hz (18-Me).

General Procedure for Hydration of Butadiynyl Derivatives. To the butadiynyl derivative (2.0 g) in methanol (50 ml) was added 10% sulfuric acid (50 ml) and mercuric sulfate (1.0 g). More methanol was added, if necessary, to keep the steroid in solution. The contents were refluxed for 16 hr, after which most of the methanol was removed by distillation under reduced pressure. Sufficient water was added and the product was isolated by extraction with chloroform. The latter was washed with a saturated solution of sodium chloride followed by water and then dried over anhydrous sodium sulfate. Removal of solvent yielded a crude residue which was processed further as required.

17β-Hydroxy-5α-androstane-3-spiro-[2′-(5′-methylfuran-3′-one)] (3a). Hydration of **2** (8 g) gave 5.5 g of **3a**. The product was recrystallized from methanol: mp 202–204°; λ_{max} (MeOH) 263 nm (log ϵ 3.98); ν_{max} (KBr) 3525, 1680, 1595 cm^{-1}; NMR 312.5 (s, 1 H, 4′-H), narrow doublet 130 ($J \simeq 1$ Hz, 5′-CH_3), 52.5 (19-Me), 44 Hz (18-Me); MS m/e 358 (M^+), 340 (M − 18), 325 [M − (18 + 15)], 255 [M − (H_2O + $C_4H_5O_2$)].

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.79; H, 9.55.

The 17β-acetate was prepared in the conventional manner.

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.54, 74.40; H, 8.95, 8.89.

3β-Acetoxypregn-5-ene-(20*R*)-spiro[2′-(5′-methylfuran-3′-one)] (12b). Conventional hydration of **11** (1 g) gave a residue (750 mg) which was acetylated and then fractionated by TLC. The recovered **12b** was crystallized from methanol: mp 190–193°; λ_{max} (MeOH) 261 nm (log ϵ 4.03); ν_{max} (KBr) 1728, 1690, 1605, 1252 cm^{-1}; NMR 32 (2 H, C-6 H and 4′-H), multiplet 272 (1 H, 3α-H), 132.5 (J = 1 Hz), 121 (acetate), 83.5 (21-Me), 61 (19-Me), and 49.5 Hz (18-Me); MS m/e 366 (M − 60), 351 [M − (60 + 15)], 2.98 (M − C_4H_4O), 255 (M − $C_6H_7O_2$).

Anal. Calcd for $C_{27}H_{38}O_4 \cdot 0.5\ H_2O$: C, 74.45; H, 8.95. Found: C, 74.65; H, 8.64.

3β,17β-Diacetoxy-5α-androstane-(7*S*)-spiro[2′-(5′-methylfuran-3′-one)] (15). The crude reaction product (10 g) containing **13** was hydrated and the recovered material (7.5 g) was acetylated in the conventional manner. The acetates were fractionated by TLC (ethyl acetate) to yield **14b** and **15b**.

The slower moving **15b** was crystallized from methanol: mp 197–198°; λ_{max} (MeOH) 266 nm (log ϵ 3.96); ν_{max} (KBr) 1735, 1725, 1690, 1590, 1250, and 1027 cm^{-1}; NMR ($CDCl_3$) 324 (s, 1-H, 4′-H), split singlet 135 (5′-CH_3), 121 (two acetates), 56 (19-Me), 46.5 Hz (18-Me).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.42; H, 8.20.

3β,17β-Diacetoxy-7β-hydroxy-7α-(3-oxo-1-butynyl)-5α-androstane (14b). The more mobile product (**14b**) recovered from the above-described TLC was crystallized from methanol: mp 209–210°; ν_{max} (KBr) 3445, 2210, 1735, 1710, 1670, 1375, 1270, and 1235 cm^{-1}; NMR ($CDCl_3$) 279 (m, 2 H, 3α- and 17α-H), 143 (CH_3CO), 121, 122 (3- and 17-acetates), 52 (19-Me), and 49 Hz (18-Me).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.49; H, 8.23.

3β,Hydroxyandrost-5-en-(17*S*)-spiro[2′-(5′-methylfuran-3′-one)] (18a). Hydration of **16** (2 g) gave a mixture of two products which were resolved by TLC (ethyl acetate) into 17 and 18.

The slower moving **18a** was recrystallized from methanol: mp 192–193°; ν_{max} (KBr) 3410, 1675, 1600 and 1075 cm^{-1}; λ_{max} (MeOH) 265 nm (log ϵ 3.83); NMR 318 (t, C-6 H) overlapping 314 (s, 4′-H), split singlet 130 (5′-CH_3), 58.5 Hz (split singlet, 19- and 18-Me).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.77; H, 8.95.

The product occasionally crystallized with a half a molecule of water, mp 146–148°.

Anal. Calcd for $C_{23}H_{32}O_3 \cdot 0.5\ H_2O$: C, 75.58; H, 9.10. Found: C, 75.26; H, 8.60.

The acetate **18b** was prepared in the conventional manner and it was isolated as a half-hydrate: mp 250–252°; λ_{max} (MeOH) 265 nm (log ϵ 3.83); ν_{max} (KBr) 1735, 1685, 1605, 1240 cm^{-1}; NMR 319 (t, C-6 H), 316 (s, 4′-H), 132 (5′-CH_3), 121 (acetate), 50.5 (19-Me), 49

Hz (18-Me); MS *m/e* 388 (M − 60), 323 [M − (60 + 15)], 270 (338 − C_4H_4O).

Anal. Calcd for $C_{25}H_{34}O_4 \cdot 0.5H_2O$: C, 73.68; H, 8.66. Found: C, 73.48; H, 8.25.

3β,17β-Dihydroxy-17α-(3-oxo-1-butynyl)androst-5-ene (17). The more mobile product recovered from the above TLC was **17.** Crystallization from methanol gave a sample: mp 178–182°; λ_{max} (KBr) 3525, 3410, 3200, 2200, 1665, and 1655 cm^{-1}; NMR 318 (t, C-6 H), 210 (m, 3α-H), 141 (s, CH_3CO), 51 (19-Me) and 42.5 Hz (18-Me); MS *m/e* 356 (M^+), 338 (M − 18), 323 [M − (15 + 18)], 320 (M − $2H_2O$), 305 [M − ($2H_2O$ + CH_3)], 295 [M − (C_2H_3O + H_2O)], 288 (M − C_4H_4O), 277 [M − (C_2H_3O + $2H_2O$)]; 270 [M − (C_4H_4O + H_2O)], 255 [(270 − 15) or $C_{19}H_{27}$].

Ozonide 5. A solution of the acetate **3b** (7 g) in anhydrous ethyl acetate (50 ml) was ozonized at −70°. After 6 min the solution turned blue and the ozonization was terminated in 15 min. Water (5 ml) and hydrogen peroxide (30%, 10 ml) were added and the mixture was shaken overnight. The aqueous phase was separated and the ethyl acetate solution was washed once with water. The organic solution was partitioned in the conventional manner into neutral and acid fractions.

The neutral portion gave a crystalline solid (700 mg) which was recrystallized rapidly from cold methanol to yield **5:** mp 103–105°; ν_{max} (KBr) 1730, 1250 cm^{-1}; NMR 328 (sharp s, 4′-H), 275 (t, *J* = 8 Hz, 17α-H), 121 (acetate), 108.5 (s, 5′-CH_3), 50.5 (19-Me), 46 Hz (18-Me).

Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.79; H, 8.09.

Methyl 3β,17β-Diacetoxy-5α-androstane-3α-oxalylate (6b). A. The acid fraction from the above ozonization experiment (230 mg) was treated with diazomethane. The methyl ester **6b** was crystallized from methanol: mp 172–174°; ν_{max} (KBr) 1740 (shoulder), 1725, 1240 cm^{-1}; NMR 275 (t, *J* = 8 Hz, 17α-H), 229 ($COOCH_3$), 123 (acetate), 122 (acetate), 52 (18-Me), and 47 Hz (19-Me); MS *m/e* 402 (M − 60), 374 (M − $C_3H_4O_3$), 343 [(402 − CH_3COO) or (374 − 31)], 333 ($C_{21}H_{33}O_3$), 257 ($C_{19}H_{29}$).

Anal. Calcd for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.25, 67.55; H, 8.23, 8.60.

B. Treatment of the crude mother liquor of ozonide crystallization with diazomethane gave **6b,** identical with the specimen described in experiment A.

Methyl 3β-Hydroxy-17β-acetoxy-5α-androstane-3α-maloylate (8c). An aliquot (0.5 g) of the crude residue of crystallization of **5** was dissolved in methanol (25 ml), then potassium hydroxide (1 g) in aqueous methanol (10 ml) was added, and the mixture was stored for 8 hr at ambient temperature. Most of the methanol was removed under reduced pressure. Water was added, and the alkaline solution was extracted several times with chloroform. No "neutral" residue was obtained after a conventional work-up of the combined chloroform extract.

The aqueous phase was acidified with dilute sulfuric acid and was exhaustively extracted first with chloroform and then with ethyl acetate. The combined extract was processed in the usual manner to yield, after solvent removal, a brown acidic residue (375 mg). Treatment of the residue with ethereal diazomethane gave **8b** as a powder (70 mg). The product was crystallized from chloroform–methanol: mp 233–235°; ν_{max} (KBr) 3502, 3480, and 1722 cm^{-1}; NMR (DMSO-d_6) 282.5 (s, 3β-OH), 261.5 (d, *J* = 5.0 Hz, 17β-OH), 218 (s, $COOCH_3$), 173 (q, J_{AB} = 5 Hz, 3α-$COCH_2COOR$), 46 (19-Me), and 36 Hz (18-Me). On exchange with D_2O the signals at 282 and 261.5 Hz disappeared. See Table II for mass spectral data.

Acetylation of **8b** gave **8c,** which was crystallized from ether–hexane: mp 170–172°; ν_{max} (KBr) 3500 (sharp), 1730, 1720, and 1235 cm^{-1}; NMR ($CDCl_3$) 274 (t, *J* = 7 Hz, 17α-H), 227 (s, $COOCH_3$), 179 (q, J_{AB} = 5 Hz, 3α-$COCH_2COOR$), 121 (s, acetate), 50 (19-Me), and 46 Hz (18-Me). See Table I for mass spectral data.

Anal. Calcd for $C_{29}H_{38}O_5$: C, 69.09; H, 8.81. Found: C, 68.51; H, 8.73.

Methyl-3β,17β-dihydroxy-5α-androstane-3α-oxalyl (6d). To a solution of **6b** (100 mg) in methanol (25 ml) was added potassium hydroxide in aqueous methanol (25 ml). The mixture was stored for 16 hr at room temperature, after which most of the methanol was removed under reduced pressure. The residual mixture was diluted with water and partitioned into "neutral" and "acidic" fractions. The acidic fraction **6c** (64 mg) was treated with diazomethane to yield **6d.** The ester was crystallized from ether–hexane: mp 180–182°; ν_{max} (KBr) 3500, 1735, 1260 (medium), and 1075 cm^{-1}; NMR (CD_3OD) 226 (s, $COOCH_3$), 52 (19-Me), and 43 Hz (18-Me).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.88; H, 9.01.

Methyl 3β,17β-Diacetoxy-5α-androstane-3α-carboxylate (4b). A. A solution of ozonide **5** in methanol was stored for 36 hr at room temperature. The recovered syrup resisted crystallization and its ir (liquid film) was different from that of **5.** The obtained mixture was resolved by TLC.

The product in the more mobile zone, probably a peroxide, had bands at 3450 and 1740 cm^{-1}. It could not be obtained in crystalline form and was not investigated further. The residue recovered from the less mobile zone was the acid **4a,** which on treatment with diazomethane gave **4b.**

B. To a solution of acid **6a** (100 mg) in benzene (8 ml) was added lead tetraacetate (250 mg) and the mixture was stored for 3.5 hr in the dark. The reaction was terminated with ethylene glycol (5 drops) and the solution was stored for 12 hr at ambient temperature. After addition of ethyl acetate (50 ml), the organic solution was washed with water and dried and the solvent was removed to yield crystalline **4a:** ν_{max} (KBr) 3600–3100 (broad), 1745, 1720, 1700, and 1250 cm^{-1}.

The acid **4a** was treated with diazomethane and the ester was crystallized from methanol to give **4b** (85 mg): mp 143–145°; ν_{max} (KBr) 1745, 1730, 1725, 1270, 1250, and 1030 cm^{-1}; NMR ($CDCl_3$) 273 (t, 17α-H), 221 (s, $COOCH_3$), 120 (two acetates), 50 (19-Me), and 46 Hz (18-Me).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.15; H, 8.98.

C. A solution of the ozonide **5** (5 mg) in methanolic potassium hydroxide (10%, 2 ml) was stored, at room temperature, for 24 hr. The solution was then processed as described for **8c.** Treatment of the acidic fraction with ethereal diazomethane, followed by TLC [silica gel, Merck $HF_{254+366}$; hexane–ethyl acetate (1:1)], gave **4c** (2 mg): MS *m/e* 350 (M^+), 332 (M^+ − 18), 314 (M^+ − $2H_2O$), 291 (M^+ − COOMe), 273 [M^+ − (COOMe + H_2O)], 255 [M^+ − (COOMe + $2H_2O$)].

Methyl 3β-Hydroxy-17-oxo-5α-androstane-3α-oxalylate (9b). A. Jones reagent was added dropwise to a stirred solution of **6c** (100 mg) in acetone (25 ml). After 10 min, excess reagent was decomposed with a few drops of 2-propanol and the mixture was poured onto crushed ice. The product was recovered with ethyl acetate to yield after a conventional work-up a crude residue (46 mg). The obtained syrup was resolved by TLC [ethyl acetate–benzene (3:2)] into two products.

The faster moving zone, after elution and crystallization, gave **1b** (6 mg), which was identified by comparison (ir, NMR, and TLC, mobility) with an authentic sample.

The less mobile band on elution gave the acid **9a,** which was treated with diazomethane to yield **9b.** A sample was crystallized from methanol: mp 162–164°; ν_{max} (KBr) 3525, 1745, 1730 (shoulder), 1250 (medium), and 1100 cm^{-1} (medium).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.47; H, 8.85.

B. The above oxidation, when carried out at 0° for 2 min, gave only **9a** which was identified as **9b.**

Methyl 2,3-Seco-5α-androstan-17-one-2,3-dioate (10b). To a solution of **6c** (100 mg) in glacial acetic acid (20 ml), a solution of chromic anhydride (120 mg) in water (5 ml) and acetic acid (20 ml) was added, and the mixture was heated at 60° for 2 hr. Water was added (150 ml) and after a conventional work-up, the acid **10a** (55 mg) was obtained: ν_{max} (KBr) 3800–3100 (broad), 1730, and 1705 cm^{-1}. Treatment of **10a** with diazomethane gave the dimethyl ester **10b,** which was crystallized from ether–hexane, mp 68–69°.

The sample proved identical with an authentic specimen of **10b** prepared from the 17β-hydroxyl analog.[9]

17β-Hydroxyandrostan-3-one Obtained by Lead Tetraacetate Oxidation of 6c. A mixture of **6c** (30 mg), methanol (2 ml), benzene (2 ml), and lead tetraacetate (100 mg) was stored in the dark for 3.5 hr. The reaction was terminated with ethylene glycol and the solution was stored overnight.

Ethyl acetate (60 ml) was added, and the organic phase was washed with water, dried, and concentrated to a residue. The syrup was dissolved in dilute aqueous methanolic sodium hydroxide, and after 30 min it was diluted with water. The alkaline phase was extracted with chloroform. The organic extract was washed, dried, and evaporated to yield **1a** (17 mg).

17β-Acetoxy-3α-(1,2-diacetoxyethyl)-5α-androstan-3β-ol (7b). To a stirred solution of ozonide **5** (100 mg) in anhydrous ether (30 ml) immersed in an ice bath was added a solution of lithium aluminum hydride (100 mg) in anhydrous ether (25 ml). Stirring was continued for 1 hr at ambient temperature, and then the

solution was refluxed for 3 hr. After cooling, a few drops of a saturated solution of sodium sulfate were added, and the white solid was removed by filtration. The solid was washed with acetone, then extracted with chloroform in a Soxhlet for 48 hr. From the filtrate and the chloroform extract a total of 51 mg of **7a** was obtained: mp 176–178°; ν_{max} (KBr) 3400, 1050 cm^{-1}. The tetrol **7a** was acetylated (pyridine–acetic anhydride, 16 hr, room temperature) and the triacetate **7b** was recovered in the conventional manner. The product was crystallized from methanol: mp 143–144°; ν_{max} (KBr) 3510 (sharp), 1730, 1725, and 1248 cm^{-1}; NMR 126.5 (acetate), 121 (two acetates), 50 (19-Me), and 46 Hz (18-Me).

Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.75; H, 8.85. Found: C, 67.45; H, 8.82.

Acknowledgment. We thank Professor Jerrold Meinwold, Department of Chemistry, Cornell University, Ithaca, N.Y., for the high-resolution mass spectra. We are indebted to Dr. T. A. Wittstruck of this laboratory for the computer LAOCOON II NMR calculations.

Registry No.—**1a**, 521-18-6; **2**, 54642-80-7; **3a**, 54632-41-6; **3b**, 54632-42-7; **4a**, 54642-81-8; **4b**, 54632-43-8; **4c**, 54632-44-9; **5**, 54632-45-0; **6a**, 54632-46-1; **6b**, 54632-47-2; **6c**, 54632-48-3; **6d**, 54632-49-4; **7a**, 54632-50-7; **7b**, 54632-51-8; **8b**, 54632-52-9; **8c**, 54632-53-0; **9b**, 54632-54-1; **10a**, 1165-38-4; **10b**, 1169-77-3; **11**, 54632-55-2; **12b**, 54632-56-3; **13**, 54632-57-4; **14b**, 54632-58-5; **15b**, 54632-59-6; **16**, 2010-48-2; **17**, 2429-68-7; **18a**, 54632-60-9; **18b**, 54632-61-0; 1,4-dichlorobut-2-yne, 831-10-3; 2-butyne-1,4-diol, 110-65-6; pregnenolone, 145-13-1; 3β,17β-dihydroxy-5α-androstan-7-one, 28375-34-0; 3β-hydroxyandrost-5-en-17-one, 53-43-0.

References and Notes

(1) This investigation was supported by National Institutes of Health Grants CA-07137, CA-13369, and CA-K3-16614.
(2) (a) Postdoctoral Fellow, 1964–1966. Assistant Drugs Controller, South Zone, Custom House, Madras-1, India. (b) Postdoctoral Fellow, 1970–1971.
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Spiro Piperidines. I. Synthesis of Spiro[isobenzofuran-1(3*H*),4′-piperidines] and Spiro[isobenzofuran-1(3*H*),3′-piperidines]

Adrian Marxer, Herman R. Rodriguez,* Joseph M. McKenna, and Hsin Mei Tsai

Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901, and CIBA-GEIGY Ltd., Basle, Switzerland

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General synthetic methods for the preparation of 3,3-disubstituted aminoalkyl phthalides are described. Their specific use in the synthesis of spiro[isobenzofuran-1(3*H*),4′-piperidines] and spiro[isobenzofuran-1(3*H*),3′-piperidines] is elaborated. The chemistry of these heterocycles is also discussed.

Although the chemistry of phthalides in general is quite extensive,[1] careful examination of the literature reveals that there are few papers concerning the synthesis of phthalides containing an aminoalkyl side chain in the 3 position.[2a-g] The most general method reported consists in condensation of phthalaldehydic acids with nitroalkanes followed by reduction of the 3-nitroalkyl phthalides produced either electrolytically,[2a] catalytically,[2b] or by dissolving metals.[2c] A lesser used method is the hydrolysis of 3-alkylidene phthalides, formation of the corresponding isonitroso ketones, and catalytic reduction to the 3-aminoalkyl phthalides.[2d] Other approaches are of limited synthetic utility.[2e,f] A serious drawback of most of these methods is that their nature precludes formation of 3,3-disubstituted aminoalkyl phthalides and therefore this class of compounds is essentially unknown.[2g,h]

The recent work of Meyers[3] and Hauser[4] utilizing aryl organometallics containing a masked carboxylic acid in the ortho position suggested the possibility of obtaining a simple, general synthesis of just such phthalides. Accordingly, we report herein this method and its application to the synthesis of the hitherto unknown[2h] spiran systems spiro[isobenzofuran-1(3*H*),4′-piperidines] and spiro[isobenzofuran-1(3*H*),3′-piperidines].[5]

Spiro[isobenzofuran-1(3*H*),4′-piperidines]. The first synthetic approach (method A) made use of the method of Meyers.[3] Reaction of the magnesium derivative of 2-(2-bromophenyl)-4,4-dimethyloxazoline (1) with *N*-alkylpiperidones **2a,b** gave the expected piperidinols **3a,b**, albeit in low yield (~35%). Subsequent acid hydrolysis led to the desired phthalides **4a,b**. Investigation of the side products of the Grignard reactions revealed starting piperidones **2a,b**

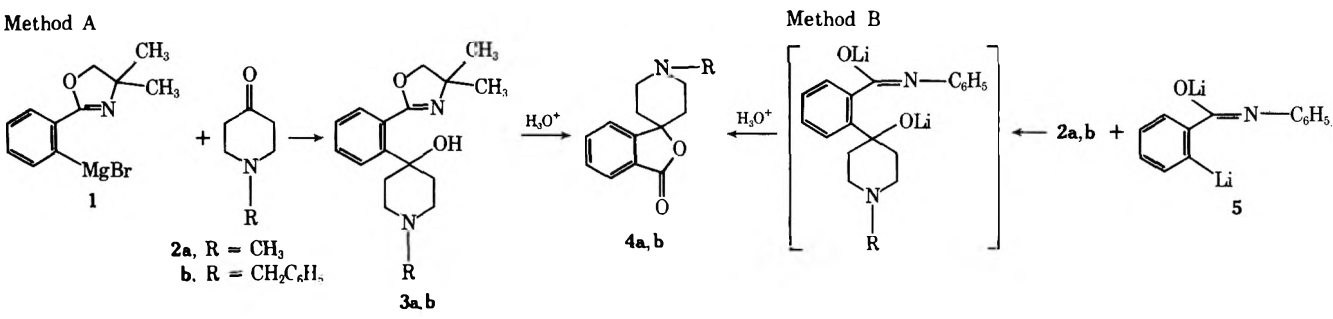
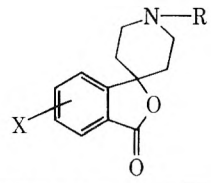


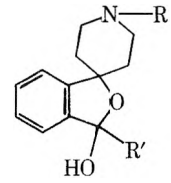
Table I
Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ones[a-c]



Registry no.	X	R	Yield, %	Method	Mp or bp, °C[d,e]	Solvent of crystn
54595-70-9	H	CH_3	31.7	A	147–148	Ether
			49.6	B	149–150	Ether
37663-42-6	H	$CH_2C_6H_5$	26.6	A	103–104[f]	Cyclohexane
			41.5	B	102–103	Cyclohexane
54595-71-0	6-Cl	CH_3	25.2	B	209–213	Ether
54595-72-1	6-Cl	$CH_2C_6H_5$	17.3	B	196–202 (0.01)	
54595-73-2	6-F	CH_3	45.0	B	176–179	THF
54595-74-3	4-OCH_3	CH_3	23.7	B	177–180	Benzene–cyclohexane
54595-75-4	6-OCH_3	CH_3	38.9	B	161–166 (0.05)	
54595-76-5	7-OCH_3	CH_3	19.0	B	141–144 (0.10)	

[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all compounds listed in the table. [b] All compounds exhibited absorption in the ir typical of phthalides[14] (1755–1758 cm^{-1}). [c] All compounds exhibited NMR spectra consistent with assigned structures. [d] All melting points and boiling points are uncorrected. Boiling points are expressed in °C (mmHg). [e] Hydrochlorides of all compounds were prepared in the usual manner. The melting point (solvent of crystallization) listed in the order of the table are as follows: 270–272° (EtOAc–MeOH), 280–283° (CH_3CN–MeOH), 265–268° (H_2O), 284–287° (H_2O), 254–255° (EtOAc–MeOH), 238–241° (EtOAc–EtOH), 236–238° (EtOAc–EtOH), 248–250° (EtOAc–EtOH). [f] Lit.[2h] mp 105–106°.

Table II
3-Alkyl-(aryl)spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-ols[a,b]



Registry no.	Compd no.	R	R′	Yield, %[c]	Mp, °C[d]	Solvent of crystn
54595-77-6	11e	CH_3	C_6H_5	92.0	170–172	EtOAc
54595-78-7	f	CH_3	*p*-FC_6H_4	64.7	168–170	EtOAc
54595-79-8	g	CH_3	*p*-$CH_3OC_6H_4$	80.5	158–161	EtOAc
54595-80-1	h	CH_3	2-Thienyl	41.0	194–196	EtOAc
54595-81-2	i	CH_3	CH_3	69.5	155–157	Ether
54595-82-3	j	CH_3	C_2H_5	87.5	158–161	Ether
54595-83-4	k	CH_3	*i*-C_3H_7	61.0	163–166	Ether
54595-84-5	l	CH_3	c-C_6H_{11}	77.0	135–137	Petroleum ether
54595-85-6	m	CH_3	$CH_2C_6H_5$	68.2	127–129	EtOAc
54595-86-7	n	CH_3	$(C_6H_5)_2CH$	66.1	168–170	Ether
54595-87-8	o	$CH_2C_6H_5$	$CH_2C_6H_5$	91.0	149–151	Cyclohexane
54595-88-9	p	CH_3	$CH_2CH_2C_6H_5$	75.3	93–96	Ether–petroleum ether

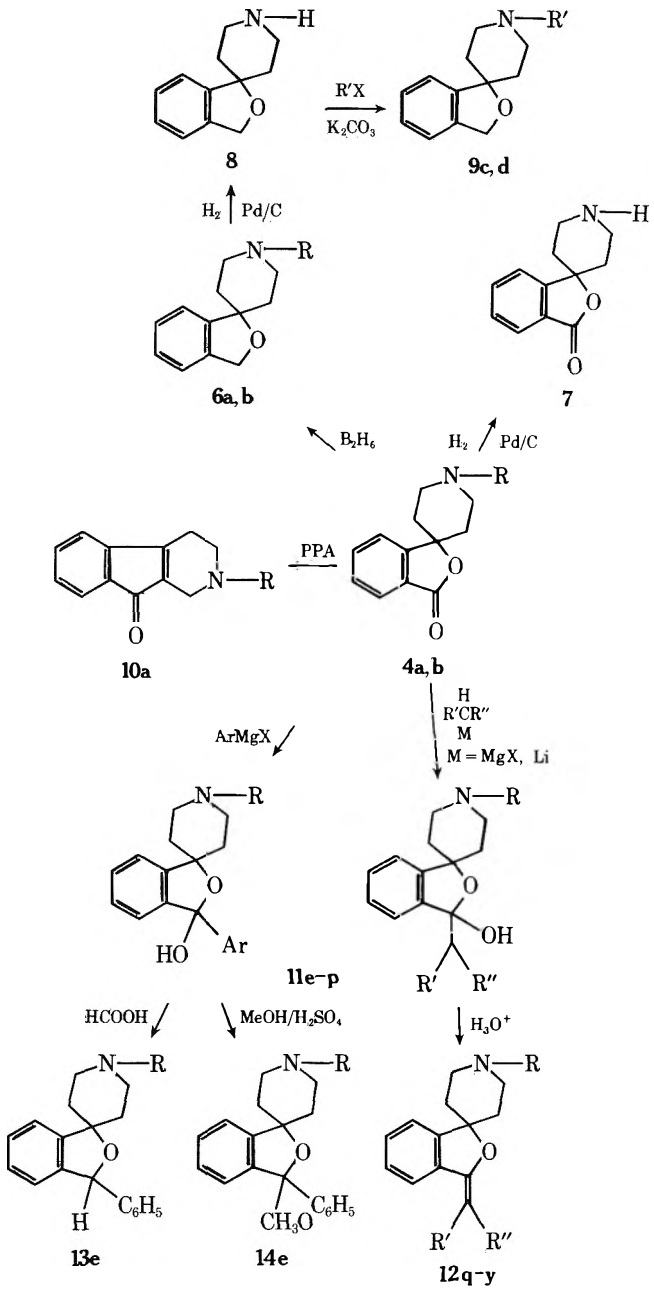
[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all compounds listed in the table. [b] All compounds exhibited NMR spectra consistent with assigned structures. [c] No attempt was made to optimize yields. [d] All melting points are uncorrected.

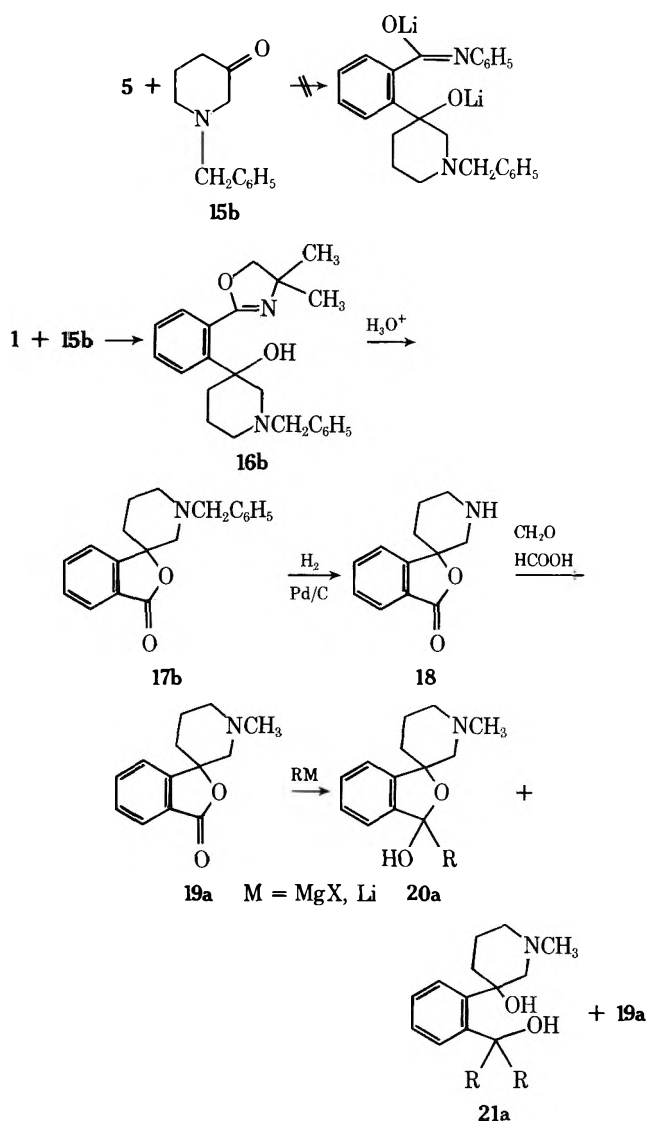
and 4,4-dimethyl-2-phenyloxazoline exclusively under a variety of reaction conditions. These results strongly suggested that the main competing reaction was enolization of **2a,b** by the Grignard reagents.[6] We therefore explored the known tendency of lithium aryls to be more reactive toward carbonyl additions with less attendant enolization of substrate.[7] Circumstances were particularly favorable in this instance, since Hauser's[4] ortho-lithiated benzamide species could be utilized.

It was determined that reaction of 2-lithio-*N*-phenylbenzamide (**5**),[8] prepared by a modification of Hauser's procedure[4] (see Experimental Section) with **2a,b,** led directly on acidic work-up[9] to phthalides **4a,b** in moderate yields (50 and 42%, respectively). This approach (method B) proved not only to be shorter and higher yielding (see Table I) but also more versatile in that a wider variety of benzo-substituted compounds (Table I) could be prepared, since the correspondingly functionalized benzoic acids are generally more accessible than the substituted 2-bromobenzoic acids. Of course the functional groups chosen were, perforce, limited to those stable to *n*-butyllithium, but in no case was there evidence of lithiation other than ortho to the amide moiety.[10a,b]

A study of some of the reactions of this ring system was next undertaken. Reduction of **4a,b** to the corresponding phthalans **6a,b** proceeded smoothly with diborane. Reductive cleavage of the benzyl group either in **4** or **6b** gave the parent NH derivatives **7** and **8.** Reaction of **8** with a variety of alkylating agents gave new *N*-alkyl derivatives **9c,d** in moderate yield. Treatment of **4a** with PPA yielded the novel indenone **10a.**

It has been reported that reaction of 3,3-dialkyl-





phthalides with Grignard reagents proceeds in a discrete manner to obtain monoadducts.[11] This was also found to be the case with this ring system. Treatment of **4a,b** with a wide variety of aryl and alkyl Grignards as well as lithium aryls and alkyls led to the corresponding phthalanols **11e–p** (Table II). Where possible structurally, these derivatives dehydrated readily to give the vinyl ethers **12q–y** (Table III).[12] 3-Aryl phthalanols such as **11e** could either be reduced with refluxing formic acid to phthalan **13e** or solvolyzed to phthalanol ether **14e** with cold $MeOH–H_2SO_4$.

Spiro[isobenzofuran-1(3*H*),3′-piperidines]. In contrast to **2b,** the isomeric 1-benzyl-3-piperidone (**15b**) gave evidence (ir absorption) of formation of practically no phthalide when treated with **5.** Fortuitously, application of the Meyers[3] approach, i.e., treatment of **1** with **15b,** yielded the corresponding piperidinol **16b** (47%). Acid hydrolysis gave the desired phthalide **17b.** Hydrogenolysis of **17b** gave the NH derivative **18,** which in turn yielded the NCH_3 derivative **19a** when treated with formaldehyde and formic acid. Contrary to the results obtained with **4a,** reaction of **19a** with a variety of organometallic reagents led to complex mixtures consisting of monoadducts **20a,** diadducts **21a,** and starting material.[13]

An examination of models provides a plausible explanation of this difference in behavior, i.e., monoadduct **20a** has the possibility of chelate formation via a favorable 1,3-diaxial interaction.[15] In this form the adduct is in the ketonic mode, which can then further react to yield diol **21a.** However, monoadducts from **4a** have no such option since

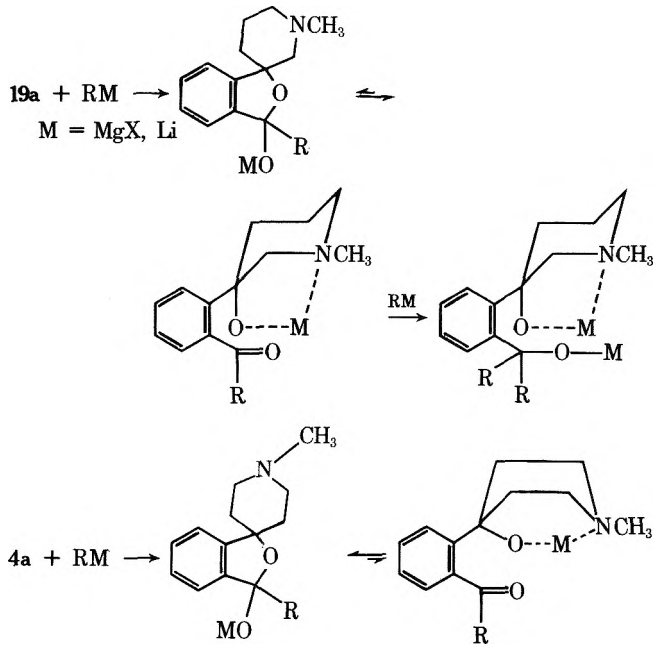
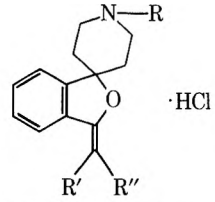


Table III
3-Alkylidenespiro[isobenzofuran-1(3*H*),4′-piperidines][a-c]



Registry no.	Compd no.	R	R′	R″	Yield, %[d]	Mp, °C[e]	Solvent of crystn
54595-89-0	12q	CH_3	H	CH_3	62.1	287–289	CH_3CN
54595-90-3	r	CH_3	CH_3	CH_3	57.0	293–295	CH_3CN–MeOH
54595-91-4	s	CH_3		c-C_5H_{10}	32.3	260–262	EtOAc
54595-92-5	t	CH_3	H	C_6H_5	68.0	289–291	CH_3CN–MeOH
54595-93-6	u	CH_3	C_6H_5	C_6H_5	98.5	>315	EtOH
54595-94-7	v	CH_3	H	$CH_2C_6H_5$	58.5	231–233	EtOAc
54595-95-8	w	CH_3	H	3-Methyl-5-isoxazolyl	38.3	>315	CH_3CN–MeOH
54595-96-9	x	CH_3	H	4-Pyridyl	44.7	155–157[f]	Cyclohexane
54595-97-0	y	$CH_2C_6H_5$	H	C_6H_5	93.5	284–286	CH_3CN–MeOH

[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all the compounds listed in the table. [b] All compounds exhibited NMR spectra consistent with assigned structures. [c] Compounds in which R″ is either aryl or heterocyclyl exhibited uv spectra consistent with the trans stilbene type structure. [d] No attempt was made to optimize yields. [e] All melting points are uncorrected. [f] This melting point is for the free base.

a chelate can form only through the unfavorable boat 1,4 interaction.[16] These monoadducts are therefore locked into the phthalanol mode and as such are stable to further reaction under these conditions.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 521 grating infrared spectrophotometer. Spectra were obtained as Nujol mulls unless otherwise specified. Absorption bands are reported in reciprocal centimeters. Ultraviolet spectra were obtained on a Carey 14 spectrophotometer in MeOH solution. NMR spectra were recorded on a Varian A-60 spectrometer. Spectra were obtained in deuteriochloroform solution unless otherwise specified with tetramethylsilane as the internal standard. The chemical shifts are reported in parts per million (δ). Melting points were determined on a Thomas-Hoover melting point apparatus. All melting points and boiling points are uncorrected.

All solvents were dried over molecular sieves. Reactions with organometallic reagents were maintained under a N_2 atmosphere. Solutions of reaction work-ups were dried either over K_2CO_3 (basic products) or Na_2SO_4 (neutral products).

Grignard reagents and organolithium reagents were obtained from Alfa Chemical Co. except for *n*-butyllithium, which was supplied by Foote Mineral Co. Diborane solutions and the Mg chips utilized for preparation of Grignards were also obtained from Alfa Chemical Co. All other reagents were supplied by Aldrich Chemical Co.

2-Bromo-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide. To a cooled solution of 2-amino-2-methyl-1-propanol (458 g, 5.15 mol) in 1.10 l. of CH_2Cl_2 was added a solution of 2-bromobenzoyl chloride (575 g, 2.50 mol) in 1.10 l. of CH_2Cl_2 at such a rate as to maintain the temperature at 0°. After addition was complete, stirring was continued for 4 hr at the same temperature. The mixture was filtered and the filtrate was washed with 3 *N* HCl and water, dried, and evaporated in vacuo. Trituration with ether gave 624 g (88%) of colorless crystals: mp 142–144° (lit.[3] mp 135–136°); ir 3240, 3190, 3070 (OH, NH), 1630 cm^{-1} (C=O); NMR (DMSO) δ 7.1–7.9 (m, 4, ArH), 4.80 (t, 1, OH), 3.50 (d, 2, CH_2), 1.33 (s, 6, CH_3).

Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.57; H, 5.19; N, 5.15. Found: C, 48.47; H, 5.09; N, 5.02.

2-(2-Bromophenyl)-4,4-dimethyl-2-oxazoline. Thionyl chloride (800 ml) was added to 2-bromo-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide (200 g, 0.73 mol) with stirring at room temperature. The resulting solution was allowed to stand overnight and was then poured into 3 l. of ether. The mixture was filtered and washed well with ether to yield 186 g (87%) of colorless crystals: mp 118–120° (lit.[3] mp 108–110°); ir 1640 cm^{-1} (C=N); NMR (TFA) 11.4 (s, 1, H), 7.5–8.2 (m, 4, ArH), 5.02 (s, 2, CH_2), 1.84 (s, 6, CH_3).

Anal. Calcd for $C_{11}H_{12}BrNO \cdot HCl$: C, 45.56; H, 4.17; N, 4.83. Found: C, 45.28; H, 4.54; N, 4.61.

The free base was prepared by dissolution of the hydrochloride in a minimum amount of ice-cold water, layering with ether, and adjustment of the aqueous layer to pH 10 by the addition of cold 20% NaOH. The layers were then separated and the aqueous phase was extracted with ether. The combined extracts were washed once with cold water, dried, and evaporated in vacuo to yield a colorless solid, mp 36–38°. Distillation in vacuo gave 148 g (91%) of analytically pure material: bp 93–95° (0.7 mm); mp 38–39°; ir 1640 cm^{-1} (C=O); NMR δ 7.1–7.9 (m, 4, ArH), 3.97 (s, 2, CH_2), 1.33 (s, 6, CH_3).

Anal. Calcd for $C_{11}H_{12}BrNO$: C, 52.01; H, 4.76; N, 5.51. Found: C, 52.11; H, 4.70; N, 5.39.

1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (4a). Method A. Freshly cut Mg (7.2 g, 0.30 g-atom) was placed in a dry flask. A small crystal of I_2 was added and just enough THF to cover the Mg. The mixture was then refluxed on a steam bath until the color had disappeared (~10 min). Approximately 10% of a solution of 2-(2-bromophenyl)-4,4-dimethyloxazoline (72.0 g, 0.284 mol) in 900 ml of THF was added all at once and reflux was continued until a brown coloration appeared. The remainder of the solution was added dropwise with continued reflux. After addition was complete heating was maintained for 2 hr, at which point almost all of the Mg had dissolved. The solution of **1** was then cooled to 0° and 1-methyl-4-piperidone (**2a**, 32.5 g, 0.33 mol) was added dropwise with stirring. The reaction mixture was stirred overnight at room temperature and poured over a mixture of ether and water. The layers were separated and the aqueous layer was extracted with ether. The combined extracts were washed with water, dried, evaporated in vacuo, and crystallized from acetone to give 28.0 g (34%) of **3a** as a colorless solid: mp 158–160°; ir 3150 cm^{-1} (OH); NMR δ 7.2–7.8 (m, 4, ArH), 3.29 (s, 2, OCH_2), 2.28 (s, 3, NCH_3), 2.0–3.5 (m, 8, CH_2), 1.30 (s, 6, CCH_3).

Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 71.03; H, 8.25; N, 9.64.

A solution of **3a** (23.0 g, 0.80 mol) in 480 ml of 3 *N* HCl was refluxed for 5 hr and then evaporated in vacuo to yield a colorless solid. This was layered between $CHCl_3$ and water and the pH of the aqueous layer was adjusted to 10 with saturated KOH solution. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined extracts were washed with water, dried, and evaporated in vacuo to give an oil which was crystallized from ether to yield 16.0 g (93%) of colorless crystals of **4a**: mp 147–148°; ir 1758 cm^{-1} (C=O); NMR δ 7.2–8.0 (m, 4, ArH), 2.38 (s, 3, NCH_3), 1.4–3.0 (m, 8, CH_2).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.52; H, 6.89; N, 6.50.

Method B. To a solution of *N*-phenylbenzamide (148 g, 0.75 mol) in 1.20 l. of THF at −70° was added 1.20 l. of a 1.6 *M* solution

of *n*-butyllithium with stirring. After addition was complete the solution of **5** was warmed to 0° and **2a** (169 g, 1.70 mol) was added dropwise over a period of 90 min. The reaction mixture was stirred overnight at room temperature and poured into a mixture of 3 *N* HCl and $CHCl_3$. The layers were separated and the organic layer was extracted with 3 *N* HCl. The combined extracts were made basic to pH 10 with saturated KOH solution and reextracted with $CHCl_3$. The latter extracts were washed well with water, dried, and evaporated in vacuo to yield an oil which was crystallized from ether to give 81.0 g (50%) of colorless crystals of **4a** exhibiting the same physical and spectral properties as **4a** obtained by method A.

1′-Benzylspiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (4b). Method A. A solution of **1** was prepared as illustrated for the synthesis of **3a** utilizing 50.0 g (0.195 mol) of 2-(2-bromophenyl)-4,4-dimethyloxazoline, 5.0 g (0.21 g-atom) of Mg, and 37.8 g (0.20 mol) of 1-benzyl-4-piperidone (**2b**). After a similar work-up there was obtained an oil which was triturated with ice-cold toluene. The resulting colorless solid was crystallized from benzene to give 22.5 g (35%) of **3b** as colorless crystals: mp 97–100°; ir 3150 (OH), 1660 cm^{-1} (C=N); NMR δ 7.2–7.9 (m, 9, ArH), 3.62 (s, 2, NCH_2Ar), 3.42 (s, 2, OCH_2), 1.5–3.2 (m, 9, CH_2, OH), 1.38 (s, 6, CH_3).

Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.94; H, 7.85; N, 7.49.

A solution of **3b** (48.0 g, 0.132 mol) in 1.20 l. of 3 *N* HCl was refluxed and worked up in a manner similar to that illustrated for the preparation of **4a** to give an oil which was crystallized from cyclohexane to give 29.5 g (76%) of **4b** as a colorless solid: mp 103–104° (lit.[2h] mp 105–106°); ir 1755 cm^{-1} (C=O); NMR δ 7.1–7.8 (m, 4, ArH), 3.62 (s, 2, NCH_2Ar), 1.4–3.2 (m, 8, CH_2).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.40; H, 6.58; N, 4.96.

Method B. A solution of **5** was prepared as for the synthesis of **4a**. To this was added **2b** (282 g, 1.49 mol) at 0°. A similar work-up yielded an oil which was crystallized from cyclohexane to give 91.0 g (42%) of **4b** as a colorless solid which exhibited identical physical and spectral properties with those obtained from method A.

1′-Methylspiro[isobenzofuran-1(3*H*),4′-piperidine] Hydrochloride (6a). To a solution of **4a** (8.0 g, 37 mmol) in 80 ml of THF cooled to 0° was added dropwise 74 ml of 1 *M* diborane (THF) with stirring. After addition was complete the mixture was kept at room temperature for 30 min and then refluxed overnight. The solution was then cooled to 0° and 29 ml of 6 *N* HCl was added dropwise. The mixture was then refluxed for 5 hr and the solvents were evaporated in vacuo to give an oil which was layered between ether and water. The pH of the aqueous layer was adjusted to 10 with saturated KOH solution. The layers were separated and the aqueous layer was extracted with ether. The combined extracts were washed with water, dried, and evaporated in vacuo to give an oil which was converted to the hydrochloride in the usual manner to obtain 5.3 g (60%) of colorless crystals: mp 281–282°; NMR (DMSO) δ 7.2–7.5 (m, 4, ArH), 5.06 (s, 2, OCH_2), 4.46 (s, 3, NCH_3), 3.1–3.5 (m, 4, NCH_2), 2.2–2.5 (m, 4, CH_2).

Anal. Calcd for $C_{13}H_{17}NO \cdot HCl$: C, 65.05; H, 7.56; N, 5.84. Found: C, 65.06; H, 7.62; N, 5.60.

1′-Benzylspiro[isobenzofuran-1(3*H*),4′-piperidine] Hydrochloride (6b). A solution of **4b** (58.6 g, 0.20 mol) in 600 ml of THF was treated with 400 ml of 1 *M* diborane (THF) as for the preparation of **6a**. A similar work-up gave an oil which was converted to the hydrochloride in the usual manner to obtain 52.0 g (93%) of colorless crystals: mp 252–253°; nmr δ 7.1–7.9 (m, 9, ArH), 5.05 (s, 2, NCH_2Ar), 4.25 (s, 2, OCH_2), 1.6–3.6 (m, 8, CH_2).

Anal. Calcd for $C_{19}H_{21}NO \cdot HCl$: C, 72.21; H, 7.02; N, 4.43. Found: C, 72.30; H, 7.28; N, 4.41.

Spiro[isobenzofuran-1(3*H*),4′-piperidin]-3-one (7). To a suspension of 1.0 g of 10% Pd/C in 250 ml of EtOH was added 5.0 g (17 mmol) of lactone **4b**. The mixture was hydrogenated at atmospheric pressure for 20 hr. Filtration and evaporation of the filtrate gave an oil which triturated with ether to yield analytically pure material, 2.2 g (63%): mp 124–127° (lit.[5] mp 130.5–131.5°); ir 3290 (NH), 1755 cm^{-1} (C=O); NMR δ 7.2–8.1 (m, 4, ArH), 2.9–3.3 (m, 4, CH_2N), 1.4–2.5 (m, 4, CH_2).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.28; H, 6.52; N, 6.88.

Spiro[isobenzofuran-1(3*H*),4′-piperidine] Hydrochloride (8). A suspension of 2.6 g of 10% Pd/C and 13.0 g (41 mmol) of **6b** in 200 ml of EtOH was hydrogenated as in the preparation of **7** to give an oil which was crystallized from CH_3CN to obtain 5.9 g (64%) of colorless crystals, mp 200–202°.

Anal. Calcd for $C_{12}H_{15}NO \cdot HCl \cdot H_2O$: C, 59.31; H, 7.47; N, 5.76. Found: C, 59.66; H, 7.62; N, 5.86.

Alkylations of Phthalan 8. A. A mixture of 8 (4.50 g, 20 mmol), 2-bromomethyl-5-methoxy-2,3-dihydrobenzofuran (2.84 g, 24 mmol), and 7.2 g of Na_2CO_3 in 20 ml of 2-butanone was refluxed for 24 hr. The mixture was filtered and the solvent was evaporated in vacuo to give an oil which was triturated with ether–petroleum ether to obtain a solid which was crystallized from cyclohexane to give 2.0 g (24%) of **9c** as a tan solid, mp 97–99°.

Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.18; H, 7.17; N, 3.99. Found: C, 74.78; H, 7.05; N, 3.86.

B. A mixture of 4.50 g (20 mmol) of **8**, 4.80 g (24 mmol) of γ-chloro-4-fluorobutyrophenone, and 7.2 g of Na_2CO_3 in 50 ml of 2-butanone was treated and processed as in example A to obtain an oil which was converted to the hydrochloride in the usual manner to yield 2.5 g (27%) of **9d** as a colorless solid when crystallized from CH_3CN–MeOH, mp 209–212°.

Anal. Calcd for $C_{22}H_{24}FNO_2 \cdot HCl$: C, 67.92; H, 6.48; N, 3.60. Found: C, 67.58; H, 6.45; N, 3.59.

3,4-Dihydro-2-methylindeno[2,1-*c*]pyridin-9(1*H*)-one (10a). A suspension of 16.0 g (74 mmol) of lactone **4a** in 320 g of PPA was stirred at 210° for 90 min. The reaction mixture was cooled to room temperature and poured onto excess ice. The pH of the mixture was adjusted to 9 with concentrated NH_4OH. This was then extracted with ether, washed, dried, charcoaled, and evaporated in vacuo to yield 5.0 g of a yellow oil. Chromatography on 480 g of neutral alumina (activity 3) by elution with ether gave 2.6 g (18%) of yellow-green solid after crystallization from cyclohexane: mp 74–77°; ir 1700 cm^{-1} (C=O); uv λ_{max} 234 nm (ε 38,380), 242 (44,320), 315 (1400), 325 (1210), 365 (670); NMR δ 6.8–7.5 (m, 4, ArH), 3.17 (m, 2, $C{=}CCH_2N$), 2.5–2.8 (m, 4, CH_2), 2.47 (s, 3, NCH_3).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.46; H, 6.58; N, 7.04. Found: C, 78.32; H, 6.50; N, 6.89.

General Procedure for Reaction of 4a with Grignard Reagents. A 10–20% solution of **4a** was added dropwise at room temperature to a 1–3 *M* solution of the appropriate Grignard reagent (20% excess). After addition was complete the milky suspension was refluxed for 6 hr. The mixture was cooled to room temperature and layered between $CHCl_3$ and water. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined extracts were washed well with water, dried, and evaporated in vacuo to obtain an oil which was crystallized from a suitable solvent (listed in Table II). The free bases were converted to the hydrochlorides in the usual manner (excluding **11f,g**). Compounds **11e, 11h,** and **11i** formed stable hydrochlorides and pertinent data are listed in Table II. Compounds **11j–p** dehydrated under these conditions to yield correspondingly **12q–v,y** whose physical properties are listed in Table III.

Reaction of 4a,b with Organolithium Reagents. A. To 400 ml of a 0.09 *M* benzyllithium solution in 1:2:10 hexane–THF–toluene[17] was added dropwise 6.5 g (30 mmol) of **4a** in 60 ml of toluene. This mixture was stirred overnight at room temperature and was then layered between $CHCl_3$ and water. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined extracts were washed well with water, dried, and evaporated in vacuo to yield an oil which crystallized from EtOAc to give 6.1 g (68%) of **11m** as a colorless solid which converted in the usual manner to the hydrochloride to yield 6.3 g (68%) of **12t** as colorless crystals: mp 289–291°; uv λ_{max} 224 nm (ε 9610), 230 (11,270), 237 (10,860), 245 (7650), 256 sh (4500), 304 sh (22,620), 314 (27,480), 326 (29,370), 342 (17,230); NMR δ 7.0–7.9 (m, 9, ArH), 6.24 (s, 1, C=CH), 3.2–3.8 (m, 4, NCH_2), 2.97 (s, 3, NCH_3), 1.7–2.7 (m, 4, CH_2).

Anal. Calcd for $C_{20}H_{21}NO \cdot HCl$: C, 73.23; H, 6.76; N, 4.27. Found: C, 73.37; H, 6.94; N, 4.40.

B. *n*-Butyllithium (1.6 *M*, 10.3 ml) was added dropwise at room temperature to diphenylmethane (16 mmol) in 10 ml of THF. After addition was complete a solution of **4a** (3.0 g, 15 mmol) in 25 ml of THF was added dropwise with stirring to the blood-red solution. The reaction mixture was stirred for 2 hr at room temperature, at which time the color had faded to pale yellow. The usual work-up yielded an oil which was triturated with ether to obtain 3.5 g (66%) of **11n** as analytically pure crystals, mp 168–170°. Formation of the hydrochloride gave 3.5 g (65%) of **12u** as colorless crystals: mp >315°; uv λ_{max} 220 nm (ε 12,950), 232 (13,970), 237 (13,810), 318–324 (21,230), 328 (21,430), 341 (14,880).

Anal. Calcd for $C_{26}H_{25}NO \cdot HCl$: C, 77.48; H, 6.50; N, 3.48. Found: C, 77.63; H, 6.69; N, 3.66.

C. A solution of 2-thienyllithium was prepared according to the literature procedure[18] utilizing 1.4 g (17 mmol) of thiophene in 5 ml of ether and 10.3 ml of 1.6 *M* *n*-butyllithium. To this solution

was added dropwise a solution of **4a** (3.0 g, 14 mmol) in 25 ml of THF. This was allowed to stand at room temperature overnight. The usual work-up gave an oil which crystallized from EtOAc to yield 1.7 g (41%) of **11h** as a colorless solid: mp 194–196°; NMR δ 6.8–7.6 (m, 7, ArH), 2.8–3.6 (m, 4, NCH_2), 2.32 (s, 3, NCH_3), 1.5–2.9 (m, 5, CH_2, OH).

Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.83; H, 6.36; N, 4.65. Found: C, 67.95; H, 6.59; N, 4.32.

D. *A solution of 3-methyl-5-isoxazolyllithium was prepared* according to the literature procedure[19] utilizing 7.8 g (81 mmol) of 3,5-dimethylisoxazole in 60 ml of THF and 52 ml (83 mmol) of 1.6 *M n*-butyllithium. A solution of **4a** (9.0 g, 42 mmol) in 75 ml of THF was added dropwise at −50°. After addition was complete the reaction mixture was allowed to warm to room temperature and stand overnight. The usual work-up gave an oil which was converted to the hydrochloride in the usual manner to yield 5.4 g (38%) of **12w** as colorless crystals (CH_3CN–MeOH): mp >315°; uv λ_{max} 236 nm (ε 8850), 245 (8330), 284 (9600), 297 (14,740), 308 (19,780), 322 (25,580), 337 (22,700); NMR (D_2O) δ 7.0–7.9 (m, 4, ArH), 6.43 (s, 1, C=CH), 5.59 (s, 1, ArC=CH), 3.42 (s, 3, NCH_3), 2.64 (s, 3, CCH_3), 2.2–4.1 (m, 6, CH_2), 1.3–1.8 (m, 2, CH_2).

Anal. Calcd for $C_{18}H_{20}N_2O_2 \cdot HCl$: C, 65.07; H, 6.32; N, 8.43. Found: C, 65.03; H, 6.47; N, 8.51.

E. *A solution of 4-picolyllithium was prepared* utilizing 1.6 *g* (16 mmol) of diisopropylamine, 10 ml (16 mmol) of 1.6 *M n*-butyllithium, and 1.5 g (16 mmol) of 4-picoline in 5 ml of THF. A solution of **4a** (3.0 g, 14 mmol) in 25 ml of THF was added dropwise at 0°. This was allowed to stand at room temperature overnight and then worked up in the usual manner to give an oil which was converted to the hydrochloride to yield 2.1 g. This material was hygroscopic and was therefore reconverted to the free base to give 1.8 g (45%) of **12x** as colorless crystals (cyclohexane): mp 154–156°; uv λ_{max} 235 nm (ε 13,500), 244 (10,430), 286 (9270), 300 (14,950), 324 (32,400), 337 (33,600), 353 (18,660); NMR δ 7.0–7.8 (m, 8, ArH), 5.80 (s, 1, C=CH), 2.46 (s, 3, NCH_3), 1.4–3.2 (m, 8, CH_2).

Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.90; N, 9.58. Found: C, 78.25; H, 6.74; N, 9.45.

3-Phenylspiro[isobenzofuran-1(3*H*),4′-piperidine] (13e). *Phthalanol* **11e** *(8.0 g, 27 mmol) was dissolved in 80 ml of 97%* HCOOH. The solution was refluxed for 2 hr and then the excess solvent was evaporated in vacuo and the residue was layered between $CHCl_3$ and water. The aqueous layer was adjusted to pH 10 with saturated KOH and the layers were separated. The aqueous layer was reextracted with $CHCl_3$ and the combined extracts were washed well with water, dried, and evaporated in vacuo to give an oil which crystallized from cyclohexane to yield 7.0 g (92%) of colorless solid, mp 120–123°. This was converted to the hydrochloride in the usual manner to obtain colorless crystals: mp 257–258° (CH_3CN–MeOH); NMR (DMSO) δ 6.9–7.5 (m, 9, ArH), 6.28 (s, 1, CH), 3.1–3.7 (m, 4, NCH_2), 2.84 (s, 3, NCH_3), 1.9–2.6 (m, 4, CH_2).

Anal. Calcd for $C_{19}H_{21}NO \cdot HCl$: C, 72.21; H, 7.02; N, 4.43. Found: C, 71.92; H, 6.99; N, 4.33.

3-Methoxy-4′-methyl-3-phenylspiro[isobenzofuran-1(3*H*),-4′-piperidine] (14e). *Phthalanol* **11e** *(8.0 g, 27 mmol) was* dissolved in 80 ml of 95% H_2SO_4. The yellow solution was kept at room temperature for 3 hr and then poured in a stream into 160 ml of MeOH. This was then layered between $CHCl_3$ and water. The usual work-up for free base gave a colorless solid which crystallized from EtOAc–cyclohexane to yield 4.5 g (54%) of colorless crystals: mp 172–174°; NMR δ 7.0–7.9 (m, 9, ArH), 3.22 (s, 3, OCH_3), 2.38 (s, 3, NCH_3), 1.6–3.0 (m, 8, CH_2).

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.78; H, 7.70; N, 4.39

1-Benzyl-3-[2-(4,5-dihydro-5,5-dimethyl-2-oxazolyl)phenyl]-3-piperidinol (16b). A solution of 1 was prepared as illustrated for the synthesis of **3a** utilizing 150 g (0.59 mol) of 2-(2-bromophenyl)-4,4-dimethyloxazoline and 15.0 g (0.63 *g*-atom) of Mg. To this was added at room temperature 122 g (0.65 mol) of 1-benzyl-3-piperidone (**15b**). The usual work-up gave after crystallization from CH_3CN 100 g (47%) of colorless solid: mp 118–120°; ir 3100 (OH), 1675 cm^{-1} (C=N); NMR δ 7.0–7.9 (m, 9, ArH), 3.56 (q, 2, OCH_2), 3.47 (s, 2, $NCH_2C_6H_5$), 3.14 (s, 1, OH), 2.3–2.9 (m, 4, NCH_2), 1.6–2.0 (*m*, 4, CH_2), 1.43 (s, 6, CH_3).

Anal. Calcd for $C_{23}H_{28}N_2O_2$: C, 75.79; H, 7.74; N, 7.69. Found: C, 75.51; H, 7.81; N, 7.78.

1′-Benzylspiro[isobenzofuran-1(3*H*),3′-piperidin]-3-one Hydrochloride (17b). A solution of 200 g (0.548 mol) of **16b** in 2 l. of 3 *N* HCl was hydrolyzed as indicated for the preparation of **4a** utilizing method A. A similar work-up gave an oil which was converted to the hydrochloride in ether to yield 135 g (75%) of analytically pure crystals: mp 248–250°; ir 1765 cm^{-1} (C=O); NMR (DMSO) δ 7.2–8.1 (m, 9, ArH), 4.45 (s, 2, $NCH_2C_6H_5$), 2.9–3.9 (m, 4, CH_2), 1.6–2.5 (m, 4, CH_2).

Anal. Calcd for $C_{19}H_{19}NO_2 \cdot HCl$: C, 69.15; H, 6.11; N, 4.24. Found: C, 69.34; H, 6.22; N, 4.31.

Spiro[isobenzofuran-1(3*H*),3′-piperidin]-3-one Hydrochloride (18). A suspension of **17b** (130 g, 0.395 mol) and 26 g of 10% Pd/C in 1 l. of EtOH was hydrogenated on a Parr apparatus at 3 atm for 3 hr. The mixture was filtered and the filter cake was washed with 1 l. of water. The filtrate was evaporated in vacuo to obtain a solid which was crystallized from CH_3CN–MeOH to yield 87.0 g (92%) of colorless crystals: mp >315°; ir 1755 cm^{-1} (C=O); NMR (D_2O) δ 7.8–8.3 (*m*, 4, ArH), 3.4–4.5 (*m*, 4, NCH_2), 1.8–3.0 (m, 4, CH_2).

Anal. Calcd for $C_{12}H_{13}NO_2 \cdot HCl$: C, 60.05; H, 5.88; N, 5.84. Found: C, 59.68; H, 6.07; N, 5.73.

1′-Methylspiro[isobenzofuran-1(3*H*),3′-piperidin]-3-one Hydrochloride (19a). The lactone **18** (65 g, 0.32 mol) was dissolved in ice-cold HCOOH (36 g, 0.78 mol). A 37% formalin solution (12 g, 0.40 mol) was added in a thin stream and the mixture was stirred at 80° for 4 hr. The excess reagents were stripped in vacuo to give an oil which was converted to the hydrochloride in the usual manner to yield 65 g (80%) of colorless crystals: mp 298–300°; ir 1750 cm^{-1} (C=O); NMR (DMSO) δ 7.5–8.2 (*m*, 4, ArH), 3.91 (q, 2, NCH_2), 3.3–3.6 (m, 2, NCH_2), 3.87 (s, 3, NCH_3), 1.6–2.6 (m, 4, CH_2).

Anal. Calcd for $C_{13}H_{15}NO_2 \cdot HCl$: C, 61.71; H, 6.38; N, 5.54. Found: C, 61.60; H, 6.53; N, 5.53.

3-Benzylidenespiro[isobenzofuran-1(3*H*),3′-piperidine] Hydrochloride (20a). A solution of **19a** (10.5 g, 4.84 mmol) in 50 ml of toluene was added to a benzyllithium solution prepared as illustrated for the preparation of **12t** utilizing 50 ml of 1.2 *M sec*-butyllithium. After addition was complete, the mixture was stirred at 60° for 15 hr. A similar work-up as for **21a** yielded an oil which was converted with attendant dehydration to the hydrochloride in the usual manner to obtain a gum which was triturated with EtOAc to yield a solid which was crystallized from CH_3CN–MeOH to give 2.0 g (17%) of colorless crystals: mp 290–292° dec; NMR (TFA) δ 6.8–8.0 (*m*, 9, ArH), 5.8 (s, 1, C=CH), 3.5–4.2 (*m*, 4, NCH_2), 3.10 (s, 3, NCH_3), 1.9–2.9 (m, 4, CH_2).

Anal. Calcd for $C_{20}H_{21}NO \cdot HCl$: C, 73.46; H, 6.78; N, 4.28. Found: C, 73.29; H, 6.59; N, 4.14.

3-[*o*-(α-Hydroxy-α-phenylbenzyl)phenyl]-1-methyl-3-piperidinol (21a). A solution of 17.0 g (78.2 mmol) of **19a** in 170 ml of THF was added dropwise at room temperature to 37.4 ml of 2.5 *M* C_6H_5MgCl with stirring. After addition was complete the reaction mixture was refluxed for 15 hr. This was then layered between $CHCl_3$ and water, dried, and evaporated in vacuo to give an oil. This was triturated with EtOAc and crystallized from EtOAc–MeOH to yield 2.0 g (7%) of **21a** as colorless crystals: mp 148–150°; NMR δ 6.5–7.5 (m, 14, ArH), 4.5 (s, broad, 2, OH), 2.3–2.9 (m, 4, NCH_2), 2.17 (s, 3, NCH_3), 1.3–2.0 (m, 4, CH_2).

Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.37; H, 7.30; N, 3.73.

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Registry No.—**2a,** 1445-73-4; **2b,** 3612-20-2; **3a,** 54595-98-1; **3b,** 54595-99-2; **4a** HCl, 54596-00-8; **4b** HCl, 54596-01-9; **4c** HCl, 54596-02-0; **4d** HCl, 54596-03-1; **4e** HCl, 54596-04-2; **4f** HCl, 54596-05-3; **4g** HCl, 54596-06-4; **4h** HCl, 54596-07-5; **6a** HCl, 54596-08-6; **6b** HCl, 54596-09-7; **7,** 37663-46-0; 8 HCl, 37663-44-8; **9c,** 54596-10-0; **9d** HCl, 54596-11-1; **10a,** 54596-12-2; **13e** HCl, 54596-13-3; **14e,** 54596-14-4; **16b,** 54596-15-5; **17b** HCl, 54596-16-6; *18 HCl,* 54596-17-7; **19a** *HCl,* 54596-18-8; **21a,** 54596-20-2; *2*-bromo-*N*-(2-hydroxy-1,1-dimethylethyl)benzamide, 54596-21-3; 2-amino-2-methyl-1-propanol, 124-68-5; 2-bromobenzoyl chloride, 7154-66-7; 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline hydrochloride, 51849-83-3; 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline, 32664-13-4.

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(7) (a) W. G. Young and J. D. Roberts, *J. Am. Chem. Soc.*, **66**, 1444 (1944). (b) Although yields are better via this method, enolization is again the predominant side reaction, as only starting materials are isolated besides the product. (c) The generality of this method was established at this point by the reaction of **5** with 1-dimethylamino-3-pentanone to yield 3-ethyl-3-dimethylaminoethylphthalide, bp 123–125° (0.3 mm) (56%). The reaction failed utilizing 3-dimethylamino-1-phenyl-1-propanone owing to complete enolization of the substrate under these conditions. However, this type of derivative is readily available via 3-arylphthalide alkylations.[2g]
(8) It was ascertained that use of *N*-phenylbenzamide rather than *N*-methylbenzamide in this reaction consistently gave better results, e.g., 50% as compared to 23% with **2a**.
(9) It was reported in ref 5 that quenching with saturated NH_4Cl will give the intermediate hydroxyamides in good yield.
(10) (a) The fact of obtaining phthalides on work-up perforce indicates ortholithiation. However, utilization of 3-methoxy-*N*-phenylbenzamide presents ambiguity owing to the presence of two nonequivalent ortho positions. In fact the product isolated was proven unequivocally to be the 7-OCH_3 isomer by NMR absorption which indicated a single downfield aromatic proton exhibiting ortho coupling.
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(12) The stereochemistry of the dehydration products deserves consideration. Products **12t,w–y** were shown to exist in the *trans*-stilbene configuration by uv absorption, e.g., **12t**, λ_{max} 314 nm (ϵ27,480), 326 (29,370), 342 (17,230). (For complete spectrum see Experimental Section.) The alkyl derivatives **12q,v** were assigned the trans configuration by analogy.
(13) Whether the monoadduct or diadduct is obtained in a pure state depends on individual crystallization properties only. No effort was then made to isolate the corresponding coproduct.
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Synthesis and Cyclization of 2-(3-Indolylmethyl)-3-hydroxy-4-piperidineacetic Acid Derivatives

Richard J. Sundberg,* Francis X. Smith, and Long-Su Lin

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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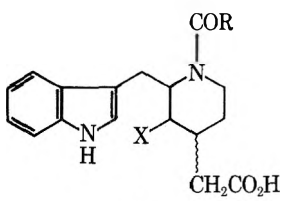
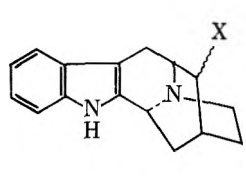
Modifications of a previously reported method for synthesis of 2-(3-indolylmethyl)-4-piperidineacetic acid derivatives by alkylation of the pyrrolidine enamine of 1-acyl-4-carbalkoxymethyl-3-piperidones are reported. The synthesis of the piperidones has been facilitated by using a selenium dioxide oxidation of ethyl 1-benzoylpiperidine-$\Delta^{4,\alpha}$-acetate. A method for inversion of the stereochemistry of the alkylated piperidones is reported. Although the trans isomer is the predominant product of the enamine alkylation, use of an easily removable *N*-acyl group (carbobenzyloxy) permits epimerization at C-2 and reacylation gives predominantly the cis isomer. A method for cyclization involving the side chain carboxyl group and C-2 of the indole ring is described. It proceeds from the alkylated piperidone *c*-10, by reduction and cyclization to the lactone 11 followed by partial reduction (diisobutylaluminum hydride) and acid-catalyzed cyclization to **16**. Structural characterization of 16 and and its derivatives is discussed. Since 16 contains the basic carbon skeleton of the sarpagine and vobasine alkaloid groups it is a potential intermediate in the synthesis of deethyl analogs of these groups of alkaloids.

In a previous paper[1] a method for the preparation of several derivatives of 2-(3-indolylmethyl)-4-piperidineacetic acid (A) was described. This molecule possesses all the atoms present in the skeletal framework (B) of the sarpagine and vobasine types[2] of indole alkaloids. The method, however, led primarily to the trans series of compounds, whereas the cis derivatives are required for cyclization to the alkaloidal skeleton. We have now developed a modified synthesis which makes the cis series available. The cyclization of one of these compounds is also reported in this paper.

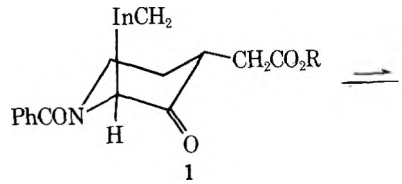


A

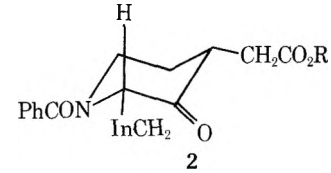


B

The underlying cause of the predominant formation of the trans ketone 1 over 2 in the earlier synthetic method is the $A^{1,3}$ strain[3] which exists between the *N*-benzoyl and C-2 substituents in the diequatorial cis conformation. The trans ketone 1 is more stable, despite the axial indolylmethyl substituent. The strategy adopted to circumvent



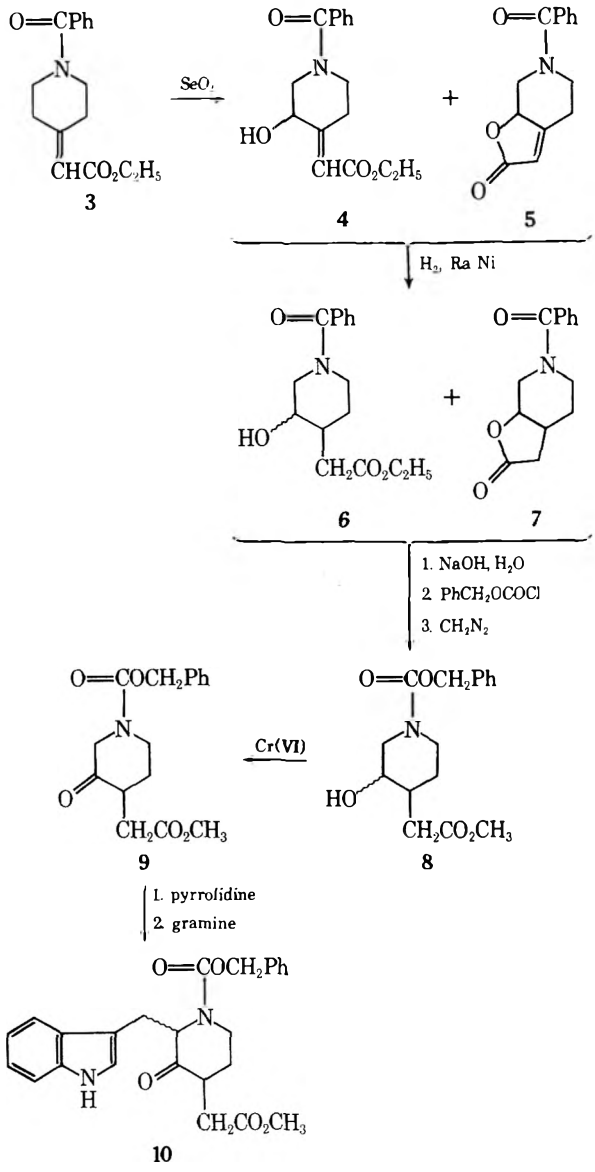
1



2

this problem was to introduce an *N*-acyl substituent which could be removed at some stage. The N-deacylated derivative would be expected to exist primarily in the diequatorial cis form at equilibrium. The original synthesis was therefore modified to incorporate a carbobenzyloxy group as the *N*-acyl substituent.

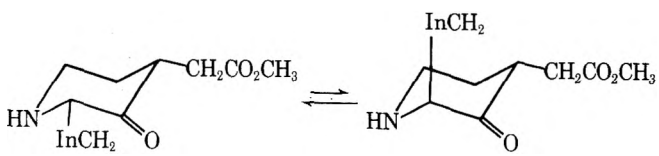
Scheme I



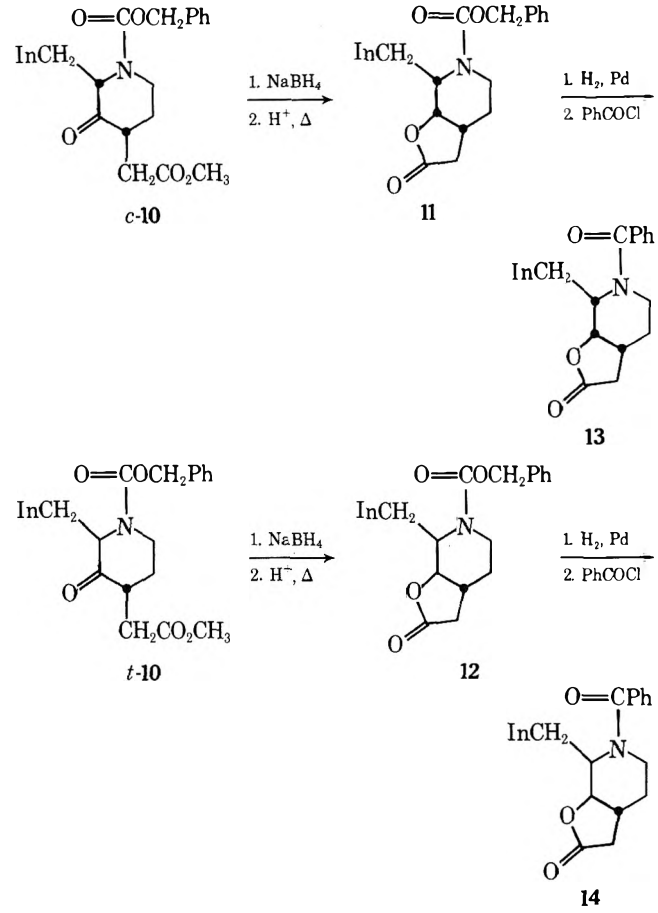
3 4 5 6 7 8 9 10

An improvement was also developed in the method for introduction of functionality at C-3 of the piperidine ring. *Selenium dioxide oxidation of 3 gave a mixture of 4 and 5* in approximately 80% yield. This compares with a three-step sequence (overall 60% yield) in the earlier method. The synthesis, which in other respects parallels that reported earlier with *N*-benzoyl derivatives, is outlined in Scheme I.

The indolylmethylpiperidone **10** obtained by this procedure consists predominantly of the trans isomer *t*-**10**, just as in the *N*-benzoyl series. Hydrogenolysis of the carbobenzyloxy group, followed by reacylation, gave a mixture rich in the cis isomer *c*-**10**. The isomer ratio in the final mixture presumably reflects the greater stability of the cis isomer in the deacylated piperidone where $A^{1,3}$ strain associated with *the N-acyl group is absent. The hydrogenation solution* (10% acetic acid in methanol) is apparently sufficiently acidic to effect enolization at C-2 or C-4 of the piperidone ring, permitting epimerization to take place. The stereochemistry of *c*-**10** and *t*-**10** was established by interrelation with



Scheme II

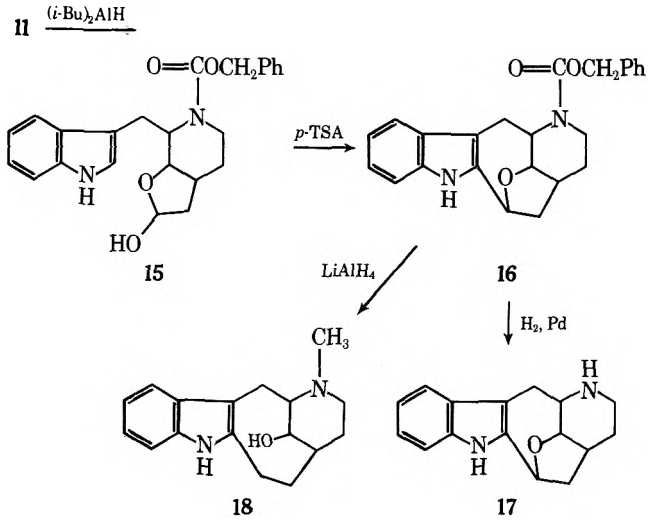


c-10 11 13 *t*-10 12 14

derivatives of **1** and **2**, whose stereochemistry was established earlier.[1] The ketones c-**10** and *t*-**10** were reduced by sodium borohydride to the corresponding alcohols, which were lactonized to **11** and **12**, respectively (Scheme II). The carbobenzyloxy group was then removed and replaced by benzoyl groups to give lactones **13** and **14**. The stereochemistry of these lactones was established in the earlier work on the benzoyl series.[1]

The primary goal at this point became the development of a means of cyclization which would attach the carboxyl *carbon of c-10 or 11 to C-2 of the indole ring. Although* a similar cyclization has been accomplished with a piperidone derivative by heating with polyphosphoric acid,[4] we were dubious that this method would be satisfactory with the more sensitive functional groups present in c-**10** or **11** and several exploratory experiments with each substance failed to yield characterizable products. The cyclization method on which the overall scheme was predicated was planned to take advantage of a mechanistic pattern established by Jackson and coworkers.[5] They have shown that Friedel–Crafts alkylation of 3-alkylindoles takes place in two stages. The electrophile initially attacks C-3 and one of the alkyl groups then migrates to C-2.[5] If this mechanism *could be brought into operation with 11* or a derivative, the eight-membered C ring could be constructed by a series of steps which would avoid the unfavorable entropic factors associated with a direct eight-membered ring closure. In practice this was accomplished by reduction of **11** to the lactol **15**, which cyclized to **16** on heating with *p*-toluenesulfonic acid (Scheme III). Compound **16** was not crystalline but two crystalline derivatives **17** and **18** were prepared from it and the evidence in support of the assigned structure is derived primarily from the spectral properties of these derivatives. Catalytic reduction of **16** removed the

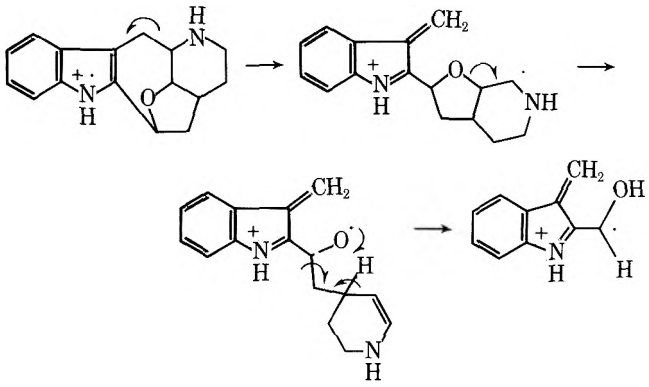
Scheme III



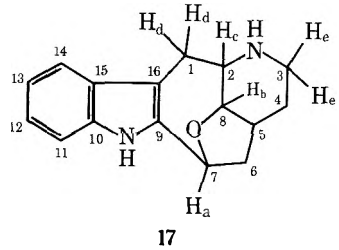
carbobenzyloxy group, giving the secondary amine **17**. Vigorous $LiAlH_4$ reduction of **16** afforded a reduction product **18** which resulted from conversion of the carbobenzyloxy group to methyl and reductive cleavage of the ether bond.[7]

The expected molecular weight and elemental composition of **17** were confirmed by low-resolution mass spectrometry and microanalysis, respectively. The mass spectral fragmentation pattern provided additional information consistent with the assigned structure. Most convincing is the identification of the base peak in the mass spectrum by high-resolution mass spectrometry as $C_{10}H_9NO^+$ (calcd 159.0684, found 159.0660). A fragmentation route is shown in Scheme IV. The composition of the fragment is consistent with the proposed structure, since it indicates that the ether oxygen is attached to a carbon which is, in turn, attached to the indole ring.

Scheme IV



That **17** is a 2,3-disubstituted indole is also clear from the nuclear magnetic resonance spectrum. Integration of a 100-MHz spectrum indicates only four aromatic protons. These resonances are sufficiently well resolved in the 250-MHz spectrum to rule out the possibility that the 2 position of the indole ring is unsubstituted. The proton spectrum of the nonaromatic skeleton shows a multiplet at 5.2 ppm (H_a), a triplet at 4.12 ppm (H_b), a multiplet at 3.32 ppm (H_c), and an AB pattern centered at 2.75 ppm further split by ~4 Hz (H_d). The multiplets at higher field are partially obscured by a solvent peak (DMSO-d_6) and not well resolved. We assign the signals described as indicated in the structure. In some conformations the protons labeled e are above the aromatic ring and may be shielded as a result.



17

Table I
^{13}C NMR Chemical Shifts of 17[a]

Carbon atom	Chemical shift, ppm	Multiplicity in off resonance decoupled spectrum
1,3	39.07, 40.64	t, t
2	58.73	d
4,6	23.54, 24.99	t, t
5	35.12	d
7,8	75.29, 78.15	d, d
9	137.42	s
10	138.93	s
11	112.06	d
12	120.31	d
13	122.61	d
14	118.79	d
15	128.98	s
16	106.29	s

[a] Relative to Me_4Si in acetic acid-d_6.

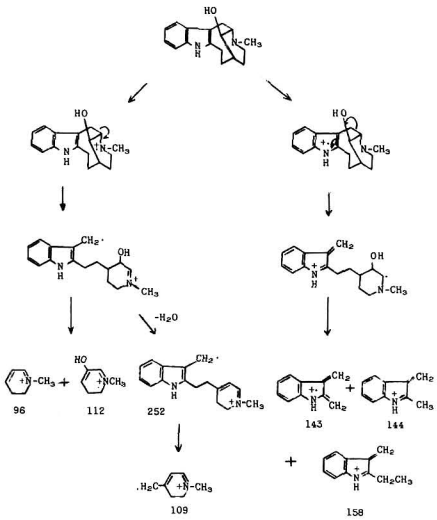
The ^{13}C spectrum of **17** was also recorded. The data are summarized in Table I with reference to the numbering scheme shown on the structure. The multiplicity of each of the peaks in the off-resonance decoupled spectrum is shown in column 3. In each instance the multiplicities observed are those expected on the basis of the assigned structure. The appearance of four singlets in the aromatic region is further evidence that **17** is a 2,3-disubstituted indole. The chemical shift pattern in the aromatic region is closely similar to that found in simple indoles.[8] The saturated portion of the molecule represents a structural unit for which no close model is available but an isomeric perhydrofuro[3,2-*c*]pyridine ring in vandrikine[9] exhibits generally comparable chemical shifts for the nonaromatic carbons.

Lithium aluminum hydride in refluxing dioxane converted **16** to a new compound, **18**, having the formula $C_{17}H_{22}N_2O$, in 76% yield. That conversion of the *N*-carbobenzyloxy group to *N*-methyl[10] had occurred was indicated by the molecular formula, and by the appearance of a prominent singlet in the NMR spectrum at 3.04 ppm. The composition also requires the addition of two hydrogen atoms. Since the indole chromophore remains intact, as evidenced by the ultraviolet spectrum, the inference is that the one of the C–O bonds in the ether ring has been cleaved. The expectation would be that the cleavage would occur α to in the indole ring.[7] Reductive cleavage of a similarly disposed pyran ring under similar conditions in the alkaloid taberpsychine has been reported.[11] The major ions in the mass spectrum of **18** can be accounted for by the fragmentation pattern shown in Scheme V. Most significant are the ions at *m/e* 143 and 144 which are consistent with the presence of a saturated ring fused to the 2,3 positions.[12]

The successful synthesis of **16**, **17**, and **18** provides intermediates which have the basic structural framework of the sarpagine and vobasine structural families. A few experiments have been carried out in an effort to accomplish ring opening of the ether rings in **16** or **17** by an elimination-addition mechanism following the presumed mechanism of

1

Scheme V



2

Experimental Section

Improved Synthesis of Ethyl 1-Benzoyl-$\Delta^{4,a}$-piperidine-4-acetate (3).

This procedure avoids the concomitant formation of ethyl 1-benzoyl-1,2,3,6-tetrahydropyridineacetate.[13] Sodium hydride (5.28 g, 50% dispersion in mineral oil, 0.11 mole) was rinsed with hexane *and dispersed in anhydrous ether (400 ml) under nitrogen. An ether* solution of triethyl phosphonoacetate (29.1 g, 0.13 mole) was added. When hydrogen evolution was complete a solution of 1-benzoyl-4-piperidone (20.3 g, 0.10 mole) in 200 ml benzene was added. The reaction is exothermic and a gummy precipitate is formed. The reaction is complete within 15 min. The solution was decanted and the precipitate triturated with additional ether. The combined ether solutions were washed with dilute hydrochloric acid and brine, dried and evaporated giving a quantitative yield of crystalline 3.[13]

Selenium Dioxide Oxidation of 3.

A solution of 3 (106 g, 0.39 mole) was dissolved in benzene (1 l.) and selenium dioxide (56 g, 0.50 mole) was added. The suspension was refluxed for 54 hr during which time precipitation of selenium occurred. At the end of this time the reaction solution was filtered through activated charcoal (20 g) and Celite.[14] The filtrate was washed with water (200 ml) and brine (200 ml), stirred over sodium sulfate and activated charcoal and then filtered through additional Celite. Evaporation of the solvent gave a gum (83 g) which solidified on standing. Nmr and tlc showed this to consist primarily of 4 and 5, both of which were characterized in the earlier work.[1]

Methyl 1-Carbobenzyloxy-3-oxopiperidine-4-acetate (9).

A crude mixture of 4 and 5 prepared by selenium dioxide oxidation (40 g) was dissolved in methanol. Raney nickel (80 g) was added. The large amount was necessary to overcome the poisoning effect of selenium impurities. The mixture was shaken under 3 atm H_2 pressure for 24 hr. The solution was filtered and concentrated leaving an oil (33.8 g) shown to be free of the starting materials by nmr and tlc. This mixture was refluxed with 10% sodium hydroxide

3

solution (230 ml) for 24 hr under nitrogen. The solution was brought to pH 1 with conc. hydrochloric acid and benzoic acid was removed by ether extraction. The aqueous phase was then made alkaline and cooled to 0°. Benzyl chloroformate (40 g) and aqueous sodium hydroxide (to maintain pH 8-10) were added intermittently with vigorous stirring over one hr. The solution was extracted with ether. This extract was retained since it contained a substantial portion of the desired product, apparently as a mixed anhydride. The aqueous layer was acidified and extracted with choloroform. Product was recovered from the ether layer by stirring overnight at room temperature with 5% aqueous sodium hydroxide. After removal of the ether, the aqueous layer was acidified and extracted with chloroform. This chloroform extract was *combined with that from the original reaction* mixture, dried and evaporated to give 30.3 g of oil. Heating of this material was avoided to prevent relactonization and the diazomethane methylation was carried out as quickly as possible. The yield of crude 8 was 38 g. This material was immediately dissolved in acetone (800 ml) and oxidized by dropwise addition of Jones reagent[15] (58 ml), maintaining the reaction temperature at 15-20° for 45 min. Excess Jones reagent was destroyed by additional of 2-propanol and the precipitated chromium salts were removed by filtration through Celite.[14] The filtered reaction mixture was diluted with brine and extracted with chloroform. The extract was washed with brine, dried and evaporated to give the unstable ketone 9 (26.5 g). The overall yield from 3 is 45%.

Methyl 1-Benzyloxycarbonyl-2-(3-indolylmethyl)-3-oxo-4-piperidine-acetate (c-10 and t-10).

A solution of 9 (38 g, 124 mmole) and pyrrolidine (24 ml, 395 mmole) in benzene (600 ml) was treated with p-toluenesulfonic acid (240 mg) and then refluxed for 24 hr. Water was collected in a Dean-Stark trap filled with molecular sieve 4-A. The benzene was removed under reduced pressure and replaced with toluene (240 ml). Gramine (36.0 g, 226 mmole) was added and the solution was refluxed under nitrogen for 13 hr. Additional gramine (8 g, 50 mmole) was added and reflux was continued for an additional 7 hr. The toluene was then evaporated and the residual oil was dissolved in a solution of 150 ml of 10% hydrochloric acid in 400 ml of methanol. After

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stirring for 20 min the solution was concentrated to about half the original volume, diluted with brine and extracted with toluene. The toluene was dried and concentrated leaving an oil which was absorbed on a column of 400 g of silica gel 60 (E. Merck). The column was eluted with toluene and then ether-toluene. A mixture of the stereoisomeric ketones c-10 and t-10 was obtained as an oil which crystallized on standing overnight (16.8 g, 31%). The stereoisomers are separated on silica gel tlc plates using ether as developing solvent. The trans isomer has a slightly larger R_f than the cis. The stereoisomers were only partially separated by all preparative chromatographic procedures attempted but pure samples were obtained by recrystallization of enriched fractions of each isomer obtained by *chromatography*.

The cis isomer c-10 was obtained from chloroform-ether, mp 138.5-140°; ir (KBr) 3340 (NH), 1760, 1740 (C=O) and 1690 cm^{-1} (amide C=O); nmr ($CDCl_3$-C_6D_6): δ 7.8-6.9 (m, 9), 6.6 (m, 1), 4.9 (broad m, 3), 3.4 (s overlapping broad m, 5), and 3.1-0.6 (m, 7); mass spectrum m/e (relative intensity): 434 (3), 306 (4), 305 (10), 223 (5), 205 (5), 170 (7), 138 (5), 131 (7), 130 (47), 104 (6), 91 (78), 79 (9), 78 (100), 77 (28), 76 (10), 74 (10), 59 (12), 52 (18), 51 (20), 50 (17), 42 (8) and 39 (16).

Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.19; H, 6.17, N, 6.36.

The trans isomer t-10 was recrystallized from chloroform-ether, mp 134-135.5°; ir (KBr): 3350 (NH), 1749, 1730 (C=O), and 1690 cm^{-1} (amide C=O); nmr ($CDCl_3$): δ 8.55 (broad s, 1), 7.8 - 6.95 (m, 9), 6.82 (broad s, 1), 3.6 (s, 3) and 3.3-1.2 (broad m, 12); mass spectrum m/e (relative intensity): 434 (9), 306 (12), 305 (60), *170 (26), 138 (10), 131 (15), 130 (100), 91 (42), 78 (94), 77 (27),* 76 (9), 59 (10), 52 (19), 51 (18), 50 (16), 42 (11) and 39 (17).

Anal. Calcd for $C_{25}H_{26}O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.12; H, 6.06, N, 6.40.

Conversion of t-10 to c-10.

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A mixture of t-10 and c-10 (7.3 g, 16.8 mmole) rich in the trans isomer was suspended in a solution of acetic acid (20 ml) and methanol (220 ml). 10% Palladium-charcoal catalyst (500 mg) was added and the solution was shaken under 2 atm. hydrogen for one hr. The catalyst was filtered off and the filtrate was evaporated. The residue was dissolved in chloroform (200 ml) and solid potassium carbonate (120 g) was added. The suspension was stirred vigorously at 0° and benzyl chloroformate (9 ml) was added dropwise. After the suspension was diluted with water, the chloroform layer was separated, washed with brine, dried and evaporated. Tlc showed this to be primarily c-10. Pure c-10 was isolated (30% yield) by crystallization from chloroform-ether. The remainder of material was *a mixture of c-10 and t-10 which could be recycled.*

Lactone of 1-Benzyloxycarbonyl-cis-3-hydroxy-cis-2-(3-indolylmethyl)-4-piperidineacetic acid (11).

A solution of c-10 (0.434 g) was reduced with sodium borohydride in methanol. Acetone was added followed by dilute hydrochloric acid and the product was extracted with chloroform. A mixture of 11 and uncyclized alcohol was present at this point. Cyclization was completed by heating in toluene with p-toluenesulfonic acid. The toluene was removed and the residue was dissolved in chloroform and washed with aqueous sodium bicarbonate solution. The solvent was dried and evaporated. The residue was crystallized from chloroform-ether-hexane to give 11 (0.372 g, 93%), mp 178-179°; ir (KBr): 3340(NH), 1800 (lactone C=O) and 1680 cm^{-1} (amide C=O); mass spectrum m/e (relative intensity): 405 (11), 404 (33), 276 (13), 275 (61), 274 (11), 230 (8), 173 (11), 172 (65), 131 (14), 130 (85), 92 (12), 91 (100), 85 (17) and 83 (26).

Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.02; H, 6.08; N, 6.85.

Lactone of 1-Benzyloxycarbonyl-trans-3-hydroxy-trans-2-(3-indolylmethyl)-4-piperidineacetic Acid (12).

A solution of t-10 (0.20 g) in methanol was treated with $NaBH_4$ and stirred for 30 min. Acetone was then added, followed by

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dilute hydrochloric acid. The mixture was extracted thoroughly with chloroform. Evaporation of the chloroform and crystallization of the residue from benzene-hexane gave the uncyclized alcohol (91% yield), mp 120-121.5°.

Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.94; H, 6.64; N, 6.28.

Cyclization to the lactone occurred on refluxing the alchol in toluene with a catalytic amount of p-toluenesulfonic acid for 12 hr. The lactone was isolated by evaporation of the toluene, dissolving the residue in chloroform, washing with aqueous sodium bicarbonate, drying and evaporation. The product was recrystallized from chloroform-hexane, (88% yield, mp 180.5°; ir (KBr): 3340 (NH), 1800 (lactone C=O), and 1680 cm^{-1} (amide C=O); mass spectrum m/e (relative intensity): 405 (7), 404 (22), 319 (3), 276 (3), 275 (14), 269 (5), 230 (5), 229 (3),173 (5), 172 (24), 144 (3), 143 (4), 131 (16), 130 (81), 105 (5), 103 (10), 92 (12), and 91 (100).

Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93; C, 71.41; H, 6.10; N, 6.87.

Lactone 11, Directly from a c-10 - t-10 Mixture.

It was expeditious to avoid separation of c-10 and t-10 in larger scale runs. A crude mixture of c-10 and t-10 (97 g) was *used immediately after the isomerization procedure.* The crude product was dissolved in methanol (200 ml) and 1.2 g of sodium borohydride was added. After 10-15 min acetone was added to destroy excess sodium borohydride and the reaction mixture was diluted with 5% hydrochloric acid. The solution was extracted with chloroform and the extract was dried and evaporated. The residue was dissolved in toluene (300 ml) and p-toluenesulfonic acid (300 mg) was added. The resulting solution was refluxed under nitrogen for 22 hr. The solvent was then removed and the residue dissolved in chloroform and washed with aqueous sodium bicarbonate, dried and evaporated. Tlc showed this to be a mixture of the lactones 11 and 12. The dominant lactone 11 crystallized from chloroform-ether (5.0 g, 75%).

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Conversion of Lactones 11 and 12 to the Known N-Benzoyl Analogs 13 and 14.

The lactone 12 (22 mg) was hydrogenated over 10% palladium on charcoal in methanol containing 7% by volume of acetic acid. The solvent was evaporated and the residue was dissolved in chloroform. Granular potassium carbonate (1.0 g) was added followed by benzoyl chloride (0.1 ml). The chloroform solution was washed with aqueous sodium bicarbonate solution, dried and evaporated. Crystallization of the residue from chloroform-hexane gave 14 (15 mg, 79%), mp 203-204° having an infrared spectrum identical with a previously characterized sample. An identical procedure converted 11 to 13.

Cyclization of Lactone 11.

The lactone 11 (404 mg, 1 mmole) was suspended in a mixture of 4 ml anhydrous dioxane and 7 ml toluene. The solution was cooled to 0° *and 1.0 ml of 20% diisobutylaluminum hydride* in hexane was added. The mixture was stirred at 0° for one hr and then poured onto a mixture of crushed ice (150 g) and 5% acetic acid (50 ml). The product was extracted with chloroform and the extract washed with sodium bicarbonate and dried. Evaporation of the residue gave a gum containing two new components and a small amount of unreacted lactone. This mixture was dissolved in toluene (20 ml) and 20 mg of p-toluenesulfonic acid was added. The solution was refluxed under nitrogen for 30 min. At this point tlc showed that one of the new materials had been converted to another substance while the second product and lactone remained unchanged. The solvent was evaporated and the residue was dissolved in chloroform. The solution was washed with aqueous sodium bicarbonate, dried and evaporated. The residue was separated using 2 mm preparative layer silica gel plates. A single development with 1:1 ether-chloroform *cleanly separated each of the* three bands. The bands were removed and extracted thoroughly with methanol-chloroform. The extracts were evaporated to dryness after filtration through Celite.[14]

The band with the highest Rf yielded 16 (141 mg, 36%) as a gum; IR (KBr): 3410, 3320 (broad, NH) 1685 (amide C=O). IR (CCl_4): 3490 (sharp, NH); UV (MeOH): 226 (4.45), 274 (3.77), 285 (3.83), 292 (3.78)

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nmr ($CDCl_3$): 1.0-2.0 (m, 4), 2.2-3.7 (m, 6), 4.4-5.4 (m, 3), 6.7-7.5 (m, 9), 7.95 (broad s, 1); mass spectrum: 389 (10), 388 (29), 297 (14), 254 (10), 253 (37), 168 (13), 167 (10), 156 (12), 144 (7), 143 (6), 130 (12), 108 (14), 105 (13), 92 (12) and 91 (100).

The intermediate band was recovered lactone 11 (17%).

The band with the lowest R_f is apparently the diol resulting from overreduction; IR(KBr): 3150-3650 (very broad), 1680 cm^{-1} (amide C=O); nmr ($CDCl_3$): 1.2-2.0 (m, 5), 2.8-4.4 (m, 10), 5.02 (s, 2), 6.8-7.7 (m, 9), 8.3 (s, 1); mass spectrum m/e (relative intensity): 408 (2), 390 (1), 300 (2), 260 (1.5) 254 (1), 234 (2.5), 216 (1.5), 130 (90), 126 (2.5), 108 (3), 107 (2.5), 97 (2), 91 (11), 79 (4), 77 (3). This material formed a diacetate on reaction with acetic anhydride-sodium acetate for 3 hr at 100°: IR(KBr): 3420 (broad NH), 1745 (C=O), 1695 cm^{-1} (amide C=O); mass spectrum m/e (relative intensity): 492 (8), 430 (2), 364 (12), 320 (63), 305 (18), 172 (16), 130 (100), 92 (34), 91 (340), 77 (15), 43 (100). Neither the diol nor diacetate was obtained in crystalline form.

2,3,4,4a,6,7,12,12a-octahydro-4,6-methano-1H-pyrido[2',3':6,7]oxepino[3,4-b]indole (17).[16]

A solution of 16 (0.200g, 0.51 mmole) was hydrogenated over 10% Pd-C catalyst in 6% acetic acid in methanol for 20 min. The catalyst was removed by filtration and the solution evaporated to dryness. The residue was dissolved in chloroform, washed with sodium carbonate solution, dried and evaporated to yield 17. Recrystallization from ethanol, gave pure 17 (0.102 g, 0.40 mmole, 78%) mp 244.5-245°; ir (KBr): 3300 cm^{-1} (NH), no C=O; nmr (DMSO-d_6) s 7.1-7.5 (m, 2), 6.8-7.0 (m, 2), 5.25 (m, 1), 4.35 (t, 1), 3.50 (m; 1),>3.0 (unresolved multiplets); mass spectrum m/e (relative intensity): 255 (18), 254 (78), 169 (17), 168 (28), 167 (24), 160 (17), 159 (100), 158 (14), 156 (34), 144 (18), 143 (20), 130 (26), 129 (15), 128 (15), 127 (14), 115 (14), 96 (55), 95 (17), 82 (18), and 77 (17).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.35; H, 7.25; N, 11.08.

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Lithium Aluminum Hydride Reduction of 16.

A solution of 16 (0.075 g) in dry dioxane (10 ml) was added to a slurry of $LiAlH_4$ (0.075 g) in dioxane (5 ml). The resulting solution was refluxed for 15 hr under nitrogen. The excess $LiAlH_4$ was destroyed by addition of ethanol and aluminum salts were precipitated by addition of water. The filtered solution was evaporated and the residue crystallized *from ethanol-ether-hexane to give* 18 (0.039 g, 76%), m.p. 236-237.5°; mass spectrum: 271 (6), 270 (25), 252 (15), 251 (11), 158 (20), 144 (28), 143 (38), 125 (31), 112 (25), 109 (100), and 96 (32); UV (EtOH): 226 (4.63), 285 (4.04), 293 (4.04); nmr $CDCl_3$ 1.25 (broad, 1), 1.50-2.7 (broad), 3.20 (s superimposed on broad multiplet), 4.08 (broad s,1), 7.1-7.3 (m,3), 7.5 (m, 1), 8.0 (s,1).

Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36 Found: C, 75.27; H, 8.44; N, 10.41.

Attempted Ring-Opening of 16.

Unchanged starting material was recovered in high yield from each of three attempts at solvolytic cleavage of the tetrahydrofuran ring: reflux with 1% NaOH in ethanol for 3 hr; reflux in acetic acid containing 10% by weight sodium acetate; reflux in 95% aqueous methanol containing 2% by weight hydrogen chloride.

Attempted Ring-Opening of 17 with Sodium Hydroxide.

A suspension of 17 (27.2 mg) in 1% sodium hydroxide solution was refluxed under nitrogen for 5 days. No reaction occurred, although 17 was partially soluble in the hot alkaline solution, as judged by tlc. After this period chloroform extraction returned 26.8 mg of 17 having an infrared spectrum identical to the starting material.

Attempted Reaction of 17 with Lithium Cyanide.

A solution of 17 (10 mg) in hexamethylphosphoramide containing LiCN (0.50 g) was heated to 90° for 10 hr and then to 120° for 6 hr.

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tlc indicated that no reaction had occurred. Unreacted 17 (5.2 mg) was obtained by removing most of the HMPA by distillation, adding water and extracting with chloroform.

Reaction of 16 with Acetic Anhydride-BF_3.

A solution of 16 (100 mg, 0.26 mmole) in acetic anhydride (25 ml) was treated with 0.5 ml of BF_3 solution in diethyl ether. Conversion to a new material was complete within a few minutes as judged by tlc. After 5 min water (50 ml) was added, followed by sodium bicarbonate (20 g) added in small portions. Additional water (50 ml) was added during the addition of the bicarbonate. When hydrolysis of the acetic anhydride was complete (~10 min) the product was extracted with chloroform. The principal product was unstable but spectral data was obtained on a sample purified by preparative layer chromatography on silica gel using ether for development. A crystalline sample, mp 119–121° was obtained from ether–heptane; mass spectrum 430 (34), 339 (16), 327 (14), 326 (10), 325 (10), 325 (12), 295 (13), 253 (34), 235 (35), 183 (54), 170 (60), 156 (38), 144 (32),

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143 (40), 130 (21), 91 (100); UV (MeOH) 211 (4.3), 225 (4.2), 266 (3.7).

Due to the instability of the product a procedure involving hydrogenation of the reaction mixture prior to hydrolysis was developed. After addition of the BF_3-etherate, platinum oxide was added and hydrogen was bubbled through the solution. Complete reduction occurred within 2 hr. The reaction mixture was then stirred into water and neutralized by careful addition of solid sodium bicarbonate. The mixture was extracted with chloroform. Two principal products were present but could not be separated on a silica gel preparative layer plate using ether for development. The mixture was dissolved in methanol (15 ml) containing acetic acid (1 ml) and hydrogenolyzed over 10% Pd/C catalyst. The catalyst was removed by filtration and the solution evaporated to dryness. The residue was neutralized and extracted with chloroform. Tlc revealed the presence of two products which were separated on a silica preparative layer plate using 15% methanol in chloroform for development. The less mobile component crystallized (23% yield) from chloroform–ether, mp 131–152°; mass spectrum: 340 (17), 298 (31), 281 (6), 256 (13), 239 (9), 238 (11),

12

237 (8), 210 (4), 196 (5), 195 (4), 180 (3), 168 (9), 153 (25), 145 (10), 144 (17), 143 (14), 130 (17), 111 (16), 106 (7), 95 (11), 93 (5), 82 (15), 80 (15); UV (MeOH) 208 (4.24); 255 (4.01), 287 (3.61).

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11, N, 8.23. Found: C, 70.32; H, 7.18; N, 8.00.

The more mobile component was noncrystalline; mass spectrum: 340 (>100), 298 (20), 297 (18), 281 (48), 280 (90), 265 (21), 239 (21), 238 (41), 237 (34), 212 (15), 201 (21), 196 (18), 195 (16), 194 (20), 182 (23), 181 (23), 169 (43), 168 (95), 156 (55), 153 (45), 145 (24), 144 (62), 143 (41), 131 (46), 130 (95), 126 (56); UV (MeOH) 208 (4.26); 256 (4.04); 285 (3.62).

A crystalline p-bromobenzenesulfonyl derivative, mp 156–8, was obtained.

Anal. Calcd for $C_{26}H_{27}N_2O_5SBr$: C, 55.81; H, 4.87. Found: C, 55.97; H, 4.91.

the $LiAlH_4$ reductive cleavage. Both compounds have proven resistant to a variety of attempts to solvolyze the ether ring. The *N*-carbobenzyloxy derivative **16** was recovered after heating with ~0.04 *M* ethanolic sodium hydroxide, sodium acetate in acetic acid, and methanolic hydrochloric acid. Compound **17** was recovered unchanged after heating for several hours with lithium cyanide in hexamethylphosphoramide. On the other hand, treatment of **16** with BF_3 in acetic anhydride led to an unstable product with an indolenine ultraviolet spectrum. Subsequent catalytic reduction led to two, probably stereoisomeric, *N*-acetylindolines. These chromophoric changes indicate that the indole ring has been involved in the reaction but a conclusive structural assignment is not possible.

Acknowledgment. The initial phase of this work was supported by NSF Grant 19374. The major support was provided by NCI Grant CA-12940-01. Pulsed Fourier transform spectra were recorded on an instrument provided by NSF Grant MPS 73-08469. The 250-MHz spectrum was recorded at the NIH Facility for Biomedical Research at Carnegie-Mellon University, Grant No. 00292.

Registry No.—**3,** 21363-69-9; **4,** 30338-63-7; **5,** 30338-65-9; **9,** 54531-62-3; *c*-**10,** 54531-66-7; *t*-**10,** 54531-67-8; *t*-**10,** OH analog, 54531-68-9; **11,** 54531-69-0; **11** diol analog, 54531-70-3; **11** diacetoxy analog, 54531-71-4; **12,** 54594-01-3; **16,** 54531-63-4; **17,** 54531-64-5; **18,** 54531-65-6; triethyl phosphonoacetate, 867-13-0; 1-benzoyl-4-piperidone, 24686-78-0; benzyl chloroformate, 501-53-1; pyrrolidine, 123-75-1; gramine, 87-52-5.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and 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 $2.50 for microfiche, referring to code number JOC-75-1433.

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Pyrido[2,3-*d*]pyrimidines. Latent 2-Aminonicotinaldehydes

Georges Evens and Paul Caluwe*

State University of New York, Polymer Research Center, College of Environmental Science and Forestry, Syracuse, New York 13210

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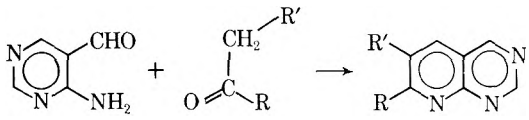
Friedländer condensation of 4-aminopyrimidine-5-carboxaldehyde with aromatic ketomethylenes resulted in the formation of 7- and 6,7-disubstituted pyrido[2,3-*d*]pyrimidines. Facile ring opening of the pyrimidine moiety of this heterocyclic system gave substituted 2-aminonicotinaldehydes.

Incorporation of the ortho amino aldehyde functional pair in aromatic substrates virtually ensures the successful construction of a variety of N-heterocyclic ring structures. However, utilization of this functional pair is severely limited by the difficult elaboration of the two functional groups in the required ortho position. It is not surprising, therefore, that in the synthesis of quinolines the Pfitzinger modification is preferred instead of the more direct Friedländer condensation utilizing *o*-aminobenzaldehyde.[1]

Methods available in the literature for the construction of the *o*-amino aldehyde functional pair are essentially twofold: nitration of a methyl aromatic compound and oxidation of the methyl group followed by reduction of the nitro function and generation of the aldehyde function from appropriate *o*-aminocarboxylic acid derivatives (e.g., McFayden–Stevens rearrangement of *o*-aminotosylhydrazides).[2a,b] Both methods require separate elaboration of the functional groups and this generally results in lengthy synthetic procedures. The first method is generally successful in carbocyclic ring structures; the second has found limited application in heterocyclic systems. Neither method is readily adapted for the introduction of substituents in the aromatic or heterocyclic ring carrying the *o*-amino aldehyde functional pair.

In earlier work we described a facile synthesis of 2-aminonicotinaldehyde from the readily available 2-(3′-pyridyl)pyrido[2,3-*d*]pyrimidine.[3] In this synthesis both the aldehyde and amino functions, in the desired ortho positions, were formed in a single reaction step. Since the inaccessibility of ring-substituted *o*-amino aldehydes constitutes the main limitation for their synthetic utility, exploration of a similar sequence for the synthesis of 2-aminonicotinaldehydes substituted in the pyridine ring seemed desirable. This paper reports a general synthesis of 7- and 6,7-substituted pyrido[2,3-*d*]pyrimidines and their acid-catalyzed conversion to substituted 2-aminonicotinaldehydes.

Two general strategies for the synthesis of pyridopyrimidines can be envisioned: annelation of the pyridine nucleus to a pyrimidine ring already in being and formation of the pyrimidine moiety from appropriately functionalized pyridines. Previous experience in the annelation of pyridine rings via the Friedländer condensation prompted us to explore a similar sequence for the synthesis of the pyridine moiety of pyrido[2,3-*d*]pyrimidine. This approach requires 4-aminopyrimidine-5-carboxaldehyde (**1**), readily obtained from 4-aminopyrimidine-5-carbonitrile by hydrogenolysis of the nitrile group.[4] Base-catalyzed condensation of **1** with

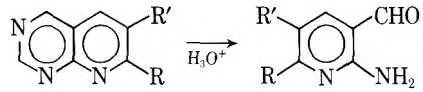


1 **2** **3**

aromatic ketomethylenes proceeded in high yield and resulted in the formation of 7- and 6,7-substituted pyrido[2,3-*d*]pyrimidines (**3**) (Table I).

Inspection of Table I indicates that this condensation reaction is generally successful for the two types of aromatic ketomethylenes: $ArC(=O)CH_2R$ and $ArCH_2C(=O)R$ (R = alkyl, aryl). Aliphatic ketones (acetone, cyclohexanone), on the other hand, failed to react similarly, although they condense smoothly with 2-aminonicotinaldehyde.[5] Apparently **1** is less reactive towards ketomethylenes, supported by the fact that no condensations take place with piperidine as catalyst, although this is highly effective in promoting condensations with 2-aminonicotinaldehyde.[5] The pyrido[2,3-*d*]pyrimidines obtained by the above reaction contain no oxo or amino substituents in their pyrimidine moiety, as is the case in most synthetic routes leading to this ring system.[6]

Acid-catalyzed hydrolysis of the substituted pyrido[2,3-*d*]pyrimidines (**3a–f**) resulted in ring opening of the pyrimidine moiety with formation of the *o*-amino aldehyde functional pair in excellent yield (Table II). The structures of the substituted 2-aminonicotinaldehydes (**4a–f**) are based upon their analytical and spectral data, which are in excellent agreement with their formulation. Their ir spectra



3 **4**

show particularly characteristic absorptions at 3400, 3250, 3150 (NH_2), and 1660 cm^{-1} (C=O) and their NMR spectra show the proper absorptions and proper counts (see Table IV, supplementary material).

Inspection of Table II indicates that a variety of substituents can be incorporated into the 5 and 6 positions of the pyridine ring carrying the *o*-amino aldehyde functional pair. This choice of substituents is limited only by the necessity of utilizing aromatic ketomethylenes in the condensation with **1**. Condensations with arylacetaldehydes which would lead to 5-aryl-2-aminonicotinaldehydes were not carried out owing to the instability of the ketomethylenes under the basic reaction conditions employed for the formation of **3**. The lower yield of 2-amino-5-phenyl-6-methylnicotinaldehyde (**4d**) is probably due to self-condensation of this highly reactive compound under the acidic conditions of the hydrolysis reaction.

The driving force for the transformation **3** → **4** is the acid-catalyzed covalent hydration of the pyrido[2,3-*d*]pyrimidine system,[7] followed by irreversible ring opening of the pyrimidine moiety.

Occurrence of covalent hydration[8] is well documented in similar N-heterocyclic systems such as pteridine, which on degradation is converted into 2-aminopyrazine-3-carboxaldehyde.[9]

The pyrimidine moiety of the pyrido[2,3-*d*]pyrimidine system is thus employed as "latent"[10] *o*-amino aldehyde functional pair, readily unmasked under mild reaction conditions. Phenomenologically the above reaction consists of the following transformation.

Table I
Pyrido[2,3-*d*]pyrimidines (3) Obtained from 4-Aminopyrimidine-5-carboxaldehyde[a]

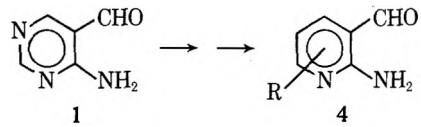
Compd	Registry no.	R	R′	Yield, %	Mp, °C	Ir, cm^{-1} [b,d]	Nmr, δ [c,d]
a	54595-53-8	C_6H_5	H	84	188.5	1600, 1580, 1530	9.63 (s, 1), 9.51 (s, 1)
b	54595-54-9	C_6H_5	C_6H_5	75	157	1600, 1570, 1540	9.60 (s, 1), 9.55 (s, 1), 8.33 (s, H-5)
c	54595-55-0	C_6H_5	CH_3	75	169	1600, 1580, 1524	9.48 (s, 1), 9.41 (s, 1), 2.58 (s, 3, CH_3)
d	54595-56-1	CH_3	C_6H_5	80	203	1605, 1585, 1575, 1550	9.53 (s, 1), 9.46 (s, 1), 2.75 (s, 3, CH_3)
e	54595-57-2	2-Pyridyl	H	85	200	1605, 1590, 1570, 1545	
f	54595-58-3	2-Naphthyl	H	82	272	1600, 1530	

[a] Satisfactory analytical data (±0.2% for C, H, N) were reported for all compounds. [b] Nujol mull. [c] $CDCl_3$. [d] Full spectral data are given in supplementary pages; see paragraph at end of paper.

Table II
2-Aminonicotinaldehydes (4) Obtained from Pyrido[2,3-*d*]pyrimidines[a]

Compd	Registry no.	R	R′	Yield, %	Mp, °C	Ir, cm^{-1} [b,d]	Nmr, δ [c,d]
a	5298-01-1	C_6H_5	H	90	137	1650, 1600, 1575, 1540	9.85 (s, 1, CHO), 6.83 (br, 2, NH_2)
b	54595-59-4	C_6H_5	C_6H_5	95	202	1670, 1605, 1580, 1525	10.03 (s, 1, CHO) (DMSO-d_6)
c	54595-60-7	C_6H_5	CH_3	90	160	1660, 1610, 1580, 1535	9.90 (s, 1, CHO), 6.75 (br, 2, NH_2)
d	54595-61-8	CH_3	C_6H_5	60	160	1660, 1610, 1535	9.86 (s, 1, CHO), 7.00 (br, 2, NH_2)
e	54595-62-9	2-Pyridyl	H	95	134	1650, 1640, 1600, 1570, 1520	9.93 (s, 1, CHO), 6.86 (br, 2, NH_2)
f	54595-63-0	2-Naphthyl	H	90	181	1670, 1600, 1570, 1540	9.98 (s, 1, CHO) (DMSO-d_6)

[a] Satisfactory analytical data (±0.2% for C, H, N) were reported for all compounds. [b] Nujol mull; all spectra contained NH_2 and CH bands at 3400–3100 and 2700–2800 cm^{-1}. [c] $CDCl_3$ unless otherwise noted. [d] Full spectral data are given in supplementary pages; see paragraph at end of paper.



1 4

From this viewpoint the pyrimidine ring of 1 can be considered as a latent pyridine nucleus. It is interesting to note that during this transformation the functionality of the system remains the same; i.e., the *o*-amino aldehyde pair is present in both 1 and 4 in the same relative positions.

In conclusion we would like to emphasize that the synthesis of substituted aminonicotinaldehydes as described herein is of particular utility since the starting materials are readily available and a variety of substituents are therefore easily introduced. Furthermore, it seems to us that the *o*-amino aldehydes thus obtained may serve as useful starting materials for functionalized pyridine derivatives via known functional group transformations.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were measured with a Varian Associates A-60 spectrometer and chemical shifts (δ) are reported in parts per million downfield from Me_4Si. Mass spectra were observed in these laboratories with an Hitachi Perkin-Elmer instrument, Model RMU6E. Microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn.

Generalized Procedure for the Preparation of Pyrido[2,3-*d*]pyrimidine (3). To a refluxing solution of 4-aminopyrimidine-5-carboxaldehyde (5 mmol) and the ketomethylene (5 mmol) in ethanol (25 ml) were added 5 drops of a 20% KOH solution in methanol. The mixture was refluxed for 12–48 hr; the precipitate was collected and recrystallized from a suitable solvent. The pyrido[2,3-*d*]pyrimidines reported in Table I are colorless crystalline compounds. Their spectroscopic characteristics are collected in Table III (supplementary material).

Generalized Procedure for the Preparation of 2-Aminonicotinaldehydes (4). The pyrido[2,3-*d*]pyrimidine (5 mmol) was refluxed in 2 *N* HCl (500 ml) for 2–5 hr. The mixture was neutralized (NH_4OH) and the precipitate was collected and recrystallized from suitable solvents.[11] The 2-aminonicotinaldehydes are yellow compounds which can be sublimed readily without decomposition. Spectroscopic data are collected in Table IV (supplementary material).

Acknowledgment. This research was sponsored by the U. S. Army Research Office, Durham, N.C. We wish to express appreciation to Professor M. Szwarc, without whose help this investigation would not have been possible. We thank Mr. Kuen-Wai Chiu for carrying out some preliminary experiments.

Registry No.—1, 16357-83-8; **2a**, 98-86-2; **2b**, 451-40-1; **2c**, 93-55-0; **2d**, 103-79-7; **2e**, 1122-62-9; **2f**, 93-08-3.

Supplementary Material Available. Additional spectral data for compounds 3 and 4 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 $2.50 for microfiche, referring to code number JOC-75-1438.

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Reaction of Diphenylcyclopropenone with 2-Aminopyridines. Synthetic and Mechanistic Implications

Albert Kascheres* and J. Augusto R. Rodrigues

Instituto de Quimica, Universidade Estadual de Campinas, Campinas, SP, Brasil 13.100

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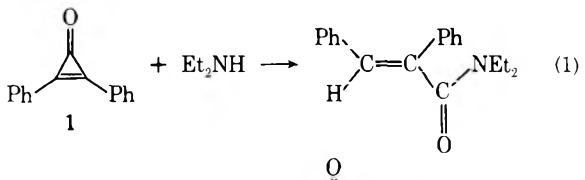
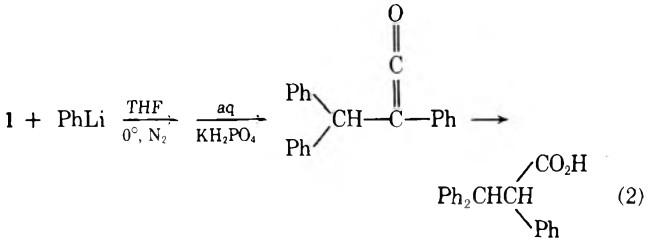
Diphenylcyclopropenone (1) reacts with 2-aminopyridines (2) in ether to produce *cis*-2,3-diphenylacrylamides (3) and insoluble *cis*-3,4-dihydro-3,4-diphenyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (4), which in chloroform solution readily rearrange to 3. In methanol, a slow reaction occurs, eventually forming 3 and 5, the stable trans isomers of 4. During shorter reaction times, mixtures of 3, 4, and 5 were observed. A lack of reactivity shown by aniline and 2-amino-6-methylpyridine suggests initial nucleophilic attack by the aminopyridine ring nitrogen on C-2 of the cyclopropenone. The mechanistic pathway of the reaction is discussed.

The reactions of nucleophilic reagents with the electrophilic cyclopropenone ring have been described in terms of "carbonyl addition" or "conjugate addition" processes.[1] Thus, diphenylcyclopropenone (1) reacted with diethylamine to give a carbonyl addition product (eq 1),[2] while reaction with phenyllithium afforded a conjugate addition product, albeit in low yield (eq 2).[3] The proposed ketene

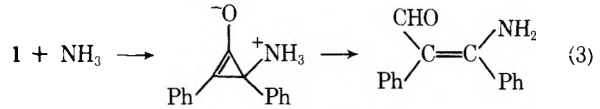


(1)

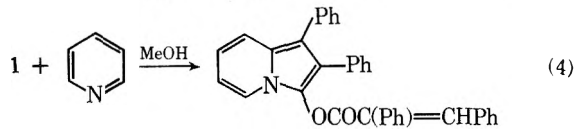


(2)

intermediate (eq 2) was detected spectroscopically at −70°. The reaction of 1 with ammonia at −78° formed an unusual conjugate addition product (eq 3).[4]



(3)



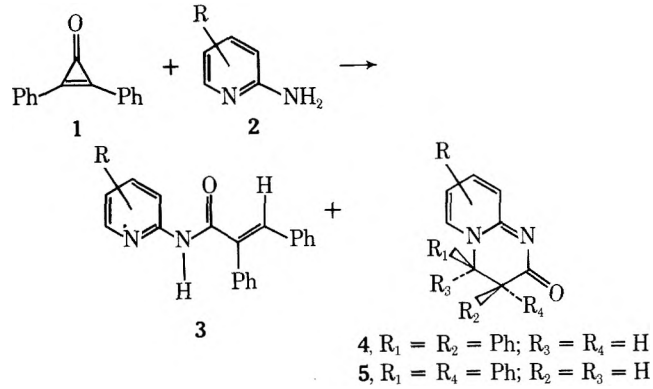
(4)

Recently, a carbonyl addition product (40% yield) was identified in the reaction of 1 with pyridine (eq 4).[5]

Our interest in the chemical behavior of cyclopropenones[6] made it desirable to explore the possibility of participation of a "conjugate addition" mode in the reaction of pyridine by appropriately substituting the nucleus with a second functional group capable of intercepting a reactive (ketene) intermediate. The 2-aminopyridine system was chosen as a probe for this pathway with emphasis on reaction conditions, structure of products, and mechanistic implications.

Results and Discussion

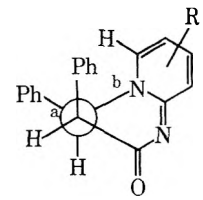
Diphenylcyclopropenone (1) underwent a smooth reaction with a variety of 2-aminopyridines (2) (see Table I) at room temperature. An ether solution of the reagents began to deposit a white solid after 10 min. After 17 hr, removal of the solvent from the ether-soluble portion at reduced



4, $R_1 = R_2 = Ph$; $R_3 = R_4 = H$
5, $R_1 = R_4 = Ph$; $R_2 = R_3 = H$

pressure afforded 3. The structure assignment was suggested by the infrared spectra ($CHCl_3$), which exhibited prominent absorption in the 3400- and 1675-cm^{-1} regions. In addition, the NMR spectra of 3a, 3c, and 3d showed large paramagnetic shifts for H-3 (on the order of −2 ppm) in excellent agreement with the "formylation" deshielding shifts reported for the endo forms of 2-formylaminopyridines.[7] Finally, the cis relationship of the phenyl groups in 3 was indicated by the presence of a sharp, one-hydrogen singlet at δ 8.0.[8] Hydrolysis of 3 (ethanolic KOH) gave 2 and *cis*-2,3-diphenylacrylic acid, both isolated in quantitative amounts.

The ether-*insoluble* material proved to be unstable in solution. The NMR spectra of freshly prepared samples ($CDCl_3$) showed a pair of doublets at δ 4.3 and 5.3 (1 H each, J = 7 Hz). The spectra of the same solutions after 15 hr at room temperature were nearly identical with those of 3. It was possible to isolate 3 from chloroform solutions in better than 80% yield after recrystallization. These observations led to the formulation of the products as 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (4). A conformational representation of 4 shows that bonds a and b are capable of an antiperiplanar arrangement, thus facilitating a concerted olefin-forming elimination reaction.[9] The cis nature of the bulky phenyl groups and the unfavorable H-6–phenyl interaction are other features which may contribute to



the instability of 4. It was not possible to generate 4 from an ether solution of 3, leading us to believe that 4 is, in fact, a primary product of the reaction.

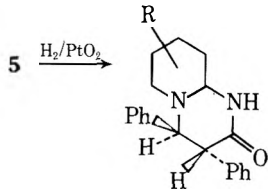
In methanol, reaction of 1 with 2 proceeded slowly at

Table I
Formation of Amide 3 and 3,4-Dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (4 or 5) in Ether and Methanol

2-Aminopyridine	Reaction: In ether[a] (% yield ± 2%)	Reaction: In methanol[a] (% yield ± 2%)[b]	Time, days	Isomerization of 4 in methanol (% yield ± 2%)
2a (R = H)	**3a** (75)	3a (75)	10	**3a** (71)
	4a (16)	5a (11)		**5a** (22)
2b (R = 3-Me)	3b (58)	3b (41)	24	3b (38)
	4b (22)	5b (44)		**5b** (55)
2c (R = 4-Me)	3c (62)	3c (60)	5	3c (58)
	4c (28)	5c (30)		5c (37)
2d (R = 5-Me)	**3d** (70)	**3d** (80)	10	**3d** (75)
	4d (17)	**5d** (10)		5d (16)

[a] Solution contained 2-mmol quantities of reagents in 15 ml of solvent. [b] Yield based upon unrecovered aminopyridine. The reactions of all 2-aminopyridines gave small quantities of the methyl ester of cis-2,3-diphenylacrylic acid (<7%). The indicated yields of 3 are slightly lower than the actual yields owing to difficulties encountered in separating the last traces of 3 from the methyl ester.

room temperature (see Table I), eventually forming 3 and ether-insoluble material, the NMR spectra of which showed a pair of doublets at δ 4.1 and 5.5 (1 H each, J = 2.5 Hz). The ir and uv spectra were very similar to those of 4 (see Experimental Section), suggesting that the compounds in question are **5**, that is, the stable trans isomers of 4. Hydrogenation of 5 (PtO_2–ethanol) gave **6**, the mass spectra of which indicated the incorporation of six hydrogens. The ir spectra ($CHCl_3$) showed absorption at 3400 and 1665 cm^{-1}.

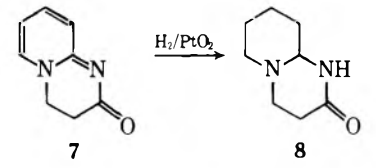


6a, R = H
b, R = 9-Me
c, R = 8-Me
d, R = 7-Me

Reaction in methanol for periods of less than several days produced in general mixtures of **3**, **4**, and **5**, in addition to starting material. In fact, 4 isomerized in methanol to a mixture of 3 and 5. Reaction times of 5–24 days were eventually chosen, depending upon the 2-aminopyridine, to ensure complete consumption of reagents as well as isomerization of 4. Table I contains the observed yields of 3 and 5 from 4 and from the reaction itself under these conditions.

A 24-hr reaction of 1 with **2b** in methanol gave an ether-insoluble fraction (16%) consisting solely of **4b** (by NMR), suggesting that 5 is a secondary product. Further confirmation of this was obtained from studies of 3 in methanol. A solution of **3c** (0.001 mol in 20 ml) slowly produced **5c** (10% after 5 days, 24% after 10 days). The tendency to cyclize was more dramatic in the case of **3b** (0.001 mol in 40 ml, 25% after 6 days; 0.001 mol in 10 ml, 29% after 8 days, 40% after 12 days), which may be attributed to a steric effect of the 3-Me group in **3b**. It appears, however, that the transformation of 3 to 5 does not account for the amount of 5 formed in the reaction (see Table I). Also, the amount of 5 formed from 4 (Table I) is higher in all cases than that observed in the reaction. These results may be rationalized by considering two pathways for the reaction, one of which involves the formation of 4 with subsequent isomerization to 3 and 5, the latter possibly forming via an enolization process.

The formation of 4 and 5 in the present study apparently represents the first report of a 3,4-disubstituted 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one. The reaction of **2a** with ethyl acrylate has been reported[10] to give **7**, which upon hydrogenation afforded **8**.[11] These reactions were repeated for the purpose of comparison of spectral data (see Experimental Section). The 3-methyl derivative of 7 has been prepared[12] from **2a** and methyl methacrylate.



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Further insight into the mechanism of formation of 3 from 1 and 2 was obtained from the following experiments. First, no reaction was observed between 1 and aniline, even under reflux conditions. Second, reaction between 1 and 2-amino-6-methylpyridine (**2e**) did not occur during 20 hr in ether or methanol, although 3 (R = 6-Me) was isolated as the only reaction product after extended periods (25% conversion after 5 days in ether, 13% conversion after 20 days

Scheme I

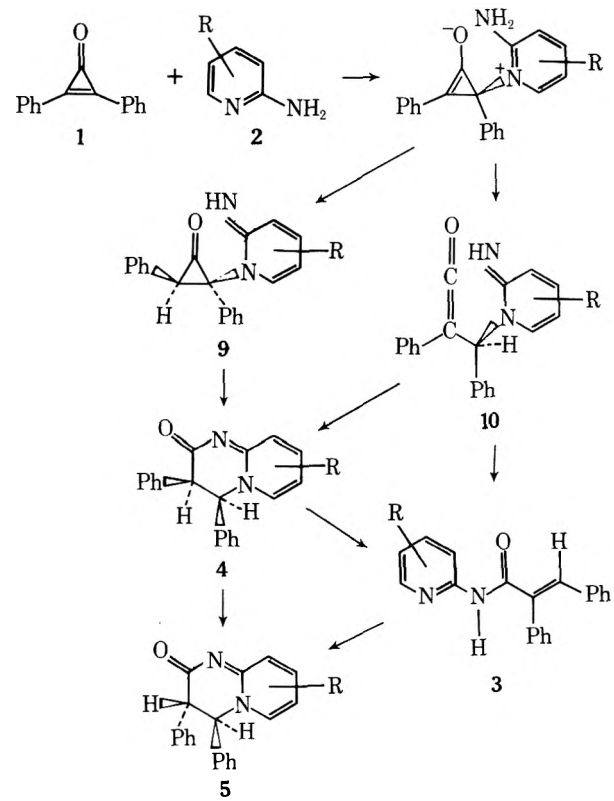

Table II
***cis*-3,4-Dihydro-3,4-diphenyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (4)[b]**

Substituent R	Mp, °C	NMR data ($CDCl_3$), δ	Uv data, λ_{max} (EtOH) (ε)	Ir data (KBr), cm^{-1}
H (**4a**)	115–117	4.3 (1 H, d, J = 7 Hz)	267 (15,700)	1660 (w)
		5.3 (1 H, d, J = 7 Hz)	344 (7900)	1620
		6.4 (1 H, dt, J = 6.5 and 1.8 Hz)		1550
		6.7–7.5 (13 H, m)		1490
9-Me (**4b**)	146–148	2.4 (3 H, s)	267 (14,000)	1650 (w)
		4.3 (1 H, d, J = 7 Hz)	340 (10,400)	1612
		5.2 (1 H, d, J = 7 Hz)		1575
		6.4 (1 H, t, J = 7 Hz)		1480
		6.7–7.5 (12 H, m)		
8-Me (**4c**)	123–125	2.35 (3 H, s)[a]	260 (10,600)	1660 (w)
		4.35 (1 H, d, J = 7 Hz)	340 (10,200)	1610
		5.3 (1 H, d, J = 7 Hz)		1540
		6.35 (1 H, dd, J = 6.5 and 1.8 Hz)		1480
		6.7–7.4 (12 H, m)		
7-Me (4d)	132–133	2.1 (3 H, s)[a]	266 (15,900)	1660 (w)
		4.35 (1 H, d, J = 7 Hz)	351 (7900)	1620
		5.35 (1 H, d, J = 7 Hz)		1550
		6.7–7.6 (13 H, m)		1490

[a] Several drops of CH_3OD were added to enhance solubility of compound. [b] Analytical data were not reported for these compounds. Ed.

Table III
***cis*-2,3-Diphenylacrylamides (3)[a]**

Substituent R	Mp, °C	Formula	NMR data ($CDCl_3$), δ	Ir data ($CHCl_3$), cm^{-1}
H (**3a**)	118–119	$C_{20}H_{16}N_2O$	6.9–7.7 (12 H, m)	3385
			7.9 (1 H, br, D_2O exchanged)	1674
			8.0 (1 H, s)	1616
			8.1 (1 H, d, J = 5 Hz)	1580
			8.4 (1 H, d, J = 8.5 Hz)	
3-Me (**3b**)	120	$C_{21}H_{18}N_2O$	2.25 (3 H, s)	3390
			6.9–7.6 (12 H, m)	1676
			7.7 (1 H, br, D_2O exchanged)	1614
			8.0 (1 H, s)	1578
			8.15 (1 H, dd, J = 5 and 1.8 Hz)	
4-Me (**3c**)	131–132	$C_{21}H_{18}N_2O$	2.35 (3 H, s)	3390
			6.8 (1 H, d, J = 5 Hz)	1675
			7.0–7.5 (10 H, m)	1610
			7.9 (1 H, br, D_2O exchanged)	1565
			8.0 (1 H, s)	
			8.1 (1 H, d, J = 5 Hz)	
			8.3 (1 H, s)	
5-Me (3d)	157–158	$C_{21}H_{18}N_2O$	2.25 (3 H, s)	3380
			7.0–7.6 (11 H, m)	1672
			7.85 (1 H, br, D_2O exchanged)	1610
			8.0 (2 H, s)	1583
			8.3 (1 H, d, J = 8 Hz)	
6-Me (**3e**)	156–157	$C_{21}H_{18}N_2O$	2.35 (3 H, s)	3398
			6.8 (1 H, d, J = 7.5 Hz)	1673
			7.0–7.65 (11 H, m)	1612
			7.9 (1 H, br, D_2O exchanged)	1582
			8.0 (1 H, s)	
			8.2 (1 H, d, J = 8 Hz)	

[a] Satisfactory analytical data (±0.3% in C, H, N) were reported for all compounds in Table. Ed.

in methanol, as indicated by NMR analysis of the crude material). An ether solution containing equimolar quantities of **1**, **2c**, and **2e** produced only the reaction products of **2c**, **2e** being recovered nearly quantitatively. 2-Picoline has been reported[5] to be unreactive toward **1**. These results demonstrate a participation by the ring nitrogen of **2** in the formation of all observed products.

Thus, the reaction of diphenylcyclopropenone (**1**) with 2-aminopyridines (**2**) in methanol can be visualized as occurring by way of a conjugate addition pathway involving initial nucleophilic attack of the ring nitrogen of **2** on the electrophilic cyclopropenone ring, as illustrated in Scheme I. Two highly reactive intermediates, **9** and **10**, are presented, either one of which may serve as a precursor of **4**. The intermediacy of **9** formally requires a stereospecific trans addition of **2** to the double bond of **1**. Such stereospecificity

Table IV
***trans*-3,4-Dihydro-3,4-diphenyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (5)[a]**

Substituent R	Mp, °C	Formula	NMR data ($CDCl_3$–CH_3OD), δ	Uv data, λmax (EtOH) (ε)	Ir data (KBr), cm^{-1}
H (**5a**)	200–202	$C_{20}H_{16}N_2O$	4.1 (1 H, d, J = 2.5 Hz) 5.45 (1 H, d, J = 2.5 Hz) 6.5 (1 H, dt, J = 7.0 and 1.8 Hz) 7.0–7.5 (13 H, m)	263 (13,900) 345 (9200)	1650 (w) 1615 1550 1488
9-Me (**5b**)	209–210	$C_{21}H_{18}N_2O$	2.35 (3 H, s) 4.15 (1 H, d, J = 2.5 Hz) 5.45 (1 H, d, J = 2.5 Hz) 6.5 (1 H, t, J = 6.5 Hz) 7.0–7.5 (12 H, m)	265 (13,400) 346 (10,400)	1650 (w) 1620 1570 1483
8-Me (**5c**)	220–222	$C_{21}H_{18}N_2O$	2.35 (3 H, s) 4.1 (1 H, d, J = 2.5 Hz) 5.45 (1 H, d, J = 2.5 Hz) 6.5 (1 H, dd, J = 6.5) and 1.8 Hz) 6.9 (1 H, s) 7.1–7.5 (11 H, m)	260 (11,200) 339 (10,150)	1660 (w) 1625 1538 1483
7-Me (**5d**)	222–223	$C_{21}H_{18}N_2O$	2.15 (3 H, s) 4.15 (1 H, d, J = 2.5 Hz) 5.5 (1 H, d, J = 2.5 Hz) 7.0–7.6(13 H, m)	265 (15,750) 351 (9850)	1662 (w) 1628 1550 1500

[a] Satisfactory analytical data (±0.2% in C, H, N) were reported for all compounds in Table. Ed.

Table V
Octahydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (6)[a]

Substituent R	Yield, %	Mp, °C	Formula	Ir data ($CHCl_3$), cm^{-1}
H (**6a**)	90	231–233	$C_{20}H_{22}N_2O$	3394, 1663, 1460
9-Me (**6b**)	93	207–209	$C_{21}H_{24}N_2O$	3390, 1665, 1455
8-Me (**6c**)	91	258–259	$C_{21}H_{24}N_2O$	3390, 1665, 1455
7-Me (**6d**)	87	241–243	$C_{21}H_{24}N_2O$	3390, 1665, 1460

[a] Satisfactory analytical data (±0.2% for C, H, N) were reported for all compounds in Table. Ed.

has been observed in the Michael reaction under conditions of kinetic control.[13]

The present study complements the report[14] of formation of 2,3-diphenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one from diphenylcyclopropenone and a sulfimide derivative of 2-aminopyridine. In this case, it is suggested that the ring nitrogen serves to intercept a ketene intermediate formed by initial conjugate addition of the exo nitrogen.

Experimental Section[15]

Reaction of 2-Aminopyridines (2) with Diphenylcyclopropenone (1). A. In Ether. A solution of the selected aminopyridine (0.0020 mol) and diphenylcyclopropenone (0.412 g, 0.0020 mol) in 15 ml of ether (dried over molecular sieve) was allowed to stand at room temperature (a precipitate began to form after 10 min). After 17 hr, the solvent was separated from the white solid, which was then washed with four 10-ml portions of dry ether to give the pyrimidones listed in Table II. Evaporation of the solvent, followed by recrystallization of the crude residue from ether–hexane, gave the amides **3** listed in Table III.

B. In Methanol. A solution of the aminopyridine (0.0020 mol) and diphenylcyclopropenone (0.412 g, 0.0020 mol) in 15 ml of anhydrous methanol was allowed to stand at room temperature for the determined time. The solvent was then evaporated and the crude residue was treated with 60 ml of dry ether, leaving **5** as an insoluble white solid which was recrystallized from CH_2Cl_2–hexane (Table IV). Recrystallization of the ether-soluble material from ether–hexane afforded pure **3**. Extraction of the mother liquor with dilute HCl gave 5–10% recovered aminopyridine. An equal quantity of the methyl ester of *cis*-2,3-diphenylacrylic acid was observed in the mother liquor. All yields were based upon unrecovered aminopyridine.

Competition Reaction of 2-Amino-4-methylpyridine (2c) and 2-Amino-6-methylpyridine (2e) with Diphenylcyclopropenone (1). To a solution of 2-amino-4-methylpyridine (0.216 g, 0.0020 mol) and 2-amino-6-methylpyridine (0.216 g, 0.0020 mol) in 15 ml of ether was added 0.412 g (0.0020 mol) of diphenylcyclopropenone (**1**). After 17 hr at room temperature, the solvent was separated from the white precipitate, which was washed with several portions of dry ether to yield 0.170 g (27%) of **4c** (mp 123–125°). Recrystallization of the ether-soluble material from ether–hexane afforded 0.390 g (63%) of **3c** (mp 131–132°). Extraction of the mother liquor with 10% HCl, followed by addition of NaOH to the extract until pH 8, gave 0.200 g (92%) of recovered 2-amino-6-methylpyridine.

Isomerization of 4 in Methanol. A solution of **4** (0.0010 mol) in 15 ml of methanol containing 0.001 mol of **2** was allowed to stand at room temperature for the determined time. Work-up as described above for the reaction in methanol gave **3** and **5** in the indicated yields (see Table I). Reaction carried out in the absence of **2** showed no significant change in the yields (i.e., **4c** gave 55% **3c** and 40% **5c**).

Cyclization of 3b and 3c in Methanol. Studies were performed on solutions of **3b** and **3c** in the presence and in the absence of **2** with work-up as usual. Thus, **3b** (0.290 g, 0.00092 mol) in 10 ml of methanol containing 0.108 g (0.001 mol) of **2b** gave, after 8 days, 0.085 g (29%) of **5b**. In the absence of **2b**, 0.082 g (28%) was isolated. From **3c**, 0.296 g (0.00095 mol), in 20 ml of methanol (saturated solution) containing 0.108 g (0.001 mol) of **2c**, there was isolated 0.030 g (10%) of **5c** after 5 days. In the absence of **2c**, 0.027 g (9%) was isolated.

Reaction of 2-Aminopyridine (2a) with Ethyl Acrylate. The reaction was carried out under the conditions described by Adams and Pachter[10] (heating the mixture for 12 hr on the steam bath) to give 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**7**): mp 187–188° (lit.[10] mp 187–188°); ir (KBr) 1650, 1610, 1555, 1495 cm^{-1}; uv (95% ethanol) λ_{max} 262 nm (ε 14,900), 341 (9700).

Octahydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (6 and 8). A solution of 0.200 g of the dihydro compound (**5** or **7**) in 10 ml of absolute ethanol was hydrogenated at 1 atm using 30 mg of platinum oxide catalyst. When hydrogen uptake ceased, the platinum was filtered off, the filtrate was evaporated at room temperature, and the resulting solid was recrystallized from CH_2Cl_2–hexane to give pure **6** or **8** (Table V). Octahydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**8**) was obtained in 90% yield, mp 142–143° (lit.[11] mp 140–142°), and showed ir absorption ($CHCl_3$) at 3398, 1665, and 1480 cm^{-1}.

Registry No.—**1**, 886-38-4; **2a**, 504-29-0; **2b**, 1603-40-3; **2c**, 695-34-1; **2d**, 1603-41-4; **2e**, 1624-81-3; **3a**, 54531-99-6; **3b**, 54532-00-2; **3c**, 54532-01-3; **3d**, 54532-02-4; **3e**, 54532-03-5; **4a**, 54532-04-6; **4b**, 54532-05-7; **4c**, 54532-06-8; **4d**, 54532-07-9; **5a**, 54532-08-0; **5b**, 54532-09-1; **5c**, 54532-10-4; **5d**, 54532-11-5; **6a**, 54531-96-3; **6b**, 54531-98-5; **6c**, 54531-97-4; **6d**, 54575-95-0; **7**, 5439-14-5; **8**, 24025-00-1; ethyl acrylate, 140-88-5.

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X-Ray and Dynamic Nuclear Magnetic Resonance Structural Study of a 1,2-Bis Exocyclic Diene. An Example of a Severely Skewed Diene

Daniel J. Pasto* and W. Robert Scheidt

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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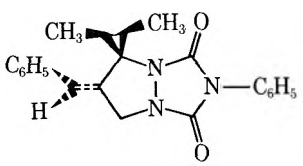
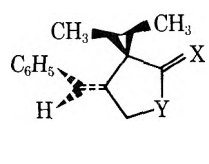
The X-ray structure determination of 3-*p*-bromophenyl-6,7-bisisopropylidene-8,8-dimethyl-1,3,5-triazabicyclo[3.3.0]octane-2,4-dione (**5a**) and a DNMR study of the debromo derivative **5b** have been carried out.

Steric interactions between functions attached to the diene chromophore of highly substituted 1,3-dienes result in a forcing of the diene to adopt nonplanar, chiral conformations. Considerable interest has recently arisen in the synthesis and structures of highly substituted dienes, and in the measurement of the barriers for rotation about the central carbon–carbon bond (i.e., enantiomerization) of such diene systems. Acyclic dienes have the potential of undergoing enantiomerization of the nonplanar chiral conformations via either s-cis or s-trans transition states. Mannshreck, Köbrich, and coworkers[1] have studied the enantiomerization of several highly substituted acyclic 1,3-dienes by NMR techniques and rotation barriers corresponding to enantiomerization via the lower energy s-trans transition states have been measured. Enantiomerization via the higher energy s-cis transition states cannot be studied with such acyclic systems.

1,2-Bisalkylidenecycloalkanes also contain skewed diene chromophores as evidenced by their ultraviolet[2,3] and NMR[3,4] spectral properties, the decreased chemical reactivity in cycloaddition reactions,[3,5] and the formation in our laboratories of the first reported optically stable, optically active dienes of structure 1 and 2.[6] In contrast to the



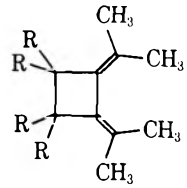
1



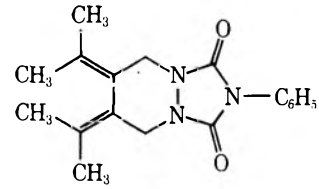
2

X = O; Y = NSO_2Cl
X = NSO_2Cl; Y = O

acyclic dienes, the enantiomerization of chiral 1,2-bisalkylidenecycloalkanes is restricted to occur only via the s-cis transition states, and thus provides opportunities for studying such processes. Kiefer and coworkers[4] have reported results of DNMR studies on **3** and **4** which possess



3, R = H, CH_3



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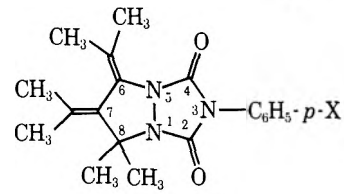


5a, X = Br
b, X = H

enantiomerization barriers of <12 and 21.1 kcal/mol, respectively. The discovery of the high degree of optical stability of **1** and **2** has prompted us to undertake an X-ray structure determination and DNMR study of a related structure **5**.[7]

X-Ray Structure of 5a. Figures 1 and 2 illustrate[8] the top-down and edge-on views of the molecule as it exists in the crystal. Tables I and II detail bond distances and angles, and interplanar angles.

Considerable distortion about the B ring is evident, the B ring existing in an "envelope" conformation with C_{15} projecting 33.2° (0.52 Å) above the general C_{14}–N_{10}–N_{11}–C_{16} plane. The diene chromophore is severely skewed,[9] the dihedral angle between the planes of the two isopropylidene functions being 52.3°. In addition, both isopropylidene groups are twisted about the double bonds (7 and

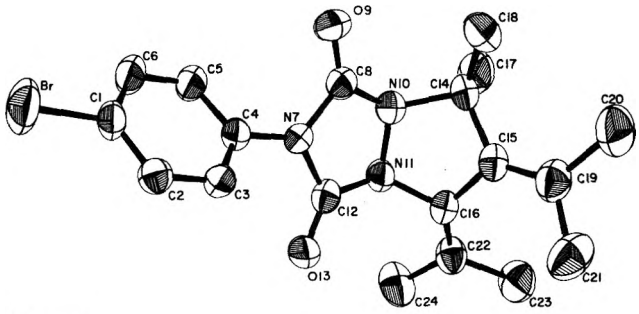


Figure 1.

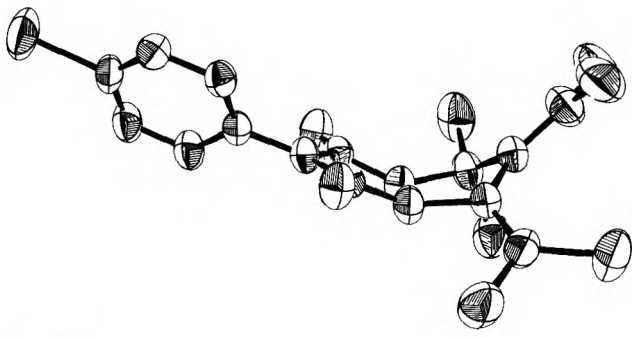
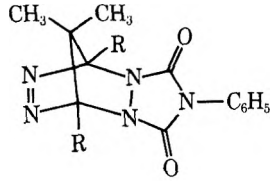


Figure 2.

12°) and bond angles deviate substantially from the normal [for example, C_{18}–C_{14}–C_{15} (118.8°), C_{15}–C_{19}–C_{20} (125.9°), C_{20}–C_{19}–C_{21} (112.1°), and C_{23}–C_{22}–C_{24} (114.4°)]. The C_{19}–C_{20}, C_{19}–C_{21}, and C_{22}–C_{23} bond lengths are considerably longer (0.03–0.04 Å) than normal vinyl C–C bonds (such as C_{22}–C_{24}). These distortions arise from severe steric interactions between the C_{18}–C_{20} and C_{21}–C_{23} methyl groups, the C–C nonbonded distances being 3.124 (8) and 3.134 (8) Å, respectively. These distances are considerably less than the sum of the van der Waals radii for two methyls of 3.4 Å.[10] The very close packing of the methyls is accomplished by intermeshing, or staggering, of the hydrogen atoms of the neighboring methyls. Inspection of a scale molecular model of **5a** indicates that for racemization of the skewed diene chromophore to occur C_{21} and C_{23} must pass within ~2.1 Å of each other if no other bond angle deformations or distortions occur. This would seem to be a prohibitively short distance which would result in a very high energy barrier for enantiomerization (unless other distortions were to occur in the molecule to lengthen this distance in the transition state).

A structural feature of great interest with respect to possible dynamic processes in **5** is the nonplanarity about the N–N bridge (interplanar angle of 19.1° between planes C_8–N_{10}–N_{11}–C_{12} and C_{14}–N_{10}–N_{11}–C_{16}). It had been implied previously from DNMR studies (over a temperature range of −60 to 60°) with **6** that the urazole ring in triazol-



6

inedione adducts was either rigid with the nitrogen atoms pyramidal or planar, or that inversion between pyramidal nitrogen forms was occurring rapidly at −60°.[11] Inspection of the scale molecular model of **5a** indicates that the nonplanar N–N bridge is a structural characteristic of the molecule and is not the result of intra- or intermolecular interactions, or the distortion about the other five-membered ring. Further evidence in support of this is derived from the results of DNMR studies with **5b** (vide infra).

Table I
Bond Lengths and Angles in Structure 5a

Bond type	Length, Å	Angle type	Value
Br–C_1	1.895 (4)	C_6–C_1–C_2	121.6 (4)
C_1–C_2	1.387 (6)	C_1–C_2–C_3	119.3 (4)
C_2–C_3	1.386 (6)	C_2–C_3–C_4	119.5 (4)
C_3–C_4	1.374 (6)	C_3–C_4–C_5	121.2 (4)
C_4–C_5	1.398 (6)	C_3–C_4–N_7	120.0 (4)
C_5–C_6	1.387 (6)	C_5–C_4–N_7	118.8 (4)
C_6–C_1	1.383 (6)	C_4–C_5–C_6	119.3 (4)
C_4–N_7	1.433 (5)	C_5–C_6–C_1	119.0 (4)
N_7–C_8	1.404 (6)	C_8–N_7–C_{12}	111.1 (3)
C_8–O_9	1.207 (5)	O_9–C_8–N_{10}	129.1 (4)
C_8–N_{10}	1.362 (6)	C_8–N_{10}–N_{11}	109.1 (3)
N_{10}–N_{11}	1.419 (5)	C_8–N_{10}–C_{14}	131.0 (4)
N_{11}–C_{12}	1.377 (5)	N_{11}–N_{10}–C_{14}	109.6 (3)
C_{12}–O_{13}	1.205 (5)	N_{10}–N_{11}–C_{12}	108.8 (3)
C_{12}–N_7	1.395 (6)	N_{10}–N_{11}–C_{16}	108.5 (3)
N_{10}–C_{14}	1.515 (5)	C_{12}–N_{11}–C_{16}	128.7 (4)
C_{14}–C_{15}	1.539 (6)	N_{11}–C_{12}–O_{13}	127.9 (4)
C_{14}–C_{17}	1.538 (7)	N_{10}–C_{14}–C_{15}	99.3 (3)
C_{14}–C_{18}	1.525 (7)	C_{17}–C_{14}–C_{15}	111.6 (4)
C_{15}–C_{16}	1.464 (6)	C_{18}–C_{14}–C_{15}	118.8 (4)
C_{15}–C_{19}	1.336 (6)	C_{19}–C_{14}–C_{18}	110.5 (4)
C_{16}–N_{11}	1.453 (5)	C_{14}–C_{15}–C_{16}	105.3 (3)
C_{16}–C_{22}	1.325 (6)	C_{14}–C_{15}–C_{19}	128.3 (4)
C_{19}–C_{20}	1.521 (7)	C_{16}–C_{15}–C_{19}	126.3 (4)
C_{19}–C_{21}	1.516 (7)	C_{15}–C_{16}–N_{11}	105.0 (4)
C_{22}–C_{23}	1.524 (7)	C_{15}–C_{16}–C_{22}	131.7 (4)
C_{22}–C_{24}	1.485 (7)	N_{11}–C_{16}–C_{22}	121.3 (4)
		C_{15}–C_{19}–C_{20}	125.9 (5)
		C_{15}–C_{19}–C_{21}	122.0 (5)
		C_{20}–C_{19}–C_{21}	112.1 (4)
		C_{16}–C_{22}–C_{23}	122.6 (4)
		C_{16}–C_{22}–C_{24}	123.0 (4)
		C_{23}–C_{22}–C_{24}	114.3 (4)

Table II
Interplanar Angles in 5a

Plane 1	Plane 2	Value, deg
Aromatic ring	C_8–N_7–C_{12}	47.1
C_8–N_{10}–N_{11}–C_{12}	C_{14}–N_{10}–N_{11}–C_{16}	19.1
C_{14}–N_{10}–N_{11}–C_{16}	C_{14}–C_{15}–C_{16}	33.2
C_{14}–C_{15}–C_{16}	C_{20}–C_{19}–C_{21}	12.0
C_{15}–C_{16}–N_{11}	C_{23}–C_{22}–C_{24}	7.0
C_{15}=C_{19} (C_{21}, C_{20})	C_{16}=C_{22} (C_{24}, C_{23})	52.3

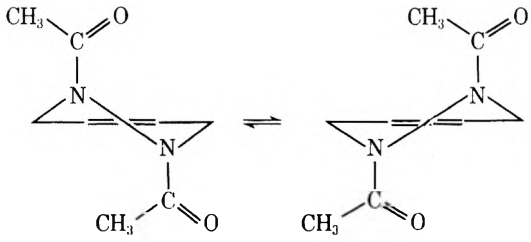
DNMR Studies with 5b. The room-temperature NMR spectrum of **5b** in 1:1 dideuteriodichloromethane–trichlorofluoromethane displays methyl singlets at δ 1.67 (6 H), 1.72 (6 H), 1.87 (3 H), and 2.13 (3 H). On lowering the temperature the high-field singlet broadens and finally at temperatures below −48° becomes two symmetrical singlets[12] with $\Delta\delta$ 52.3 Hz (at 100 MHz). The coalescence temperature for the dynamic process is −28°, which gives $\Delta G^{\ddagger}_{-28}$ = 11.9 kcal/mol. Further cooling to −110° resulted in no further changes.

Assignment of the resonances to the various methyl groups in **5b** can be unambiguously made by comparison of chemical shifts with those observed for other adducts of similar structure,[3] and by consideration of the environ-

ments of the methyl groups in **5b**. The lowest field methyl resonance represents the "outside" methyl of the C_6 isopropylidene group which resides in the plane of the neighboring carbonyl group and is thus deshielded.[13] The δ 1.87 resonance represents the "outside" methyl of the C_7 isopropylidene group. The high-field resonance which broadens and forms two widely separated singlets at lower temperatures must represent the geminal methyls attached to C_8. The scale model of **5a** shows that one of the methyls is axially oriented while the other is equatorially oriented and resides in the plane of the neighboring carbonyl group and thus must be deshielded. It is this equatorial methyl which gives rise to the new low-field singlet at low temperatures.

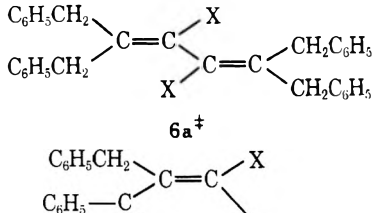
Two dynamic processes are possible in **5a** which would result in the exchange in the chemical environments of the two methyl groups attached to C_8: enantiomerization of the skewed diene chromophore or N–N bridge inversion. A number of considerations indicate that N–N bridge inversion is the phenomenon giving rise to the observed results.

The barrier for ring inversion in diacyltetrahydropyridazines and -piperidazines, i.e.

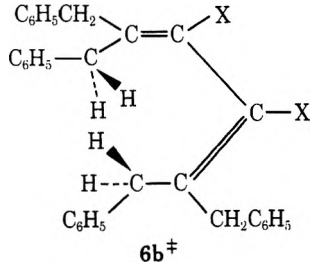


has been observed to be ~20 kcal/mol.[14] In the planar transition state for this inversion process considerable steric strain must be generated between the acyl functions. In the inversion about the bridge nitrogens of **5**, however, the functions attached to the nitrogens are contained in a cyclic structure and the steric strain between these groups is not increased on going to the transition state. Therefore, the barrier for inversion should be considerably lower than 20 kcal/mol.

The studies of Mannschreck, Köbrich, and coworkers[1] have revealed enantiomerization barriers of ≥21 kcal/mol for the substituted butadienes **6**. They attribute this barrier to rotation via the s-trans transition state (**6a**‡), which, on the basis of overall steric considerations, they believe to be lower in energy than rotation via the s-cis transition state (**6b**‡). As the inside benzyl groups in **6b**‡ can adopt conformations in which the phenyl groups are oriented outward, the steric strain between the benzyl groups should



6a‡



6b‡

X	$\Delta G^{\ddagger}_c$ (kcal/mol)
Cl	~21
Br	>22
I	>24

approximate that between the methyls in the transition state for enantiomerization of **5**. As the barrier in **6b**‡ must be >21 kcal/mol, one would similarly predict a barrier for enantiomerization in **5** of >21 kcal/mol, a value far too high compared to the experimentally observed value of 11.9 kcal/mol for the dynamic process in **5**. Finally, our isolation of optically active **1** and **2**, which retain their optical activity unchanged for 10 days at 25°, indicates that the enantiomerization barrier must be considerable, certainly much greater than the observed 11.9 kcal/mol. Thus, all of the evidence thus far available indicates that the dynamic process observed with **5b** involves nitrogen bridge inversion and not enantiomerization of the skewed diene.

The barrier of 21.1 kcal/mol for the dynamic process observed with **4**[4] is considerably higher than that observed with **5**. If the arguments and conclusions given in this paper are correct, the barrier in **4** is too high for ring nitrogen inversion. The lower barrier in **4** relative to that anticipated for enantiomerization of **5** could conceivably be due to the more flexible nature of the six-membered ring in **4** compared to the rather inflexible five-membered ring in **5**, thus allowing more facile distortion to lower the barrier to enantiomerization.

Experimental Section

Preparation of 5a. 4-(4-Bromophenyl)-1,2,4-triazoline-3,5-dione was prepared from 4-bromoaniline following the procedure of Cookson and coworkers[15] giving a very reactive, purple-colored material. A solution of 0.26 g of the crude material in 10 ml of dichloromethane was added to 0.15 g of 2,2,3,3-tetramethylisobutenylidenecyclopropane dissolved in 5 ml of dichloromethane. The purple color of the triazolinedione was discharged immediately. The solvent was removed under reduced pressure and the residue was chromatographed on a 1.5 × 10 cm column of silica gel. Elution with 5% ethyl acetate–chloroform gave 150 mg of product as colorless crystals, mp 122.5–124.0°. A crystal suitable for X-ray structural analysis was derived by evaporative recrystallization from methanol.

Crystal data: $C_{19}H_{22}BrN_3O_2$, mp 122.5–124.0°, monoclinic, space group $P2_1/c$, a = 12.418 (5), b = 15.799 (6), c = 10.095 (4) Å, and β = 102.70 (2)°. The calculated density was 1.416 g/cm^3; an experimental density could not be determined owing to the limited amount of compound. Lattice constants were obtained from a least-squares refinement of the setting angles of 26 reflections, each collected at ±20, given by the automatic centering routine supplied with the diffractometer (λ 0.71069 Å) at the ambient laboratory temperature of 20 ± 1°. Intensity data were collected on a Syntex P1 diffractometer using the θ–2θ scanning technique with graphite-monochromated MO Kα radiation. Details of the data collection and data reduction are essentially those given previously;[16] 1983 reflections had $F_o > 3\sigma(F_o)$ and were considered to be observed. Only the observed data were used in the solution and refinement of structure. The structure was solved by the standard heavy-atom method[17] and refined by full-matrix least-squares techniques[18] to a final $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ of 0.043 and a weighted $R_2 = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$ of 0.055. The shift errors in the last cycle of refinement were all less than 0.05. All hydrogen atom positions were determined from a difference Fourier synthesis; electron density maxima appropriately located for hydrogen atom positions were about three times higher than the general background level in the map. These hydrogen atoms were included in the final cycles of least-squares refinement as fixed contributors. A final difference Fourier map was essentially featureless with the largest peak being 0.15 e/A.^{3} (See paragraph at end of paper regarding supplementary material.)

Variable-Temperature NMR Studies with 5b. A dilute solution (~1%) of **5b**[3] in 1:1 dideuteriodichloromethane–trichlorofluoromethane (the low concentration was necessitated by the limited solubility of **5b** in the chosen solvent system at low temperatures) was triply freeze degassed in an NMR tube and sealed under a nitrogen atmosphere. The NMR spectra were recorded on a Varian XL100-15 spectrometer equipped with a variable-temperature probe and a Transform Technology TT100 Fourier transform. Because of the low concentration of the substrate and the different T1's of the hydrogens in **5b** the spectra were recorded using the Nicolet T1 Program/II (ten scans) with D1 = 10 sec, conditions

under which the hydrogens of **5b** are >98% relaxed giving singlets of appropriate relative intensities.

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Registry No.—**5a**, 54595-52-7; **5b**, 40755-74-6.

Supplementary Material Available. A listing of atomic coordinate positions and anisotropic thermal parameters 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 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 $2.50 for microfiche, referring to code number JOC-75-1444.

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Photochemical Reactions of α,β-Unsaturated Acids, Esters, and Nitriles

Thomas S. Cantrell

Chemistry Department, The American University, Washington, D.C. 20016

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Cyclohexene-1-carboxylic acid, the corresponding methyl ester, and cyclohexene-1-carbonitrile undergo slow addition to electron-rich alkenes upon irradiation. Reaction occurs, very slowly, at the carbon–carbon double bond of the ester and nitrile to give [2 + 2] cycloadducts, sometimes accompanied by products of ene-like reactions. Cyclohexene-1-carboxylic acid gives ester **15** and lactone **16** via retro-type II processes.

The photochemical behavior of five- and six-membered ring conjugated enones is diverse and interesting, with reactions such as α-cleavage, oxetane formation, [2 + 2] cycloaddition to the carbon–carbon double bond, the lumirearrangement to bicyclo[3.1.0]hexanones (in certain cases), and others being observed, depending on the presence or absence of coreactants.[1] It is believed that these molecules have lowest lying n,π* and π,π* triplet states of approximately equal energies, and that the precise structural details of the compound defines which state is of lowest energy, but that reactions from either state are possible in most cases.

On the other hand, the photochemical behavior of α,β-unsaturated acids and their derivatives, such as esters and nitriles, has, with the exception of a few specific compounds, been much less thoroughly investigated. The structures of the several [2 + 2] photodimers produced on irradiation of cinnamic acid in the solid state have been well worked out.[2] Cinnamic esters have been reported to undergo [2 + 2] photochemical addition to olefins in solution.[3] Maleic anhydride, fumaric acid, and maleic acid, and also fumaronitriles, undergo [2 + 2] photodimerization most efficiently in the solid state.[4] Coumarin undergoes direct and sensitized dimerization and sensitized addition to olefins, the former process apparently occurring via both singlet and triplet excited states.[5a,c] α-Phenylcinnamic acids on irradiation close to β-lactones.[6] Acrylonitrile dimerizes in the [2 + 2] fashion on photosensitization, whereas 2-cyanobutadiene undergoes two types of electrocyclic ring closure,[7] just as does butadiene itself. This would imply that the reactive excited states of butadiene and the 2-cyano derivative are similar (i.e., π,π*).

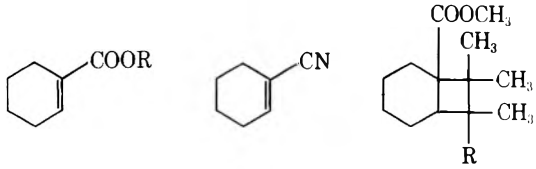
In other simple α,β-unsaturated acids, esters, and nitriles which have been examined, the photochemistry which has been observed has been similar to that exhibited by acylic ketones. Both classes of compounds undergo processes such as (a) migration of the double bond to the β,γ position, probably via hydrogen abstraction by the carbonyl oxygen, as in the type II elimination (this has been observed in crotonic acid and crotonic esters);[8,9] (b) cis–trans isomeriza-

tion about the double bond;[8,9] (c) occasionally, as in the case of acrylonitrile, mentioned above, [2 + 2] cyclodimerization.[7]

Our recent studies of the photochemical behavior of benzoic acid,[10] benzoate esters,[11] and benzonitrile[12] have shown that these benzene derivatives exhibit a varied and interesting photochemistry, undergoing reactions with alkenes at both the functional group and also ring positions, depending on the exact structure of the alkene and on reaction conditions. In order to provide a basis for comparison, it was deemed worthwhile to study the behavior of nonaromatic unsaturated acids and their derivatives which might serve as models. This report records some of our results with this class of compounds.

Attention was directed mainly at cyclohexene-1-carboxylic acid and the corresponding ester and nitrile for two reasons: (1) these are of the same ring size as the benzene derivatives previously studied, and hence strain effects will be minimized, and (2) a five- or six-membered cyclic system should be incapable of undergoing processes a or b mentioned above, which are the major processes observed in the photochemistry of acyclic aldehydes and ketones.[13] However, cyclic enones, especially those containing five- and six-membered rings, undergo cycloaddition, lumirearrangements, and other interesting and useful reactions.[1]

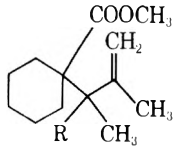
Accordingly, methyl cyclohexene-1-carboxylate (**1**) was irradiated through Vycor in the presence of excess 2,3-dimethyl-2-butene (DMB). There was formed in 38% yield (based on unrecovered **1**) a mixture of [2 + 2] cycloadduct **5** and compound **7** in a ratio of ~5:1. Their structures were apparent from their NMR and mass spectral characteristics, the two-hydrogen multiplet in the NMR and mass spectrum of **7** at τ 5.1 being especially helpful. From irradiation of ester **1** and 2-methyl-2-butene, the ene-type adduct **8** was isolated in pure form, as the sole product, unaccompanied by cycloadducts such as **6.** The reasons for the difference in reaction pathway caused by one methyl group are not clear.



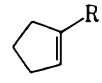
1, R = CH_3
2, R = H

3

5, R = CH_3
6, R = H

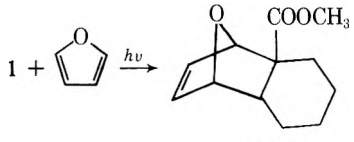


7, R = CH_3
8, R = H



4a, R = $COOCH_3$
b, R = CN

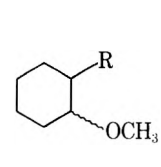
Irradiation of **1** in excess furan led cleanly to the [4 + 2] cycloadduct, **9**, in 65% yield. The nature of adduct **9** was

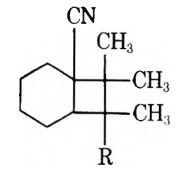


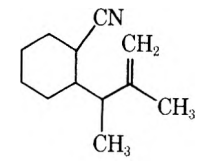
9

apparent from its NMR spectrum. The two vinyl hydrogens appear as an AB-like multiplet centered at τ 3.86; the two bridgehead hydrogens α to oxygen exhibit narrow multiplets at τ 5.37 and 5.45. The chemical shifts and general appearance of these signals are typical of [4 + 2] thermal and photochemical adducts of furan with α,β-unsaturated ketones.[14] The two vinyl hydrogens of 2,3-dihydrofurans, including [2 + 2] cycloadducts of furan, exhibit chemical shifts differing by 1.1–1.4 ppm.[14,15]

In agreement with the results of Kropp and Krauss,[9] we find that irradiation of **1** in methanol gives a modest (24%) yield of the isomeric 2-methoxycyclohexanecarboxylic esters of structure **10.**







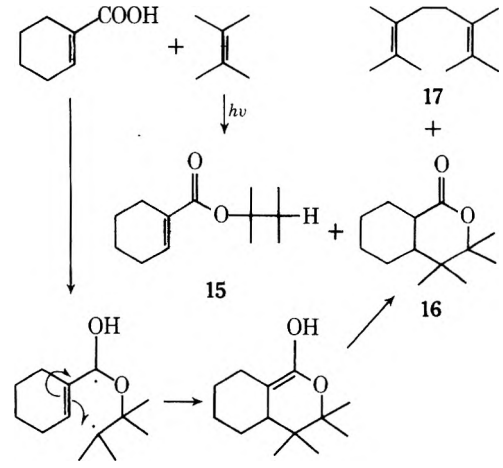
10, R = $COOCH_3$
14, R = CN

11, R = CH_3
12, R = H

13

1-Cyclohexenecarbonitrile (**3**) upon irradiation in the presence of excess DMB underwent a slow but clean [2 + 2] cycloaddition to give adduct **11** in 53% yield. When 2-methyl-2-butene was employed as substrate, both cycloadduct **12** and the ene-like adduct, **13,** were observed (28 and 18%, respectively). Irradiation of **3** in methanol in the presence of xylene as sensitizer gave a modest (36%) yield of the isomeric 2-methoxycyclohexanecarbonitriles (**14**). Use of 1,1-dimethoxy-2,2-dimethylethylene as substrate with **3** gave, in addition to considerable amounts of tarry materials, low conversions of a complex mixture of products. The individual components were not separated; however, the spectral properties of the mixture indicate that it does not contain an appreciable amount of 2-azabutadienes, a type of compound previously shown to result from addition of photochemically excited benzonitrile to electron-rich alkenes such as DMB and 1,1-dimethoxy-2,2-dimethylethylene.[12] Irradiation of 1-cyclohexenecarbonitrile and excess furan led only to the rapid formation of highly colored tarry material.

The five-membered ring analog of **3,** cyclopentene-1-carbonitrile, compound **4b,** showed similar photochemical behavior, giving a mixture of [2 + 2] cycloadduct and ene-like product (2:1) on irradiation in the presence of excess DMB.



15

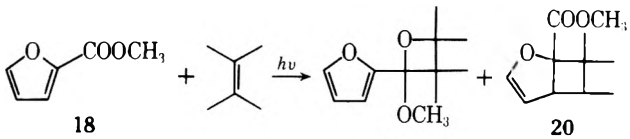
16

17

Cyclohexene-1-carboxylic acid (**2**) exhibits photochemical behavior indicative of biradical intermediates. Irradiation through Vycor of mixtures of **2** and excess DMB gave 2,3-dimethyl-2-butyl cyclohexene-1-carboxylate (**15,** 32%), lactone **16** (26%), and a mixture of C_{12} hydrocarbons, the predominant isomer being identified as 2,3,6,7-tetramethylocta-2,6-diene (**17**). The hydrocarbon has also been isolated from mixtures obtained on irradiation of benzoic acid and methyl benzoate with DMB.[10,11] Ester **15** was identi-

fied initially by its spectral properties (see Experimental Section) and later by hydrolysis to acid **2**. The structure of **16** was deduced from its various spectral parameters, including an infrared carbonyl stretching band at 1748 cm^{-1}, consistent with a δ-lactone, and a broad one-hydrogen NMR signal at τ 7.72 attributable to the hydrogen α to carbonyl. A plausible mechanism for the formation of **16** is shown above, involving the same diradical intermediate which accounts for the production of **15**. Lactone **16** most likely arises via a retro-type II elimination, as was postulated for photolysis of benzoic acid–DMB mixtures.[10]

While compound **2** reacts at the carboxylic acid function, **1**, **3**, and **4** all prefer to react with alkenes at the carbon–carbon double bond. This reluctance to react at the functional group is in contrast to the behavior which we earlier observed with the corresponding benzene derivatives.[10-12] The furan system is regarded as lying on the borderline between olefinic and aromatic character.[16] Consequently, we decided to study the behavior of a representative furan derivative, viz., methyl furoate (**18**). Interestingly, irradiation of methyl furoate (**18**) in the presence of excess DMB gave appreciable amounts of both oxetane **19** and compound **20**,



18 19 20

the product of [2 + 2] cycloaddition across the 1,2 positions of the furan ring (20 and 31%, respectively). The structures of these compounds were evident from their spectral parameters (see Experimental Section).

The most striking feature of the results described above is the absence of any products resulting from reaction of the unsaturated acid derivatives at the functional group itself of **1**, **3**, and **4**. A priori, one might argue that this is a reflection of the intrinsically greater reactivity of the alkenic double bonds of **1–4** as compared to that of the ring positions of the benzene derivatives previously studied.[10-12] However, the pronounced sluggishness of the presently observed reactions makes that explanation unlikely. Quantitative measurements were quite difficult to perform because of the low rates of reaction, and because the compounds **1–4** absorb light only at very short wavelengths. However, for the reaction between **1** and DMB, a quantum yield for disappearance of **1** of 0.004 is estimated. Although they are two orders of magnitude slower, the reactions of **1–4** with alkenes occur at the C=C double bond, as is the case with five- and six-membered ring cyclic unsaturated ketones.[17]

Experimental Section

Irradiations were conducted in an annular apparatus using light from a Hanovia 450-W medium-pressure mercury arc lamp, filtered through Vycor (transmits >220 nm) and cooled by ice water in an immersion well. All photochemical reaction solutions were flushed with argon for 1 hr prior to irradiation and an argon atmosphere was maintained during irradiation. NMR spectra were obtained on Varian A-60 and XL-100 instruments. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E. Gas chromatography was performed on the following columns: column A, 2 ft × 0.25 in., 10% SE-30 on Chromosorb W; column B, 2 ft × 0.25 in., 15% Carbowax 20M on Chromosorb W; column C, 6 ft × 0.25 in., 10% SE-30; column D, 6 ft × 0.25 in., 15% Carbowax 20 M; column E, 6 ft × 0.375 in., 25% SE-30; and column F, 6 ft × 0.25 in., 15% FFAP on Chromosorb W.

Photolysis of Methyl Cyclohexene-1-carboxylate (1) with Excess 2-Methyl-2-butene. A solution of ester **1** (3.0 g, 0.02 mol) and 2-methyl-2-butene (30 g) in spectrograde pentane (80 ml) was irradiated through Vycor for 36 hr. Evaporation of the solvent and excess alkene gave, after two vacuum distillations of the residue, recovered starting material (1.8 g), bp 40–44° (1 mm), and ene-like product **8**, bp 73–75° (0.5 mm) (0.72 g, 51%); ir (film) 1730 cm^{-1}; NMR ($CDCl_3$) τ 5.3 (2 H, m), 6.37, (3 H, s), 7.3–8.5 (9 H, m), 8.42 (3 H, s, br), and 9.00 (3 H, d, J = 6.7 Hz); mass spectrum m/e (rel intensity) 210 (11, P), 195 (6), 141 (100), 109 (48). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.29; H, 10.45. Found: C, 74.16; H, 10.30.

Photochemical Reaction of Ester 1 with 2,3-Dimethyl-2-butene. A solution of ester **1** (3.0 g) and 2,3-dimethyl-2-butene (30 g) in spectrograde hexane (90 ml) was irradiated through Vycor for 42 hr. Evaporation of excess alkene and solvent gave an oily residue which was fractionally distilled. Besides unchanged **1**, bp 38–43° (1 mm) (1.8 g), there was obtained two product fractions: a, bp 76–78° (0.3 mm) (0.32 g, 22%), and b, bp 88–90° (0.3 mm) (0.36 g). Fraction a appeared to be ene-like product **7**: ir (film) 1730 cm^{-1}; NMR ($CDCl_3$) τ 5.2 (2 H, m), 6.31 (3 H, s), 7.7–8.5 (10 H, m) 8.45 (3 H, s br), and 9.02 (6 H, s); mass spectrum m/e (rel intensity) 224 (11), 209 (21), 141 (100), and 109 (56). Anal. Calcd for $C_{14}H_{24}O_2$: C, 75.04; H, 10.74. Found: C, 74.91; H, 10.60. Fraction b was assigned the [2 + 2] structure **5**: ir (film) 1732 cm^{-1}; NMR ($CDCl_3$) τ 6.33 (3 H, s), 7.7–8.7 (9 H, m), 8.71 (3 H, s), 8.77 (3 H, s), and 9.04 (6 H, s); mass spectrum m/e (rel intensity) 244 (16, P), 209 (30), 141 (46), 109 (80), and 84 (100). Anal. Found: C, 75.26; H, 10.50.

Photochemical Cycloaddition of Ester 1 to Furan. A solution of ester **1** (2.00 g, 14 mol) in furan (120 ml) was irradiated through Corex for 9 hr. Evaporation of the excess furan and vacuum distillation of the residue gave recovered **1** [0.8 g, bp 35–38° (0.8 mm)], and [4 + 2] adduct **9**: bp 82–84° (0.08 mm) (1.23 g, 68%); ir (film) 1740 cm^{-1}; NMR ($CDCl_3$) τ 3.86 (2 H, AB, J = 2.6 Hz), 5.37 (1 H, m), 5.45 (1 H, m), 6.51 (3 H, s), and 7.7–8.8 (9 H, m); mass spectrum m/e (rel intensity) 208 (12, P), 149 (23), 148 (23), 140 (60), 109 (51), 108 (58), 81 (90), and 68 (100). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.25, H, 7.70. Found: C, 69.39; H, 7.55.

Irradiation of Ester 1 in Methanol. Photolysis of **1** (1.0 g) in methanol (125 ml) through Vycor for 30 hr gave a mixture of *cis*- and *trans*-methyl 2-methoxycylohexanecarboxylate [0.31 g, bp 52–56° (0.08 mm)] identified by comparison of the spectral with the reported parameters.[9]

Irradiation of 1-Cyclohexenecarbonitrile (3) with 2,3-Dimethyl-2-butene. A solution of nitrile **3** (2.0 g, 19 mol) and DMB (30 g) in spectrograde hexane (80 ml) was irradiated through Vycor for 60 hr. Evaporation of the solvent and excess alkene, followed by distillation of the residue, gave recovered **3** (0.6 g) and [2 + 2] cycloadduct **11**: bp 82–84° (0.1 mm) (0.78 g, 46%); ir (film) 2241 cm^{-1}; NMR (CCl_4) τ 7.6–8.5 (9 H, m), 8.69, 8.90, 9.01, and 9.04 (3 H each, s); mass spectrum m/e (rel intensity) 191 (28, P), 159 (17), 158 (46), 107 (100), and 84 (72). Anal. Calcd for $C_{13}H_{21}N$: C, 81.69, H, 11.00. Found: C, 81.42; H, 11.18.

Irradiation of Nitrile 3 with 2-Methyl-2-butene. A solution of nitrile **3** (2.0 g) and 2-methyl-2-butene (25 g) was made up to 140 ml with spectrograde pentane and irradiated through Vycor for 50 hr. Evaporation of the solvent and excess alkene gave a brown residue, which on distillation yielded unchanged **3** (1.0 g) and a mixture of **12** and **13**, bp 68–70° (0.1 mm). Separation on column B gave the components in 60:40 ratio. Eluted first was **12**: ir (film) 2244 cm^{-1}; NMR ($CDCl_3$) τ 7.4–8.4 (10 H, m), 8.75 (3 H, s), 8.83 (3 H, s), and 8.90 (3 H, d, J = 7 Hz); mass spectrum m/e (rel intensity) 177 (20, P), 162 (11), 107 (100), and 70 (56). Anal. Calcd for $C_{12}H_{19}N$: C, 81.37; H, 10.78. Found: C, 81.14; H, 10.70.

The second ene-like product collected, **13**, showed ir (film) 2240 cm^{-1}; NMR (CCl_4) τ 5.2 (2 H, br), 7.15–8.4 (9 H, m), 8.26 (3 H, s, br), and 8.78 (3 H, d, J = 7 Hz); mass spectrum m/e (rel intensity) 177 (14, P),

Irradiation of 3 with Miscellaneous Substrates. Irradiation of 1:10 mixtures of **3** and 1,1-dimethoxy-2,2-dimethylethylene gave, besides unchanged **3**, a small amount of distillate, bp 85–100° (0.1 mm), which exhibited NMR absorption in both the methoxyl (τ 6.1–6.9) and CH_2 (τ 7.8–8.5) regions. Analysis on several GC columns indicated the mixture to be quite complex and poorly resolved on the columns used.

Irradiation of **3** in furan at 25 and at −10° led to rapid darkening of the solution. Distillation gave only recovered **3** and a small amount of brown tarry material.

Irradiation of Cyclohexene-1-carboxylic Acid (2) and 2,3-Dimethyl-2-butene. A solution of acid **2** (3.0 g) and DMB (30 g) in spectrograde hexane (100 ml) was irradiated through Vycor for 8 hr. Evaporation of solvent and excess alkene gave a slightly yellow residue which was distilled to give two fractions: a, 1.2 g, bp 38–40° (0.01 mm), identified as **17** by comparison with authentic material,[10] and b, 2.2 g of colorless oil, bp 75–90° (0.08 mm). This

latter material was dissolved in ether and washed with 5% sodium bicarbonate. Acidification of the bicarbonate extracts gave 1.1 g of recovered **2**. Redistillation of the neutral fraction gave 0.96 g of colorless oil, bp 77–80° (0.08 mm). Separation on column F at 120° gave, in order of elution, ester **15** (32% yield): ir (film) 1710 cm^{-1}; NMR ($CDCl_3$) τ 3.25 (1 H, m, br), 7.7–8.5 (9 H, m), 8.59 (6 H, s), and 9.09 (6 H, d, J = 7 Hz); mass spectrum m/e (rel intensity) 210 (0.2); 109 (30), 105 (100), and 84 (64). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.31; H, 10.76. Found: C, 74.17; H, 10.52. The second peak collected was identified as lactone **16:** ir (film) 1748 cm^{-1}; NMR ($CDCl_3$) τ 7.7 (1 H, d, br, J = 7 Hz), 8.0–9.1 (9 H, m), and 8.90, 8.95, 8.98, and 9.04 (all 3 H each, s); mass spectrum m/e (rel intensity) 210 (P, 3), 192 (22), 177 (12), 150 (51), 122 (39), 121 (32), 109 (100), and 99 (48). Anal. Found: C, 74.55; H, 10.65.

Irradiation of Methyl 2-Furoate (18) with 2,3-Dimethyl-2-butene. A solution of **18** (3.0 g) and DMB (30 g) in spectrograde hexane was irradiated for 9 hr. Evaporation of solvent and excess alkene gave a brown oil which gave on distillation 1.0 g of recovered **18** and 1.2 of a mixture of **19** and **20**. Separation was accomplished by GC on column D to give, first, oxetane **19** [ir (film) 1100 cm^{-1} (s, br); NMR ($CDCl_3$) τ 2.62 (1 H, 2 d, J = 2.0, 0.9 Hz), 3.58 (1 H, 2d, J = 2.4, 2.0 Hz), 3.66 (1 H, m), 6.95 (3 H, s), 8.60, 8.84, 9.09, and 9.15 (all 3 H, s); mass spectrum m/e (rel intensity 210 (0.2, P), 195 (1.4), 126 (48), 84 (100). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.58; H, 8.54. Found: C, 68.84; H, 8.40.] and second, [2 + 2] cycloadduct **20** [ir (film) 1732 cm^{-1}; NMR ($CDCl_3$) τ 3.67 (1 H, d, J = 28 Hz), 5.03 (1 H, t, J = 2.8 Hz), 6.62 (1 H, m), 6.97 (3 H, s), 8.75, 8.84, 8.92, and 9.10 (all 3 H, s); mass spectrum m/e (rel intensity) 210 (6, P), 195 (9), 151 (21), 126 (45), and 84 (100). Anal. Found: C, 68.39; H, 8.31.].

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Registry No.—**1**, 18448-47-0; **2**, 636-82-8; **3**, 1855-63-6; **5**, 54642-98-7; **7**, 54642-99-8; **8**, 54643-00-4; **9**, 54643-01-5; **11**, 54643-02-6; **12**, 54643-03-7; **13**, 54643-04-8; **15**, 54643-05-9; **16**, 54643-06-0; **17**, 18495-18-6; **18**, 611-13-2; **19**, 54643-07-1; **20**, 54643-08-2; 2-methyl-2-butene, 513-35-9; 2,3-dimethyl-2-butene, 563-79-1; furan, 110-00-9.

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Model Studies Directed toward the Total Synthesis of Vernolepin. III. Synthesis of the α-Methylene-δ-valerolactone AB Ring Model

Paul A. Grieco,* Kunio Hiroi, James J. Reap, and J. A. Noguez

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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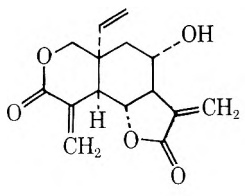
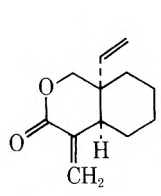
Two routes to the α-methylene-δ-valerolactone AB ring system (**2**) of vernolepin have been developed. The first approach involves a second-order Beckmann fragmentation on oxime **8**. The other approach employs an ozonolysis (reductive) of a Δ^2-enol acetate of an appropriately functionalized 3-ketodecalin. Introduction of the angular vinyl group in the latter approach is accomplished by facile elimination of the *o*-nitrophenyl selenoxide **20**. Introduction of the α-methylene unit involves α-hydroxymethylation of the enolate derived from lactone **3** followed by mesylation and β-elimination.

Our model studies directed toward the total synthesis of the growth-inhibitory sesquiterpene bislactone vernolepin (**1**)[3] have concentrated on the synthesis of the novel cis-fused AB ring system possessing an angular vinyl group. We wish to describe here the details of our model studies initiated a few years ago which led to the first synthesis of the vernolepin AB ring model **2**.[4] Several recent reports have described the synthesis of the δ-valerolactone system **3**[5-8] as well as its conversion to the α-methylene lactone **2**.[5]



1



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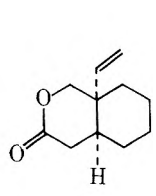

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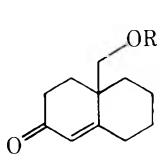
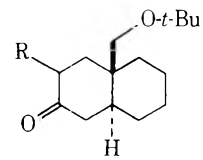
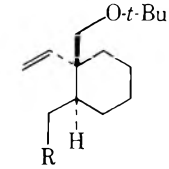


4, R = H
5, R = *t*-Bu



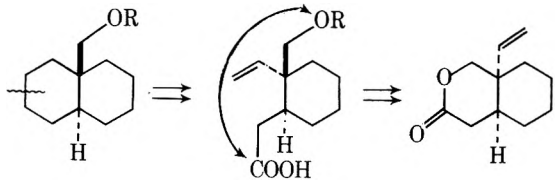
6, R = H
7, R = SCH_3



10, R = CN
11, R = COOH

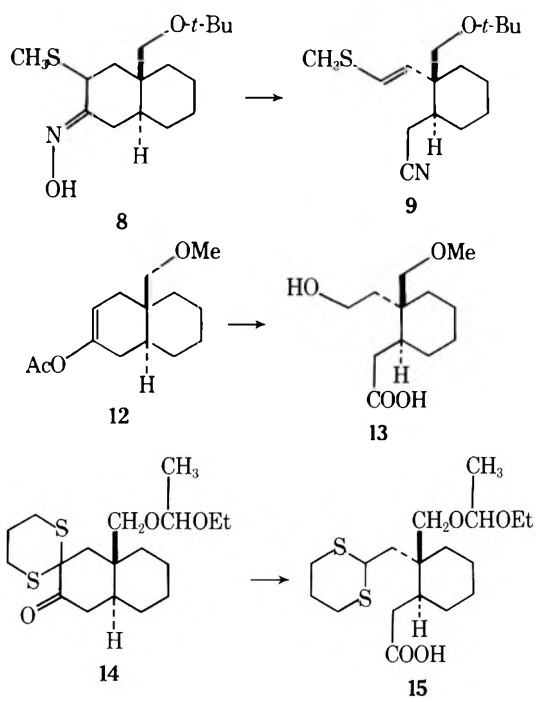
Our approach (see Scheme I) required a reaction or series of reactions which would allow for the specific cleavage of the C-2–C-3 bond (steroid numbering) of a suitably functionalized *trans*-decalin system with conversion of C-1 and C-2 into an olefin or potential olefin and formation of a carboxylic acid function or its equivalent at C-3. Such a carboxylic acid would upon lactonization provide the vernolepin cis-AB ring system possessing the angular vinyl

Scheme I



group. What would remain is a method for the introduction of the required α-methylene unit.

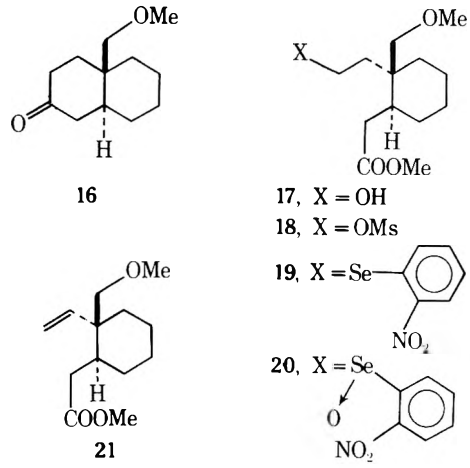
Several reaction schemes can be imagined for specific bond breaking of the C-2–C-3 carbon–carbon bond. In our hands the desired cleavage was carried out employing two approaches: a second-order Beckmann fragmentation[9] on the oxime of a 2-methylsulfenyl-3-keto decalin derivative (e.g., **8** → **9**)[4] and ozonolysis (reductive) of the Δ^2-enol acetate derived from a 3-keto *trans*-decalin (e. g., **12** → **13**).[8]



Both approaches meet the requirements stated above. Another approach developed by Marshall[6] involves base-induced C-2–C-3 carbon–carbon bond cleavage of the 3-keto dithiane derivative **14** (e.g., **14** → **15**).

The required oxime **8** was prepared from the hydroxymethyl octalone **4**[10] in the following manner. The hydroxymethyl group of **4** was protected as its *tert*-butyl ether. Metal–ammonia reduction of **5** afforded ketone **6**. Formylation of decalone **6** followed by treatment with methyl thiotosylate[11] provided the methylsulfenyl decalone **7**, which upon oximation yielded oxime **8**. Addition of methanesulfonyl chloride to oxime **8** in refluxing pyridine resulted in cleavage of the desired C-2–C-3 bond with formation of **9**. Cleavage of the carbon–sulfur bond of **9** followed by hydrolysis of the nitrile function would establish the first requirement stated above, namely, formation of an olefin between carbon atoms C-1 and C-2, and a carboxylic acid at C-3. Desulfurization with W-2 Raney nickel (deactivated) in ethanol yielded nitrile **10** in 90% yield. Hydrolysis of nitrile **9** afforded carboxylic acid **11** (85%), which upon treatment with *p*-toluenesulfonic acid in refluxing benzene resulted in a 95% yield of crystalline lactone **3**.

An alternate approach to **3** involves the ozonolysis (reductive) of the Δ^2-enol acetate **12** which specifically cleaves the C-2–C-3 carbon–carbon bond establishing a carboxylic acid function at C-3 and a hydroxy group at C-2. The approach, however, is dependent upon a method for the conversion of the hydroxy ethyl side chain into the novel angular vinyl substituent (e.g., **17** → **21**).

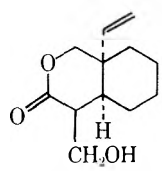


Cleavage of enol acetate **12** obtained from the hydroxymethyl decalone **16**[12] with 1 equiv of ozone followed by reductive work-up with sodium borohydride–sodium hydroxide results in >95% yield of the hydroxy carboxylic acid **13**. Attempts to eliminate alcohol **17** with formation of vinyl compound **21** via elimination of the corresponding primary alkyl phenyl selenoxide[13] resulted in a disappointingly low yield of olefin. However, attempts at converting **17** to **21** via elimination of the o-nitrophenyl selenoxide derivative **20** proved successful.[14] In a study on the elimination of a series of para- and ortho-substituted aryl alkyl selenoxides, Sharpless[15] observed that electron-withdrawing groups increased both the rate of the selenoxide elimination and the final yield of olefin.

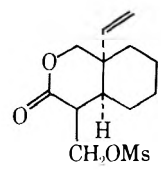
Mesylation of alcohol **17** afforded mesylate **18**, which upon treatment with o-nitrophenylselenium anion (generated from di-o-nitrophenyl diselenide[16] and sodium borohydride in absolute ethanol) yielded selenide **19**. Elimination of selenoxide **20** prepared by addition of 50% hydrogen peroxide to selenide **19** in tetrahydrofuran resulted in a 92% yield of vinyl compound **21**. Cleavage of the methyl ether was executed with boron tribromide in methylene chloride at low temperature with simultaneous ring closure to the crystalline bicyclic δ-valerolactone **3**, mp 44–45°, identical in all respects with the sample prepared above.

What remained was a method for the introduction of the desired α-methylene unit (e.g., **3** → **2**). Despite considerable effort at the time we initiated our synthetic studies, the methods which had been developed for construction of the α-methylene function were unsatisfactory or not applicable to six-membered ring lactones.[17] Thus, we decided to develop a method which would prove useful for the construction of both α-methylene-γ- and -δ-lactone structural units.

We observed that both five- and six-membered ring lactones when treated with strong bases (e.g., lithium diisopropylamide) can be converted into their corresponding enolate anions and efficiently trapped with formaldehyde thus providing a ready route to α-hydroxymethyl-γ- and -δ-lactones.[18] Introduction of the α-methylene unit found in **2** was achieved via direct α-hydroxymethylation of lactone **3**. The crude α-hydroxymethylated lactone **22** was converted into its corresponding mesylate (**23**) and thence (refluxing pyridine) to the bicyclic lactone **2** in 50% overall yield from **3**. Heathcock has reported a synthesis of **2** employing the two-step α-hydroxymethylation procedure.[5]



22



23

Experimental Section

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting and boiling points are uncorrected. The following spectrometers were used: nuclear magnetic resonance (NMR), Varian T-60 and A-60D (in δ units, with Me_4Si as the internal reference in CCl_4 unless stated otherwise); infrared (ir), Perkin-Elmer Model 247; mass spectrometer (MS), LKB-9000 and Varian MAT CH5-DF. All reactions were performed under an atmosphere of nitrogen.

10-*tert*-Butoxymethyl-$\Delta^{1,9}$-2-octalone (5). Isobutylene (ca. 6 ml) was added to a solution of 10-hydroxymethyl-$\Delta^{1,9}$-2-octalone[10] (200 mg, 1.1 mmol) in methylene chloride (20 ml) containing concentrated sulfuric acid (0.1 ml) cooled to 0°. After stirring at 0° for 2 hr, the temperature was raised to 25° and maintained at that temperature for 16 hr. The reaction mixture was treated with saturated sodium bicarbonate solution, washed with brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gave a brown oil (236 mg) which was chromatographed on alumina. Elution with benzene afforded 206 mg (79%) of pure **5**: ir (film) 6.05, 6.19 μ; nmr (CCl_4) δ 1.20 (s, 9 H), 3.40 (s, 2 H), 5.64 (s, 1 H). Distillation [125° (bath temperature) (0.05 mmHg)] gave an analytical sample.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.33; H, 10.20.

9-*tert*-Butoxymethyl-*trans*-decalin-3-one (6). A solution of 5 (200 mg, 0.85 mmol) in dry tetrahydrofuran (8 ml) containing *tert*-butyl alcohol (63 mg, 0.85 mmol) was added to a solution of lithium metal (30 mg, 4.2 mmol) in liquid ammonia (80 ml). After refluxing for 40 min, the excess lithium was decomposed by very slow dropwise addition of methyl iodide just until the blue color disappeared. After evaporation of the liquid ammonia, water (10 ml) was added to the pasty residue. The product was extracted with ether. The combined ethereal extracts were washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give an oil (206 mg). Purification by column chromatography on alumina (elution with benzene) gave 150 mg (75%) of pure **6**: ir (film) 5.85 μ; NMR (CCl_4) δ 1.2 (s, 9 H), 3.52 (s, 2 H), no olefinic hydrogens. The semicarbazone derivative (colorless needles, mp 204–205°, recrystallized from ethanol) was prepared for the analytical sample.

Anal. Calcd for $C_{16}H_{29}O_2N_3$: C, 65.08; H, 9.83; N, 14.24. Found: C, 64.94; H, 9.84; N, 14.08.

2-Methylsulfenyl-9-*tert*-butoxymethyl-*trans*-decalin-3-one (7). To a suspension of sodium hydride (4.0 g, 57% dispersion in mineral oil) in 60 ml of absolute benzene was added a mixture of decalone 6 (3.30 g, 13.9 mmol), ethyl formate (11.6 ml), and absolute methanol (5.6 ml) in 20 ml of benzene. The reaction mixture was stirred at room temperature for 48 hr. The reaction was quenched by the addition of ice water. The aqueous layer was separated, acidified with 10% hydrochloric acid, and extracted with ether. The combined ethereal extracts were washed with brine, dried over $MgSO_4$, and evaporated in vacuo. There was obtained 2.90 g (80%) of formyl ketone.

A solution of methyl thiotosylate[11] (1.89 g, 9.4 mmol) in absolute ethanol (10 ml) was added to a mixture of the above formyl ketone (2.40 g, 9.0 mmol) and potassium acetate (2.75 g) in absolute ethanol (110 ml). The mixture was refluxed for 38 hr. After evaporation of the solvent, the product was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and evaporated to give a dark brown oil which was purified by column chromatography (silic gel–benzene) to give analytically pure 7 (1.35 g, 53%): mp 62°; ir ($CHCl_3$) 5.85 μ; NMR (CCl_4) δ 1.18 (s, 9 H), 2.00 (s, 3 H), 3.43 (q, 1 H). An analytical sample was prepared by recrystallization from petroleum ether (colorless prisms, mp 62–63°).

Anal. Calcd for $C_{16}H_{28}O_2S$: C, 67.61; H, 9.86. Found: C, 67.87; H, 9.97.

Fragmentation of Oxime 8. A mixture of ketone 7 (960 mg, 3.38 mmol), hydroxylamine hydrochloride (750 mg), and sodium hydroxide (500 mg) in 95% aqueous ethanol (40 ml) was refluxed for 2 hr. After evaporation of the solvent, the product was extracted with ether. The ethereal extracts were washed with brine, dried over $MgSO_4$, and evaporated to give 1.01 g (quantitative) of oxime 8.

Methanesulfonyl chloride (1.16 g, 10.1 mmol, freshly distilled) was added to a solution of crude oxime 8 (1.01 g, 3.37 mmol) in dry pyridine (15 ml). The mixture was refluxed for 1.5 hr. The product was extracted with ether. The combined ether layers were washed with 10% hydrochloric acid, saturated sodium bicarbonate, and brine. After drying ($MgSO_4$) and removal of the solvent in vacuo there was obtained 1.04 g of crude material which was chromatographed on silica gel. Elution with benzene gave 430 mg (45%) of pure nitrile **9**: ir (film) 4.48, 6.17, 10.68 μ (trans-substituted enol thioether); NMR (CCl_4) δ 1.20 (s, 9 H), 2.20 (s, 3 H), 3.30 (AB q, 2 H), 5.62 (AB q, J = 16 Hz, 2 H). An analytical sample was prepared by distillation [140° (bath temperature) (0.1 mmHg)].

Anal. Calcd for $C_{16}H_{27}NOS$: C, 68.27; H, 9.67; N, 4.98. Found: C, 68.43; H, 9.76; N, 5.25.

2-Vinyl-*cis*-2-*tert*-butoxymethylcyclohexylacetonitrile (10). A suspension of nitrile **9** (130 mg) and W-2 Raney nickel (2 ml, deactivated by refluxing in acetone for 3 hr) in ethanol (20 ml) was refluxed for 4 hr. Filtration of the Raney nickel afforded a filtrate which gave upon removal of the solvent 110 mg of crude **10** as a pale yellow oil. Column chromatography on silica gel (benzene) yielded 100 mg (90%) of pure **10**. An analytical sample was prepared by distillation [100–105° (bath temperature) (0.1 mmHg)]: ir (film) 3.24, 4.48, 6.12, 10.95 μ; NMR (CCl_4) δ 1.20 (s, 9 H), 3.30 (AB q, 2 H), 4.80–5.95 (m, $CH{=}CH_2$, 3 H).

Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 6.38. Found: C, 76.60; H, 10.65; N, 6.17.

9-Vinyl-2-oxa-*cis*-3-decalone (3). A mixture of **10** (1.00 g) and potassium hydroxide (12.0 g) in diethylene glycol (11 ml) and water (9 ml) was refluxed for 10 hr. After cooling, water (40 ml) was added and the mixture was washed with ether. The aqueous layer was acidified with concentrated hydrochloric acid. The product was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over magnesium sulfate, and evaporated in vacuo to give 920 mg (85%) of acid **11**, ir (film) 2.74–4.10, 5.86 μ.

A solution of acid **11** (513 mg) in benzene (150 ml) was refluxed in the presence of *p*-toluenesulfonic acid (100 mg) with azeotropic removal of water (Dean-Stark apparatus) for 19 hr. The reaction mixture was washed with saturated sodium bicarbonate solution and brine. After drying ($MgSO_4$) and removal of the solvent under reduced pressure there was obtained 345 mg (95%) of lactone **3** (colorless prisms, mp 44–45°): ir ($CHCl_3$) 5.79, 6.12, 10.90 μ; NMR (CCl_4) δ 5.16–5.68 (m, $CH{=}CH_2$, 3 H), 4.14 (AB q, OCH_2–, 2 H). An analytical sample was prepared by recrystallization from petroleum ether, mp 44–45°.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.30; H, 9.01.

α-Methylene-δ-valerolactone (2). *n*-Butyllithium (0.51 ml of a 1.60 *M* solution in hexane) was added to a solution of diisopropylamine (83 mg, 0.82 mmol) in dry THF (5 ml) cooled to −78°. After 30 min, a solution of lactone **3** (122 mg, 0.68 mmol) in dry THF (2 ml) was added dropwise over a period of 15 min. The reaction mixture was allowed to stir for 30 min at −78°. Then the temperature was raised to −25° and formaldehyde [generated by heating paraformaldehyde (0.4 g) at 150°] was passed into the reaction vessel with the aid of a stream of nitrogen. After complete depolymerization the reaction mixture was stirred for an additional 30 min at −25°. The reaction was quenched by the addition of 10% hydrochloric acid. The product was extracted with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and condensed to give 144 mg of crude **22**. This crude product was used directly in the next reaction.

A solution of **22** (144 mg) and methanesulfonyl chloride (156 mg) in pyridine (4.5 ml) was allowed to stir at room temperature for 20 hr. The product was extracted with ethyl acetate. The ethyl acetate layers were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave 200 mg of crude mesylate **23** as a yellow oil. This material was used immediately in the next reaction.

A solution of mesylate **23** (200 mg) in pyridine (3.6 ml) was refluxed for 5 hr. The product was extracted with ether. The combined ethereal extracts were washed with water, dried over $MgSO_4$, and condensed in vacuo to give 100 mg of an oil. Chromatography on silica gel (hexane–ether, 1:1) gave pure α-methylene lactone **2** (60 mg, 46%): ir ($CHCl_3$) 5.84, 6.10, 6.17 μ; NMR (CCl_4) δ 6.34 (s, 1 H), 5.44 (s, 1 H), 5.00–5.80 (m, $CH{=}CH_2$, 3 H), 4.12 (AB

2, 2 H). An analytical sample was prepared by distillation [100° (bath) (0.2 mmHg)].

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.69; H, 8.40

Methyl 2-Methoxymethyl-*trans*-2-β-hydroxyethylcyclohexylacetate (17). A solution of enol acetate **12** [1.5 g, 6.3 mmol (prepared from **16**,[12] isopropenyl acetate, $TsOH \cdot H_2O$, reflux, 24 hr)[19]] in 30 ml of methylene chloride cooled to −78° was treated with ca. 1 equiv of ozone. After ozone addition was complete, 30 ml of methanol was added at −78° to the reaction mixture followed by sodium borohydride (269 mg). An equal amount of sodium borohydride was added every 15 min for approximately 1 hr (−78°). After all the sodium borohydride was added, the reaction was warmed to room temperature and was treated with 11.4 ml of 1.0 *N* aqueous sodium hydroxide. After ca. 30 min, the solvents were evaporated under reduced pressure and the residue was taken up in a minimum amount of water and washed with ether (15 ml). The aqueous layer was cooled (5°), treated with 5% hydrochloric acid until acidic, and extracted with chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated in vacuo, affording 1.4 g (97%) of acid **13**: ir (film) 5.86 μ; NMR ($CDCl_3$) δ 3.35 (s, 3 H, OMe), 3.68 (t, 2 H, CH_2OH); MS *m/e* 230.

The above carboxylic acid (628 mg) in ether was treated with diazomethane, affording 609 mg of crude ester **17**. Chromatography on silica gel (30 g) (elution with hexane–ethyl acetate, 1:1) gave 550 mg (83%) of pure methyl ester **17**: ir ($CHCl_3$) 2.95, 2.80 μ; NMR (CCl_4) δ 3.59 (s, 3 H, COOMe), 3.30 (s, 3 H, OMe); MS *m/e* 244. An analytical sample was prepared by distillation [130° (bath temperature) (0.15 mmHg)].

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.73; H, 9.87.

Methyl 2-Methoxymethyl-*trans*-2-β-mesyloxyethylcyclohexylacetate (18). Methanesulfonyl chloride (56 μl, 0.74 mmol) (freshly distilled) was added to a solution of ester alcohol **17** (130 mg, 0.52 mmol) in 1.5 ml of anhydrous pyridine cooled to 0°. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was taken up in ether and washed with cold 5% hydrochloric acid and brine. The ether layer was dried (anhydrous magnesium sulfate) and the solvent was removed under reduced pressure, providing 154 mg (96%) of crude mesylate **18**: ir (film) 5.80 7.41, 8.55 μ; NMR (CCl_4) δ 4.22 (t, J = 7 Hz, 2 H, CH_2OMs), 3.59 (s, 3 H, COOMe), 3.25 (s, 3 H, OMe), 2.90 (s, 3 H, $-SO_2Me$).

Methyl 2-Methoxymethyl-*trans*-2-vinylcyclohexylacetate (21). To a suspension of di-o-nitrophenyl diselenide (64 mg, 0.16 mmol) in absolute ethanol (0.5 ml) at room temperature was added sodium borohydride (12 mg, 0.32 mmol). After approximately 30 min, the reaction mixture became homogeneous (deep red color). To the selenium anion cooled to 0° was added the crude mesylate **18** (100 mg, 0.30 mmol) in 0.5 ml of absolute ethanol. After addition was complete, the reaction mixture was stirred for 14 hr at room temperature. The reaction mixture was taken up in ether, washed with water, and dried over $MgSO_4$. Removal of the solvent in vacuo afforded the crude selenide, which was purified by preparative thin layer chromatography (silica gel plates). Elution with hexanes–ether (2:1) gave 74 mg (64%) of pure selenide **19**: ir (film) 5.80, 6.62, 7.51 μ; NMR (CCl_4) δ 8.18 (d, 1 H), 7.38 (m, 3 H), 3.58 (s, 3 H), 3.30 (br s, 5 H, CH_2OCH_3), 2.81 (t, 2 H, CH_2Se).

A solution of *o*-nitrophenyl selenide **19** (74 mg, 0.17 mmol) in anhydrous tetrahydrofuran (1.0 ml) cooled to 0° was treated with 50% hydrogen peroxide (47 μl). After addition was complete, the temperature was raised to 25° and maintained at that temperature for 12 hr. The reaction mixture was taken up in ether followed by washing of the organic layer with water and brine. The organic layer was dried (anhydrous magnesium sulfate) and the solvent was removed under reduced pressure, leaving 42 mg of crude olefin **21**. Purification by column chromatography (elution with hexanes–ether, 4:1) gave 36 mg (92%) of pure **21**: ir ($CHCl_3$) 5.79, 6.13, 10.00, 10.90 μ; NMR (CCl_4) δ 4.8–6.0 (typical vinyl pattern, 3 H), 3.58 (s, 3 H, COOMe), 3.25 (br s, 5 H, CH_2OCH_3); MS *m/e* 226.

Anal. Calcd for $C_{13}H_{22}O_3$: 226.1569. Found: 226.1561.

9-Vinyl-2-oxa-*cis*-decalin-3-one (3). The methoxymethyl ester **21** (30 mg, 0.13 mmol) in dry methylene chloride (1.0 ml) cooled to −78° was treated with boron tribromide (93 μl, 0.79 mmol). After addition was complete, the temperature was raised to −20° and kept at that temperature for 30 min, followed by warming to 0°. Stirring was continued for 1 hr at 0°. The reaction was quenched by the addition of 2.0 ml of ether at 0° followed by the addition of aqueous sodium bicarbonate solution. When carbon dioxide evolution ceased, the product was extracted with ether. The combined ether extracts were washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gave 30 mg of crude material which was purified by passage through a column of silica gel (2.0 g). Elution with hexanes–ether (2:1) gave 21 mg (88%) of crystalline **3**, mp 44–45°, identical in all respects (melting point, mixture melting point, TLC, ir, NMR, MS) with a sample previously prepared in our laboratory.[4]

Acknowledgment. This investigation was supported by Public Health Service Research Grant RO1 CA 13689-03 from the National Cancer Institute and in part by Eli Lilly and Co. and the Research Corporation. We thank Professor K. B. Sharpless for informing us of unpublished results prior to publication.

Registry No.—**2**, 42391-68-4; **3**, 42391-78-6; **4**, 18992-92-2; **5**, 42391-70-8; **6**, 42391-71-9; **6** semicarbazone, 42391-72-0; **7**, 42391-73-1; **8**, 42391-74-2; **9**, 42391-75-3; **10**, 42391-76-4; **11**, 42391-77-5; **12**, 54549-34-7; **13**, 54549-35-8; **17**, 54549-36-9; **18**, 54667-58-2; **19**, 54549-37-0; **21**, 54549-38-1; isobutylene, 115-11-7; *tert*-butyl alcohol, 75-65-0; methyl thiotosylate, 4973-66-4; methanesulfonyl chloride, 124-63-0.

References and Notes

(1) Fellow of the Alfred P. Sloan Foundation, 1974–1976.
(2) Research Fellow of the Universidad Nacional Autonoma de Mexico, 1974–1975.
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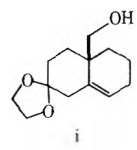

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Cyclic Ether Formation in Oxidations of Primary Alcohols by Cerium(IV). Reactions of 5-Phenyl-1-pentanol, 4-Phenyl-1-butanol, and 3-Phenyl-1-propanol with Ceric Ammonium Nitrate

Michael P. Doyle,*[1a] Laura J. Zuidema,[1b] and Thomas R. Bade

Department of Chemistry, Hope College, Holland, Michigan 49423

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Ceric ammonium nitrate in 70% aqueous acetonitrile oxidizes 5-phenyl-1-pentanol and 4-phenyl-1-butanol to 2-benzyl- and 2-phenyltetrahydrofuran, respectively. Competing processes include benzylic oxidation leading to ketone formation and to oxidative cleavage products. The effects on tetrahydrofuran formation by changing the cerium concentration and by varying the solvent are given. Oxidation of 3-phenyl-1-propanol yields chromanone as the only major reaction product when 2 equiv of ceric ammonium nitrate is employed. Chromanone is oxidized to chromone when >2 equiv of the oxidant is used. The mechanistic implications of these results are discussed.

Cerium(IV) oxidations of primary alcohols, unlike those of benzylic,[2] cyclopropylcarbinyl,[3] or certain secondary alcohols,[4] yield tetrahydrofuran derivatives. Tetrahydrofuran formation represents but one of the three modes of reaction identified with cerium(IV) oxidations of alcohols, the others being oxidative cleavage resulting in substrate fragmentation and α-carbon–hydrogen cleavage yielding aldehydes or ketones.[5]

Trahanovsky, Young, and Nave have studied the oxidation of 1-pentanol by ceric ammonium nitrate (CAN) and found 2-methyltetrahydrofuran as the only isolable reaction product.[6] Although the similarity of this reaction to that of the corresponding lead tetraacetate oxidation[7] has been pointed out, the synthetic utility and mechanistic course of cerium(IV) oxidations of primary alcohols have not been further documented.

Phenyl-substituted alkanols have been used previously to determine the effect of the phenyl group on the course of lead tetraacetate oxidations.[8] The phenyl label is useful for identifying the hydrogen transfer step and for determining its specificity in reactions of alcohols with one-electron oxidants.

Results

5-Phenyl-1-pentanol. Oxidation of 5-phenyl-1-pentanol (10 mmol) by ceric ammonium nitrate (20 mmol) in 25 ml of 70% aqueous acetonitrile at 75° afforded 2-benzyltetrahydrofuran (1) and benzoic acid as the only major identifiable reaction products (eq 1). Two other products, tentatively identified as benzaldehyde and 5-phenyl-1-pentyl nitrate, were observed by GLC analysis but in combined amounts of less than 8%; unreacted alcohol, by far the major constituent of the reaction mixture (77%), was also identified. The yield of **1**, based on reacted 5-phenyl-1-pentanol, was 40%; benzoic acid was formed in less than 10% yield.

$$C_6H_5CH_2CH_2CH_2CH_2CH_2OH \xrightarrow[70\%\ aq\ CH_3CN]{CAN} \underset{\mathbf{1}}{\text{2-benzyltetrahydrofuran}} + C_6H_5COOH \quad (1)$$

4-Phenyl-1-butanol. The ceric ammonium nitrate oxidation of 4-phenyl-1-butanol in 70% aqueous acetonitrile gave a complex mixture of products consisting of 2-phenyltetrahydrofuran (**2**), 3-benzoyl-1-propanol, benzoic acid, and 4-phenyl-1-butyl nitrate (eq 2). No aldehyde product

$$C_6H_5CH_2CH_2CH_2CH_2OH \xrightarrow[70\%\ aq\ CH_3CN]{CAN} \underset{\mathbf{2}}{\text{2-phenyltetrahydrofuran}} + C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2OH + C_6H_5COOH + C_6H_5CH_2CH_2CH_2CH_2ONO_2 \quad (2)$$

was detected. The variation in the yields of 2-phenyltetrahydrofuran and of recovered 4-phenyl-1-butanol and 4-phenyl-1-butyl nitrate with increasing cerium(IV) concentration and with modifications in the oxidation procedure is given in Table I. As can be seen from this data, the optimum yield of the tetrahydrofuran (58%) occurs when 4-

Table I
Product Yields from the Cerium(IV) Oxidation of 4-Phenyl-1-butanol[a]

[Ce(IV)],[b] *M*	[ROH], *M*	Solvent	2-PhTHF, %[c]	2-PhBuONO$_2$, %[c]	Recovered 4-PhBuOH, %[c]	Yield of 2-PhTHF based on oxidized ROH[d]
0.10	0.10	70% CH_3CN–H_2O	11	8	68	46
0.20	0.10	70% CH_3CN–H_2O	23	8	52	58
0.20[e]	0.10	70% CH_3CN–H_2O	0		90	0
0.20	0.10	70% HOAc–H_2O	6	13	38[f]	12
0.20	0.10	70% CH_3CN–H_2O–HNO_3[g]	13	8	52	33
0.40	0.10	70% CH_3CN–H_2O	22	9	20	31
0.60	0.10	70% CH_3CN–H_2O	24	12	7	30
0.80	0.10	70% CH_3CN–H_2O	24	Trace	19	30
1.60	0.10	70% CH_3CN–H_2O	3	Trace	10	3

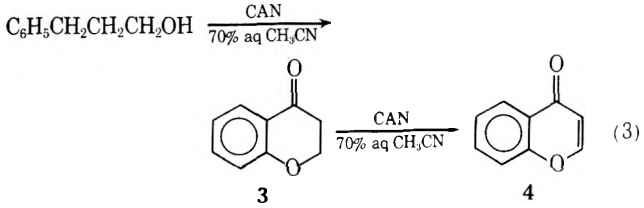
[a] The cerium(IV) salt was added to a flask containing the alcohol, usually in 25 ml of the aqueous solvent. The homogeneous mixture was heated on a steam bath for 0.5–1.0 hr or until the orange-red color of cerium(IV) had disappeared. [b] Ceric ammonium nitrate was used, unless specified otherwise. [c] Absolute yield determined by GLC analysis with reference to an internal standard. From duplicate runs the precision in the yields of 4-PhBuOH + 4-PhBuONO$_2$ was determined to be within ±2%. [d] (% 2-PhTHF/100 − [% 4-PhBuOH + % 4-PhBuONO$_2$]) × 100. [e] Ceric ammonium sulfate was used. [f] Combined yield of alcohol and acetate. [g] [HNO_3] = 0.90 *M*.

phenyl-1-butanol is oxidized with 2 equiv of CAN; increasing the cerium concentration results in a decrease in the yield of **2** and in recovered alcohol. In 70% aqueous acetic acid or when the 70% aqueous acetonitrile solvent contained nitric acid, the yield of **2** was substantially decreased relative to that from the corresponding oxidation in 70% aqueous acetonitrile.

Upon addition of ceric ammonium nitrate to alcohol in 70% aqueous acetonitrile the bright red color characteristic of a 1:1 cerium(IV)–alcohol complex[9] was observed. When ceric ammonium sulfate (CAS) was used instead of CAN, however, complex formation between alcohol and cerium(IV) was not detected. Only unreacted alcohol was obtained after attempted oxidations of 4-phenyl-1-butanol by CAS.

To determine whether alkyl nitrates or nitrites are intermediates in the CAN oxidation of alcohols, 1-pentyl nitrate and 4-phenyl-1-butyl nitrite were individually treated with 2 equiv of ceric ammonium nitrate under the same conditions as those used in alcohol oxidations. 1-Phenyl nitrate was recovered unchanged from the reaction mixture. 4-Phenyl-1-butyl nitrite rapidly decolorized the CAN solution; however, only 4-phenyl-1-butanol was produced.

3-Phenyl-1-propanol. Oxidation of 3-phenyl-1-propanol with 2 equiv of CAN in 70% aqueous acetonitrile at steam-bath temperatures yielded 4-chromanone (**3**) as the only identifiable nonacidic reaction product (eq 3). When



(3)

additional ceric ammonium nitrate was used, 4-chromanone was converted to chromone (**4**). The yields of **3**, **4**, and recovered alcohol with increasing cerium(IV) concentration are given in Table II. 2,3-Benzo-5,6-dihydro-γ-pyran (chroman) was not observed as a product from these oxidations (<2% yield).

Table II
Product Yields from the Cerium(IV) Oxidation of 3-Phenyl-1-propanol[a]

[CAN], *M*	[ROH], *M*	[CAN]/[ROH]	4-Chromanone, (3), %[b]	Chromone, (4), %[b]	Recovered 3-PhPrOH, %[b]
0.073	0.073	1.0	7	0	87
0.194	0.097	2.0	14	Trace	81
0.292	0.073	4.0	27	5	63
0.464	0.058	8.0	30	17	37
0.232	0.029	8.0	30	14	25

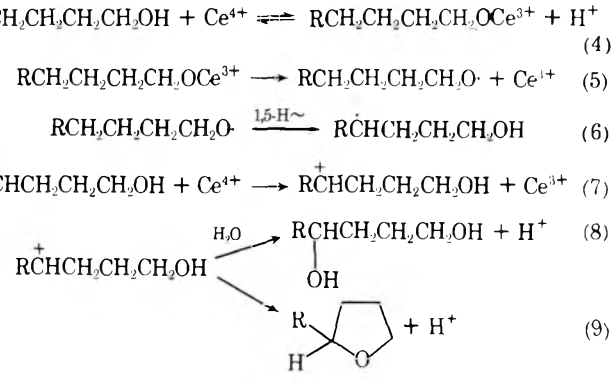
[a] Ceric ammonium nitrate was added to a flask containing the alcohol in 70% aqueous acetonitrile. The aqueous solution was heated on a steam bath until the orange-red color of cerium(IV) had disappeared. [b] Absolute yield determined by GLC and/or ^{1}H NMR analysis. From duplicate runs the precision in product yields was ±2%.

In contrast to the results from oxidations in 70% aqueous acetonitrile, in water only trace amounts of **3** and **4** were produced when 3-phenyl-1-propanol was oxidized by CAN (8 equiv);[10] 3-phenyl-1-propanol was recovered in 35% yield, 2% benzaldehyde was detected, and the major product was benzoic acid (30% yield). In anhydrous acetonitrile a complex mixture of products was produced in which **3** and **4** were only minor components.

Discussion

A mechanism consistent with the results from the oxidation of 5-phenyl-1-pentanol and 4-phenyl-1-butanol by ceric ammonium nitrate is given in Scheme I. Complex for-

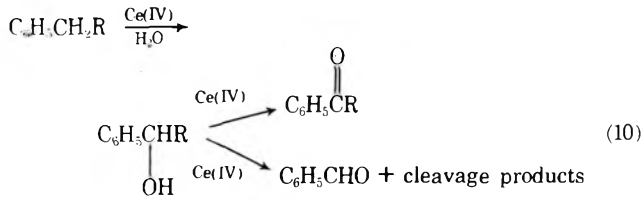
Scheme I



mation between the alcohol and cerium(IV) appears to be a necessary condition for the subsequent production of an alkoxy radical (eq 5) leading to 1,5-hydrogen transfer (eq 6), electron transfer (eq 7), and carbenium ion trapping (eq 8 and 9). Under conditions in which the extent of complex formation is less than that with CAN in 70% aqueous acetonitrile, reaction with CAS, or in 70% aqueous acetic acid,[9] the yield of the tetrahydrofuran product is substantially decreased.

The specificity of the hydrogen transfer step and the lack of α-C–H bond cleavage in tetrahydrofuran formation point to the intermediacy of an alkoxy radical in the CAN oxidations of primary alcohols. 1,5-Hydrogen transfer is observed exclusively in oxidations of 5-phenyl-1-pentanol by CAN and by lead tetraacetate,[8] even though 1,6-hydrogen transfer would yield the more stable benzylic radical; a similar specificity is observed in intramolecular hydrogen transfer reactions to alkoxy radicals generated from nitrite esters and hypochlorites.[11] The influence of cerium on the hydrogen-transfer step, if any, could not be distinguished in this study.

The carbenium ion produced by electron transfer to cerium(IV) from the carbon radical (eq 7) can conceivably undergo intramolecular trapping to give the observed tetrahydrofuran (eq 9) or intermolecular trapping yielding a diol (eq 8). The diol produced by intermolecular trapping would be expected to be rapidly oxidized to the corresponding hydroxy ketone and oxidative cleavage products;[2c] both processes have been observed in this study. However, an alternate pathway to hydroxy ketone and oxidative cleavage products involving oxidation at the benzylic position (eq 10), similar to that observed in toluene oxidations,[12] cannot

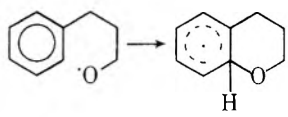


(10)

be excluded. 2-Phenyltetrahydrofuran may also be considered to be a source of hydroxy ketone and oxidative cleavage products either through direct oxidation of the furan or through hydrolysis followed by oxidation. However, since the yield of **2** remained constant when the ratio of CAN to alcohol was varied from 4.0 to 8.0, this pathway does not

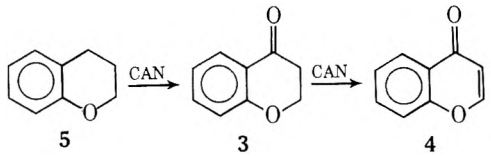
appear to be dominant. With a ratio of 16 for [CAN]/[ROH] the low recovered yield of 2 suggests that this compound is subject to further oxidation.

In the oxidation of 3-phenyl-1-propanol by CAN, 1,5-hydrogen transfer is not possible. However, intramolecular alkoxy radical addition to the aromatic nucleus (eq 11)



(11)

does occur. Unlike the corresponding oxidation by lead tetraacetate,[8] chroman is not detected; only chromanone is observed. To determine if chromanone is produced directly from chroman in a rapid oxidation reaction at the benzylic position, chroman (5), prepared and isolated from the lead tetraacetate oxidation of 3-phenyl-1-propanol,[8a,13] was oxidized in the presence of a 2 molar excess of 3-phenyl-1-propanol with CAN. A 4 molar equiv excess of CAN to the combined alcohol–chroman was used, and reaction conditions duplicated those of Table II. Under these conditions, which closely relate to those under which 3-phenyl-1-propanol was oxidized by CAN to chromanone, complete conversion of chroman to chromanone and chromone (76 and 16%, respectively, based on chroman) was observed (eq 12).



(12)

The reactant alcohol was recovered in 85% yield after oxidation was complete. From these qualitative results chroman is estimated to be at least ten times more reactive than 3-phenyl-1-propanol toward oxidation by CAN.

The oxidation of chromanone (3) to chromone (4) represents an oxidation process not previously reported for reactions with CAN[5a] but known for two-electron oxidants.[14] The stability of the heteroaromatic ring system of 4 is certainly a major factor in this transformation. Dehydrogenation reactions in other systems yielding stable heteroaromatic compounds may also be feasible using ceric ammonium nitrate oxidation.

Experimental Section

General. Instrumentation has been previously described.[15] For GLC analyses use was made of 5-ft columns of 20% Carbowax 20M on Chromosorb P. 5-Phenyl-1-pentanol and 4-phenyl-1-butanol were prepared by lithium aluminum hydride reductions of the corresponding carboxylic acids; 3-phenyl-1-propanol was commercially available. 4-Phenyl-1-butyl nitrite was produced from the reaction between the corresponding alcohol and nitrosyl chloride:[16] bp 50–52° (0.3 Torr); ^{1}H NMR (CCl_4) δ 7.1–7.4 (m, 5 H), 4.68 (distorted t, 2 H), 2.66 (distorted t, 2 H), and 1.9–1.5 (m, 4 H); ir (film) 1652 and 1612 cm^{-1} (–ONO). G. F. Smith analyzed reagent-grade ceric ammonium nitrate and reagent-grade ceric ammonium sulfate were used.

General Oxidation Procedure. To a stirred solution of the alcohol (2.5 mmol) in 20 ml of 70% aqueous acetonitrile, contained in a round-bottom flask equipped with a reflux condenser, was added a weighed amount of ceric ammonium nitrate. An additional 5 ml of 70% aqueous acetonitrile was used to wash the cerium salt into the flask. The dark-red homogeneous solution was heated on a steam bath until a color change to colorless could no longer be observed. The resulting solution was cooled and 10 ml of water was added followed by 10 ml of ether. After thorough mixing the ether layer was separated from the aqueous layer, and the aqueous layer was washed twice with 15-ml portions of ether. The combined ether solution was washed with 25 ml of a saturated sodium bicarbonate solution and with 25 ml of water. The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure.

Oxidation of 5-Phenyl-1-pentanol. Product Analyses. GLC analysis of the nonacidic products from the CAN oxidation of 5-phenyl-1-pentanol showed three compounds in addition to the starting alcohol. The major product was collected and identified as 2-benzyltetrahydrofuran by ir and ^{1}H NMR spectral analysis through comparison with an authentic sample. Benzaldehyde and 5-phenyl-1-pentyl nitrate were identified from the ^{1}H NMR spectrum of the reaction mixture. Benzoic acid was isolated after acidification of the bicarbonate wash solution.

Oxidation of 4-Phenyl-1-butanol. Product Analyses. Products from the CAN oxidation of 4-phenyl-1-butanol were separated by GLC methods or in the extraction procedure and identified by spectral analysis of the individual compounds through comparison with authentic samples. Absolute yields of 2-phenyltetrahydrofuran, 4-phenyl-1-butyl nitrate, and 4-phenyl-1-butanol were determined by GLC analysis using an internal standard, 2-phenylethanol. The areas of the product peaks were compared with the area of the standard peak, and the absolute yields of products were determined with the use of experimentally measured thermal conductivity ratios (0.96 for 4-phenyl-1-butanol and 1.31 for 2-phenyltetrahydrofuran). 4-Phenyl-1-butyl nitrate was assumed to have the same thermal conductivity ratio as 4-phenyl-1-butanol.

Oxidation of 3-Phenyl-1-propanol. Product Analyses. Only one major reaction product (>3% yield) was observed by GLC analysis and ^{1}H NMR spectroscopy of the reaction mixture from the oxidation of 3-phenyl-1-propanol with 2 equiv of CAN. This product was collected and identified as 4-chromanone by ^{1}H NMR and ir spectroscopy. When greater than 2 equiv of CAN was used a second product, chromone, was similarly isolated and identified. Product yields were determined by ^{1}H NMR analyses of the reaction mixtures. Chromanone (3): ^{1}H NMR (CCl_4) δ 8.0–7.8 (m, 1 H), 7.65–6.85 (m, 3 H), 4.55 (t, 2 H, J = 6.5 Hz), and 2.73 (t, 2 H, J = 6.5 Hz); ir (film), 1685 cm^{-1} (C=O). Chromone (4): ^{1}H NMR (CCl_4) δ 8.35–8.10 (m, 1 H), 7.75–7.10 (m, 3 H), 7.83 (d, 1 H, J = 6 Hz), and 6.27 (d, 1 H, J = 6 Hz); ir (CCl_4) 1665 cm^{-1} (C=O).

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Registry No.—**3**, 491-37-2; **4**, 491-38-3; CAN, 16593-75-2; CAS, 19495-85-3; 5-phenyl-1-pentanol, 10521-91-2; 4-phenyl-1-butanol, 3360-41-6; 3-phenyl-1-propanol, 122-97-4; 4-phenyl-1-butyl nitrite, 17337-03-0; nitrosyl chloride, 2696-92-6.

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Configuration Determination of (*R*)-(+)-1,1,2-Triphenylpropane. Configuration Inversion of (*R*)-(+)-α-Phenylethyltrimethylammonium Iodide by Benzhydryllithium

Isaac Angres and Herman E. Zieger*

Department of Chemistry, Brooklyn College of the City University of New York, Brooklyn, New York 11210

Received December 2, 1974

The absolute configuration of (*R*)-(+)-1,1,2-triphenylpropane (**2**) has been determined by its synthesis from (*S*)-(+)-hydratropic acid (**1a**). The reaction of benzhydryllithium with (*R*)-(+)-α-phenylethyltrimethylammonium iodide occurs 100% stereospecifically with inversion of configuration forming **2**. High yields (>90%) of polyphenylethanes are secured in reactions of benzylic organolithiums with benzylic quaternary ammonium iodide salts.

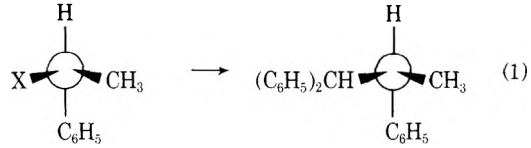
We were interested in the stereochemistry of the coupling reactions of benzhydryllithium with α-phenylethyltrimethylammonium iodide salts to form 1,1,2-triphenylpropane derivatives. This reaction is related to the work of Sommer and Korte[1] and Sauer and Braig,[2] who have shown that charge-delocalized carbanions in organolithium reagents couple stereospecifically with chiral secondary halides with inversion of configuration. In the reaction of benzhydryllithium with 47% optically pure (−)-α-phenylethyl chloride to give (+)-1,1,2-triphenylpropane, a value of 100% for the stereospecificity of the inversion process was estimated, but caution was recommended since optically pure hydrocarbon of known configuration was unavailable.[1]

Now we are able to assign the absolute configuration of (+)-1,1,2-triphenylpropane as the *R* stereoisomer based on its synthesis from (*S*)-(+)-2-phenylpropanoic acid [(*S*)-(+)-hydratropic acid, **1a**]. We also can report that benzhydryllithium reacted with (*R*)-(+)-α-phenylethyltrimethylammonium iodide stereospecifically with >98.2% inversion of configuration to give (*R*)-(+)-1,1,2-triphenylethane (**2**). In addition we have secured uniformly high yields of ethane coupling products from reactions of charge-delocalized organolithium compounds with benzylic trimethylammonium quaternary salts (see Table I) in harmony with the stereochemical results reported earlier for reactions of secondary halides with allylic[2] or benzylic[1] organolithium reagents.

Results

(*S*)-(+)-Hydratropic acid, 98.2% optically pure **1a**, was converted with diazomethane into methyl (*S*)-(+)-hydratropate, 95% **1b**. Ester **1b** reacted with 2 mol of phenylmagnesium bromide to give 46.4% of (*S*)-(−)-1,1,2-triphenyl-1-propanol (**1c**). Alcohol **1c** was reduced with sodium in liquid ammonia to give 50% of (*R*)-(+)-1,1,2-triphenylpropane (**2**). See Scheme I.

Scheme I

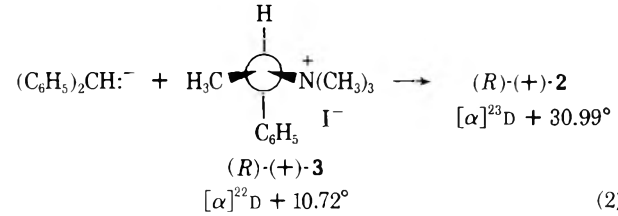


(1)

(*S*)-**1**
a, X = COOH
b, X = $COOCH_3$
c, X = $COH(C_6H_5)_2$

(*R*)-**2**
$[\alpha]^{22}D$ + 30.15°

When benzhydryllithium was treated with (*R*)-(+)-α-phenylethyltrimethylammonium iodide of 97.5% minimum optical purity, **2** was obtained in 65% yield. See eq 2. Since the sample of **2** obtained by displacement of trimethylamine from **3** has a slightly higher rotation than the authentic sample of Scheme I, its optical purity is higher, indicating that the stereospecificity of reaction 2 is quite high, if not 100%. As the arrangement of groups in (*R*)-(+)-**3** is opposite to that in (*R*)-(+)-**2**, reaction 2 occurs stereospecifically with inversion of configuration.[3]



(2)

The reactions of trityl-, benzhydryl-, and benzyllithium with benzhydryl- (**4**) and benzyltrimethylammonium iodides (**5**) to give polyphenylethane coupling products in greater than 90% yields are summarized in Table I. No evidence for Sommelet–Hauser rearrangement products could be detected, although such products are the predominant ones in reactions of **4** and **5** with alkyllithium reagents.[4]

Discussion

Early work reported failure to convert **1b** into **1c** but described the reaction of (+)-α-chloroethylbenzene, $[\alpha]D$ +19.5°, to (+)-**2**, $[\alpha]D$ +6.67°, with benzhydrylsodium.[5] That the starting material and product were of low optical purity can be seen from the data on the later conversion of (−)-α-chloroethylbenzene (**6**, 47% optically pure, $[\alpha]^{25}D$ −59.3°, neat) into (−)-**2** ($[\alpha]^{24}D$ 21.7°).[1]

The conclusion[1] that benzhydryllithium reacted with (−)-**6** with inversion of configuration is correct, although the percent stereospecificity using the rotation value from this work is 70%. No doubt benzhydryllithium reacts with **6** not only by displacement but also to establish a halogen–metal interconversion[6] equilibrium forming α-lithioethylbenzene, which upon reversion to **6** suffers racemization.

An alternate mechanistic explanation of stereochemistry involving electron transfer to form radicals[8] would conflict with the general view proposed by Sauer and Braig[2] that organolithiums containing allylic or benzylic groups react with halides by SN2 mechanisms while alkyllithiums react with halides to form products intelligible only if radical intermediates were formed.

In the present study, halogen–metal interconversion is not a serious possibility and if the coupling product of eq 2 is forming by an electron-transfer process, then a geminate radical pair in a cage tight enough to prevent racemization is required. That radical intermediates form in reactions of charge-delocalized organolithiums with halides was shown recently[9] by the electron detachment oxidation of triphenylmethyl carbanion by triphenylmethyl halide which undergoes dissociative electron attachment.[10] Quaternary

Table I
Coupling Reactions of Charge-Delocalized Organolithium Reagents with Trimethylammonium Quaternary Salts

RLi reagent	$R'N(CH_3)_3^+ I^-$ reactant		RR' product	Yield,[c] %
$(C_6H_5)_3CLi$[a]	$(C_6H_5)_2CH$	4	$(C_6H_5)_3CCH(C_6H_5)_2$	91
$(C_6H_5)_3CLi$[a]	$C_6H_5CH_2$	5	$(C_6H_5)_3CCH_2C_6H_5$	93
$(C_6H_5)_2CHLi$[a]	$(C_6H_5)_2CH$	4	$(C_6H_5)_2CHCH(C_6H_5)_2$	95
$(C_6H_5)_2CHLi$[a]	$C_6H_5CH_2$	5	$(C_6H_5)_2CHCH_2C_6H_5$	92
$C_6H_5CH_2Li$[b]	$(C_6H_5)_2CH$	4	$(C_6H_5)_2CHCH_2C_6H_5$	91
$C_6H_5CH_2Li$[b]	$C_6H_5CH_2$	5	$C_6H_5CH_2CH_2C_6H_5$	90

[a] Prepared by metalation of the hydrocarbon in tetrahydrofuran with *n*-butyllithium. [b] Prepared by cleavage of benzylmethyl ether with lithium metal. [c] Isolated yields. Gas chromatographic analysis of mother liquors indicated additional amounts of material for all compounds except pentaphenylethane, which cannot be gas chromatographed.

ammonium halide salts are known to oxidize potassium in liquid ammonia[11] or lithium naphthalenide in tetrahydrofuran[12] by electron transfer processes to produce radical species of finite lifetime as judged by trapping products formed through intermolecular processes. If such pathways are being followed during the present coupling reactions, they do not produce radicals of sufficient lifetime to allow diffusion followed by reduction, coupling, or disproportionation reactions. Since the quaternary ammonium salts of Table I are the same as those which formed radical intermediates upon treatment with lithium naphthalenide,[12] the displacement of trimethylamine from salt by a charge-delocalized organolithium occurs by a polar process without chemical evidence for an electron transfer component.[13]

Our results should be contrasted with those obtained during a study of the stereochemistry of free-radical recombination reactions after thermal decomposition of (*S*)-(−)-azobis-α-phenylethane to produce α-phenylethyl radicals.[14] The results showed that the principal products were derived from α coupling to produce meso and nonmeso 2,3-diphenylbutanes. Thus a substantial loss of stereochemistry through randomization or turnover occurs in the loose radical cages which are required for departing nitrogen in such systems.

Experimental Section

All reactions were performed under an argon atmosphere, and solvents were evaporated on a rotary evaporator under vacuum. Melting points were taken on a Fisher-Johns or Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on Varian T-60 and A-60A 60-MHz instruments and except where noted, in $CDCl_3$ solvent. Chemical shift values are reported in parts per million relative to TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer Model 267 spectrophotometer. Organolithium reagents were obtained from Alfa Inorganics and were titrated using the procedure of Eastham.[15]

All compounds were dried thoroughly before use. Optical rotation measurements were determined with a Rudolph polarimeter (Model 70). Elemental analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Preparation of Hydratropic Acid via Hydratroponitrile.[16] Racemic hydratropaldehyde (159 g, 1.17 mol in 480 ml of ethanol) and hydroxylamine hydrochloride (99.0 g, 1.41 mol in 120 ml of H_2O) was treated with 96 ml of 19 *N* aqueous NaOH to give 135 g (76%) of hydratropaldoxime, a colorless oil: bp 110° (3.5 mm) [lit. bp 133° (11 mm)]; ir ν_{max} (neat) 3220 and 1500 (bonded OH) and 1670 cm^{-1} (C=N).

The oxime (135 g, 0.90 mol) was refluxed for 0.5 hr with 200 ml of acetic anhydride following the literature procedure to yield 84 g (71%) of hydratroponitrile: bp 74° (0.5 mm) [lit. bp 106° (12 mm)]; ir ν_{max} (neat) 2245 cm^{-1} (C≡N).

Hydrolysis of the nitrile (84 g, 0.63 mol) with aqueous NaOH, followed by acidification (HCl), ether extraction, and distillation, provided (±)-hydratropic acid: 72 g, 76%, bp 113° (1.0 mm) [lit.[16] bp 147° (11 mm)]; ir ν_{max} (neat) 2960 and 1701 cm^{-1}; NMR ($DCCl_3$) δ 1.4 (3 H, d), 3.1 (1 H, q), 7.35 (5 H, s), 12 (1 H, s).

Resolution of Hydratropic Acid. Hydratropic acid (48 g) and strychnine (88 g) were dissolved in 200 ml of 75% (v/v) aqueous ethanol. After 3 days at 0°, the crystallized strychnine hydratropate was collected and crystallized five additional times to constant mp 176–177° of dried salt.

Treatment of the salt with 6 *N* HCl liberated the free acid which was extracted into ether, dried, and distilled to produce 9.0 g of (*S*)-(+)-hydratropic acid: bp 101–103° (0.4 mm); $[\alpha]^{22}D$ +97.00° (neat, *l* = 1.0 dm) [lit.[17] $[\alpha]^{21}D$ 98.8° (neat, *l* = 1.0 dm)]; optical purity 97.5%; NMR ($DCCl_3$) δ 1.4 (3 H, d), 3.1 (1 H, q), 7.35 (5 H, s), 12 (1 H, s).

Preparation of Methyl (*S*)-(+)-Hydratropate (1b). Aldrich Chemical Co. Diazald (21.5 g, 0.1 mol of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in 130 ml of ether) was added dropwise to KOH (5 g in 8 ml of H_2O, 25 ml of ethanol) at 65° to produce diazomethane (ca. 0.01 mol) as a distillate in ether. Addition of this solution to an ether solution of (+)-hydratropic acid (7.5 g, 0.05 mol) until the yellow color of CH_2N_2 persists and N_2 gas is no longer evolved was followed by distillation of excess reagent, solvent, and methyl ester, bp 60–65° (2 mm), to furnish 7.80 g of methyl (*S*)-(+)-hydratropate (95%): NMR ($DCCl_3$) δ 1.2 (3 H, d), 3.5 (3 H, s), 3.6 (1 H, q), 7.35 (5 H, m); $[\alpha]^{22}D$ +103.50° (neat, *l* = 1 dm).

Preparation of (*S*)-(−)-1,1,2-Triphenyl-1-propanol (1c). Phenylmagnesium bromide was prepared from bromobenzene (23.4 g, 0.149 mol) and singly sublimed Dow Chemical Co. Mg (3.2 g, 0.13 mol) in 50 ml of THF at the boiling point of the solvent. To this Grignard solution was added dropwise methyl (*S*)-(+)-hydratropate (5.0 g, 0.03 mol). The reaction mixture was refluxed for 2 hr, decomposed with 100 ml of ammonium chloride, and extracted with ether. After drying of the ether solution and evaporation of the solvent, the oil was distilled to afford 4.0 g of (*S*)-(−)-1,1,2-triphenyl-1-propanol: bp 180–182° (3.0 mm); NMR ($DCCl_3$) δ 1.4 (3 H, d), 2.4 (1 H, s), 4.0 (1 H, q), 7.3 (15 H, m); $[\alpha]^{22}D$ −142° (CH_3OH, *c* 1.717 g/25 ml, *l* = 2 dm).

Anal. Calcd for $C_{21}H_{20}O$; C, 87.50; H, 6.94. Found: C, 87.60; H, 7.20.

Reduction of (*S*)-(−)-1,1,2-Triphenyl-1-propanol (1c) to (*R*)-(+)-1,1,2-Triphenylpropane (2), with Sodium in Liquid Ammonia. The carbinol **1c** (5.76 g, 0.02 mol) and ethanol (2.02 g, 0.044 mol) were dissolved in a mixture of 50 ml of THF and 200 ml of liquid ammonia. Sodium (1.01 g, 0.044 mol) was added in small pieces during 45 min. After all the sodium dissolved, ammonia was evaporated and the residue was treated with crushed ice. The product was extracted with ether; the ether was dried ($MgSO_4$), and evaporated and the product was distilled in vacuo to give (*R*)-(+)-1,1,2-triphenylpropane (2.72 g, 50%). Upon addition of petroleum ether, the oil solidified, mp 63–65°, $[\alpha]^{22}D$ +30.15° (acetone, *l* = 2 dm, *c* 0.5998 g/25 ml). This material was identical with the sample secured as described below in all of its physical and spectral properties.

(+)-1,1,2-Triphenylpropane (2) from Reaction of Benzhydryllithium with (*R*)-(+)-*N,N,N*-Trimethyl-α-phenylethylammonium Iodide (3). To approximately 0.04 mol of benzhydryllithium in 100 ml of THF (see below) at 0° was added 11.64 g of (*R*)-(+)-*N,N,N*-trimethyl-α-phenylethylammonium iodide (0.04 mol). The reaction mixture was stirred for 1.0 hr, after which the red color of the carbanion had disappeared. After acidification with HCl, extraction with ether, drying of the ether ($CaCl_2$), and removal of the solvent in a rotary evaporator, the remaining oil was fractionally distilled in vacuo to give a middle fraction of bp 165° (1 mm). Treatment of this oil with cold methanol caused crystallization of 7.02 g (65%) of crude (+)-1,1,2-triphenylpropane, mp 60–64°, $[\alpha]^{23}D$ +29.56° (acetone, *l* = 2 dm). Five recrystallizations

from methanol afforded the analytical sample, mp 64–66°, $[\alpha]^{23}D$ +30.99° (acetone, *l* = 2 dm, c 0.6061 g/25 ml).

Anal. Calcd for $C_{21}H_{20}$: C, 92.64; H, 7.35. Found: C, 92.51; H, 7.41.

NMR ($DCCl_3$) δ 1.20 (3 H, d), 3.6 (1 H, m), 4.1 (1 H, d), 7.3 (15 H, m).

The literature[18] melting point (73–75°) is for racemic hydrocarbon. It thus appears that the individual enantiomers melt lower than the racemates, as was found in the 2,3-diphenylbutanes.[14]

Preparation of (−)-1,1,2-Triphenylpropane. The reaction of benzhydryllithium (0.04 mol) in THF at 0° under argon with (*S*)-(−)-*N,N,N*-trimethyl-α-phenylethylammonium iodide produced (−)-1,1,2-triphenylpropane, mp 65–67°, $[\alpha]^{22}D$ −28.74° (acetone, *l* = 2 dm, c 0.6096 g/25 ml).

Anal. Calcd for $C_{21}H_{20}$: C, 92.64; H, 7.35. Found: C, 92.58; H, 7.23.

The NMR and ir spectral properties were indistinguishable from those for (+)-**2**.

Resolution of (±)-α-Phenylethylamine. α-Phenylethylamine was resolved according to the method of Theilacker and Winkler.[19] The specific rotation for the (*R*)-(+) amine is $[\alpha]^{22}D$ +39.60° (neat), optical purity 98.2% using the best literature value[20] $[\alpha]^{25}D$ +40.60° (neat). The specific rotation for the (*S*)-(−) amine is $[\alpha]^{22}D$ −39.30° (neat), 98.0% optically pure.

NMR (CD_3CN) δ 1.3 (3 H, d), 1.4 (2 H, s), 4.0 (1 H, q), 7.5 (5 H, m). The spectra were identical for the two isomers.

(*R*)-(+)-*N,N*-Dimethyl-α-phenylethylamine. (*R*)-(+)-α-phenylethylamine (12.1 g, 0.1 mol) was added with cooling to 90% formic acid (25.5 g, 0.5 mol). Formaldehyde (19 g, 0.22 mol of a 35% H_2O solution) was added and the system was heated on a steam bath for 4 hr. Concentrated HCl (9 ml, 0.1 mol) was added and the formic acid and excess formaldehyde were removed with the rotary evaporator. The cold reaction mixture was made alkaline with 25% NaOH and extracted (3 × 15 ml) with ether and the organic layer was dried over KOH. Distilling of the solvent and the product produced 11.90 g (80%) of (*R*)-(+)-*N,N*-dimethyl-α-phenylethylamine: bp 92–94° (30 mm); $[\alpha]^{22}D$ +60.50° (neat, *l* = 1 dm) [lit.[21] $[\alpha]^{26}D$ 61.76° (neat, *l* = 1 dm)]; optical purity 98.0%; NMR (CD_3CN) δ 1.0 (3 H, d), 1.95 (6 H, s), 2.8 (1 H, q), 7.1 (5 H, m).

(*S*)-(−)-*N,N*-Dimethyl-α-phenylethylamine. This amine was prepared as described above for the (*R*)-(+) isomer, $[\alpha]^{22}D$ −60.48° (neat, *l* = 1 dm). The NMR and ir spectra were indistinguishable from those for the (+) isomer: NMR (CD_3CN) δ 1.0 (3 H, d), 1.95 (6 H, s), 2.8 (1 H, q), 7.1 (5 H, m).

(*R*)-(+)-*N,N,N*-Trimethyl-α-phenylethylammonium Iodide (3). To a solution of (*R*)-(+)-*N,N*-dimethyl-α-phenylethylamine (14.9 g, 0.1 mol) in ether (100 ml) was added slowly 21.3 g (0.15 mol) of methyl iodide. After 15 min the mixture solidified. The flask was cooled in an ice bath for 2 hr and allowed to stand at 25° for 16 hr and the product was collected by filtration, washing with ether (50 ml) and drying in vacuo for 24 hr to give 27.64 g (95%) of the title salt, mp 155–156° (lit.[22] mp 157–157.5°), $[\alpha]^{22}D$ 10.72° (H_2O, *l* = 2 dm, *c* 0.6184 g/25 ml), $[\alpha]^{20}D$ +23.28° (95% C_2H_5OH, *l* = 2 dm, *c* 0.9393 g/25 ml). The literature value[22] is $[\alpha]^{20}D$ +19.60° (C_2H_5OH). NMR ($CDCl_3$) δ 1.8 (3 H, d), 3.2 (9 H, s), 4.9 (1 H, q), 7.8 (5 H, s).

(*S*)-(−)-*N,N,N*-Trimethyl-α-phenylethylammonium Iodide. This solid was prepared as described for the (*R*)-(+) isomer, $[\alpha]^{22}D$ −12.03° (*l* = 2 dm, c 0.6749 g/25 ml H_2O), $[\alpha]^{20}D$ −22.95° (95% C_2H_5OH, *l* = 2 dm, c 0.8568 g/25 ml) [lit.[22] $[\alpha]^{20}D$ −19.60° (C_2H_5OH)].

Preparations of Triphenylmethyllithium and Diphenylmethyllithium. To a solution of triphenylmethane (4.88 g, 0.02 mol) or diphenylmethane (3.3 g, 0.0196 mol) in 100 ml of THF under argon at 0° was added 19.4 ml of *n*-butyllithium (0.021 mol of 1.13 *M* in hexane from Alfa Inorganics). The solutions were allowed to stir for 1.0 hr (3.0 hr in the case of Ph_2CH_2) before use. The coupling reactions shown in Table I demonstrate that metalation yields exceeded 90% while the 65% yield of **2** secured in eq 2 shows the lower yields sometimes secured in metalating diphenylmethane.

Preparation of Benzyllithium. Benzyl methyl ether (17.0 g, 0.085 mol) and lithium wire (6.0 g, Alfa Inorganics) in diethyl ether solvent were allowed to react according to a published procedure.[23]

Preparation of *N*-Diphenylmethyl-*N,N,N*-trimethylammonium Iodide. Benzhydryltrimethylammonium iodide was prepared as described in the literature,[24] mp 175° dec (lit. mp 174–175° dec), NMR ($DCCl_3$) δ 3.2 (9 H, s), 6.3 (1 H, s), 7.4 (10 H, m).

Preparation of *N*-Benzyl-*N,N,N*-trimethylammonium Iodide. Benzyltrimethylammonium iodide was prepared as described previously,[25] mp 178–179° dec (lit. mp 179°), NMR (D_2O) δ 3.2 (9 H, s), 4.6 (2 H, s), 7.7 (5 H, m).

Pentaphenylethane from Triphenylmethyllithium and *N*-Diphenyl-methyl-*N,N,N*-trimethylammonium Iodide. To a solution of tritylllithium (0.02 mol) in THF at 0° under argon was added 7.06 g of solid benzhydryltrimethylammonium iodide (0.02 mol). After 25–30 min the red color of the lithium reagent disappeared completely. After work-up using ether and water, the ether layer was washed with 5% HCl, neutralized with 5% NaOH, and dried over $MgSO_4$. The ether was removed in the rotary evaporator to give a light yellow powder which was dissolved quickly in the minimum amount of hot benzene and precipitated by adding excess absolute ethanol, 6.54 g (80%), mp 156–161°. Concentration under reduced pressure gave 1.22 g (10%) additional pentaphenylethane which was identical with a sample described recently in this laboratory,[9] NMR ($DCCl_3$) δ 5.8 (1 H, s), 7.2 (25 H, m).

***unsym*-Tetraphenylethane from Triphenylmethyllithium and Benzyltrimethylammonium Iodide.** To a solution of tritylllithium (0.02 mol) in 100 ml of THF at 0° under argon was added solid benzyltrimethylammonium iodide (5.54 g, 0.02 mol) with stirring for 4 hr. Using the work-up procedure described for pentaphenylethane, 6.01 g (90%) of *unsym*-tetraphenylethane, mp 143–145° (lit.[26] mp 144°) was obtained, NMR ($DCCl_3$) δ 3.95 (2 H, s), 7.2 (20 H, m).

***sym*-Tetraphenylethane from Diphenylmethyllithium and *N*-Diphenylmethyl-*N,N,N*-Trimethylammonium Iodide.** To a solution of benzhydryllithium (0.01 mol in THF) was added 3.53 g of solid benzhydryltrimethylammonium iodide (0.01 mol) with stirring for 1 hr. Using the procedure described for pentaphenylethane above with recrystallization of the crude product from benzene–alcohol (5:1), a 3.01-g yield of *sym*-tetraphenylethane was secured, mp 214–215° (lit.[18] mp 214–215°).

1,1,2-Triphenylethane from Benzyllithium and *N*-Benzhydryl-*N,N,N*-trimethylammonium Iodide (4). The title salt (3.53 g, 0.01 mol) and benzyllithium (0.01 mol) in ether at 0° were stirred until disappearance of the carbanion color. Hydrolysis with 100 ml of 5% HCl, extraction into 100 ml of ether, and drying with $MgSO_4$ was followed by removal of solvent to give 2.34 g (91%) of 1,1,2-triphenylethane (needles from alcohol), mp 55–56° (lit.[18] mp 55–56°), NMR ($DCCl_3$) δ 3.5 (2 H, d), 4.3 (1 H, t) 7.2 (15 H, m).

1,2-Diphenylethane from Benzyllithium and *N*-Benzyl-*N,N,N*-trimethylammonium Iodide (5). Using the procedure described above, benzyltrimethylammonium iodide (2.77 g, 0.01 mol) reacted with benzyllithium (0.01 mol) to give 1.63 g of 1,2-diphenylethane, mp 50–51° (lit.[27] mp 52.0–52.5°), NMR ($DCCl_3$) δ 2.9 (4 H, s), 7.1 (10 H, s).

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Registry No.—**1a,** 7782-24-3; **1b,** 28645-07-0; **1c,** 54667-59-3; (*R*)-(+)-**2,** 54667-60-6; (*S*)-(−)-**2,** 54667-61-7; (*R*)-(+)-**3,** 54712-34-4; (*S*)-(−)-**3,** 17279-33-3; **4,** 6338-76-7; **5,** 4525-46-6; (±)-hydratropaldehyde, 34713-70-7; hydroxylamine hydrochloride, 5470-11-1; hydratropaldoxime, 54667-62-8; hydratroponitrile, 42253-96-3; (±)-hydratropic acid, 2328-24-7; strychnine, 57-24-9; strychnine hydratropate, 54667-63-9; benzhydryllithium, 881-42-5; (±)-α-phenylethylamine, 618-36-0; (*R*)-(+)-α-phenylethylamine, 3886-69-9; (*S*)-(−)-α-phenylethylamine, 2627-86-3; (*R*)-(+)-*N,N*-dimethyl-α-phenylethylamine, 19342-01-9; formaldehyde, 50-00-0; (*S*)-(−)-*N,N*-dimethyl-α-phenylethylamine, 17279-31-1; triphenylmethyllithium, 733-90-4; benzyllithium, 766-04-1; pentaphenylethane, 19112-42-6; *unsym*-tetraphenylethane, 2294-94-2; *sym*-tetraphenylethane, 632-50-8; 1,1,2-triphenylethane, 1520-42-9; 1,2-diphenylethane, 103-29-7.

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The Chemistry of Carbanions. XXVII. A Convenient Precursor for the Generation of Lithium Organocuprates[1]

Herbert O. House,* Chia-Yeh Chu, Joyce M. Wilkins, and Michael J. Umen

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

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To avoid side reactions resulting from the presence of Cu(II) compounds and other metal salt impurities in the Cu(I) salts used to form lithium organocuprate reagents, use of the easily prepared, crystalline complex, Me_2S-CuBr(**2**), is recommended. This complex **2** is readily soluble in mixtures of Me_2S and ethereal solvents, and the sulfide ligand, Me_2S (bp 37°), is easily separated from reaction products. This procedure is illustrated with several additional reactions involving the cuprate reagents, Me_2CuLi and $(CH_2{=}CH)_2CuLi$. The difficultly reduced enone **22** and the moderately acidic saturated ketones **32** and **37** undergo a relatively slow reaction with Me_2CuLi at 25° to form enolate anions that are inert to further reaction with the cuprate. The saturated ketones **32, 37,** and **40** are also slowly converted to alcohol products by a solution of Me_2CuLi at 25°; this latter reaction may involve a small concentration of MeLi present in equilibrium with the cuprate reagent.

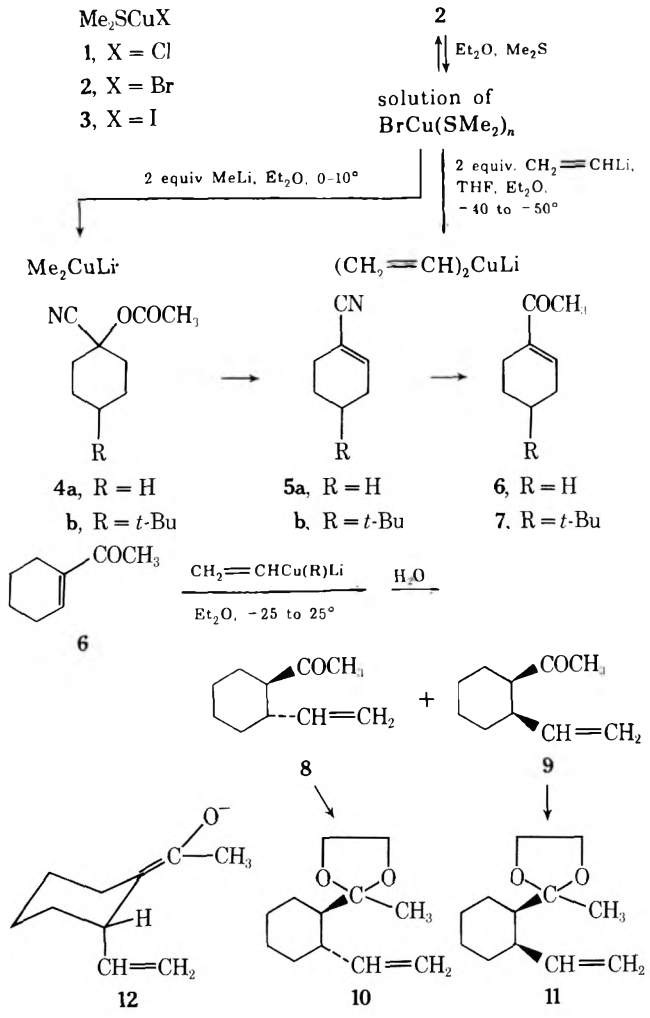
From various studies of the preparation and use of lithium organocuprate reagents,[2] it has become apparent that two practical problems complicating the general use of these reagents are inadvertent thermal decomposition[3] and inadvertent oxidation leading to coupling of the organic residues.[4] Both of these initial side reactions often lead to the formation of Cu(0), which usually appears as a black colloidal suspension in the reaction mixture and is believed to catalyze the decomposition of still more copper reagent.[5]

The most common preparative procedure for lithium dialkylcuprates consists of addition of 2 molar equiv of an alkyllithium solution to an ethereal slurry of one of the commercially available Cu(I) salts, CuI, CuBr, or CuCl. As noted previously,[6] use of this procedure may be accompanied by partial decomposition, especially if the reagent is one of the relatively thermally unstable cuprates, such as a vinyl derivative or a derivative with alkyl substituents that have β H atoms. Among the causes of this decomposition are the presence of other transition metal impurities in the commercial Cu(I) salts and the occurrence of local overheating during the exothermic reaction of alkyllithium with insoluble Cu(I) salts.[6] Another cause of decomposition is the presence of significant amounts of Cu(II) salts, which are effective oxidants for cuprates,[4,6b] in many commercial samples of Cu(I) halides. Other Cu(I) compounds that have been used to form cuprate reagents include the insoluble derivatives CuCN[7] and n-$C_3H_7C{\equiv}CCu$[8] and the more soluble derivatives t-BuOCu,[9] PhSCu,[9] and t-Bu$C{\equiv}CCu$.[6a] The latter, soluble Cu(I) acetylide offers the advantage of being a scavenger for oxidizing agents such as Cu(II) salts, undergoing oxidation to form the volatile diyne, t-Bu$C{\equiv}CC{\equiv}CBu$-t.[6] Unfortunately, the advantages of ether solubility and "protection" from oxidants offered by t-Bu$C{\equiv}CCu$ are offset by the fact that the precursor, t-Bu$C{\equiv}CH$, is not presently available commercially at a reasonable cost. This fact has led us to examine other possible Cu(I) derivatives that might offer the advantages of both ether solubility and easy purification to separate unwanted Cu(II) impurities. In earlier work,[6,10] we have noted the solubility advantages offered by several Cu(I) halide complexes such as n-Bu_3PCuI, $(MeO)_3PCuI$,$(MeO)_3PCuBr$, and especially, the *liquid complexes* $(n\text{-}Bu_2S)_2CuI$ and $(n\text{-}Bu_2S)_2CuBr$. The use of these complexes in synthetic work is made less attractive by the relatively high boiling points of the ligands, n-Bu_2S (bp 189°), n-Bu_3P [bp 150° (50 mm)], and $(MeO)_3P$ (bp 112°) that complicate their removal from reaction products and by the persistent disagreeable odor associated with phosphine and phosphite ligands. We were attracted by reports indicating that complexes of certain Cu(I) salts with the ligand Me_2S (bp 37°) were both soluble in ether[11] and could be obtained as crystalline solids.[12] Upon exploring the reaction of Me_2S with Cu(I) halides, we found that each of the 1:1 complexes **1, 2,** and **3** (Scheme I) could easily be obtained as a *colorless,* crystalline solid that was readily separated from Cu(II) contaminants. Since Cu(II) salts form solutions of highly colored complexes with Me_2S (dark green solution with $CuCl_2$ and dark red solution with $CuBr_2$), the absence of these Cu(II) impurities in the colorless Cu(I) complexes is readily discerned. Although the iodide complex **3** spontaneously lost Me_2S on standing, the bromide complex **2** proved to be both convenient to prepare in pure form and stable to storage. Thus, by conversion to the complex **2,** commercial samples of CuBr are readily purified to remove Cu(II) salts and other impurities.

Although none of the complexes **1–3** was soluble in ether,

solutions were readily obtained when additional Me_2S was added. The bromide complex **2** could be dissolved in Et_2O, PhH, or $CHCl_3$ when Me_2S was added, suggesting the reversible formation of complexes such as $(Me_2S)_2CuBr$ or $(Me_2S)_3CuBr$ in these solutions. Treatment of solutions of the complex **2** in Et_2O–Me_2S with 2 molar equiv of either MeLi (at 0–10°) or CH_2=CHLi (at −40 to −50°) produced solutions of the corresponding cuprate reagents, Me_2CuLi and $(CH_2{=}CH)_2CuLi$.

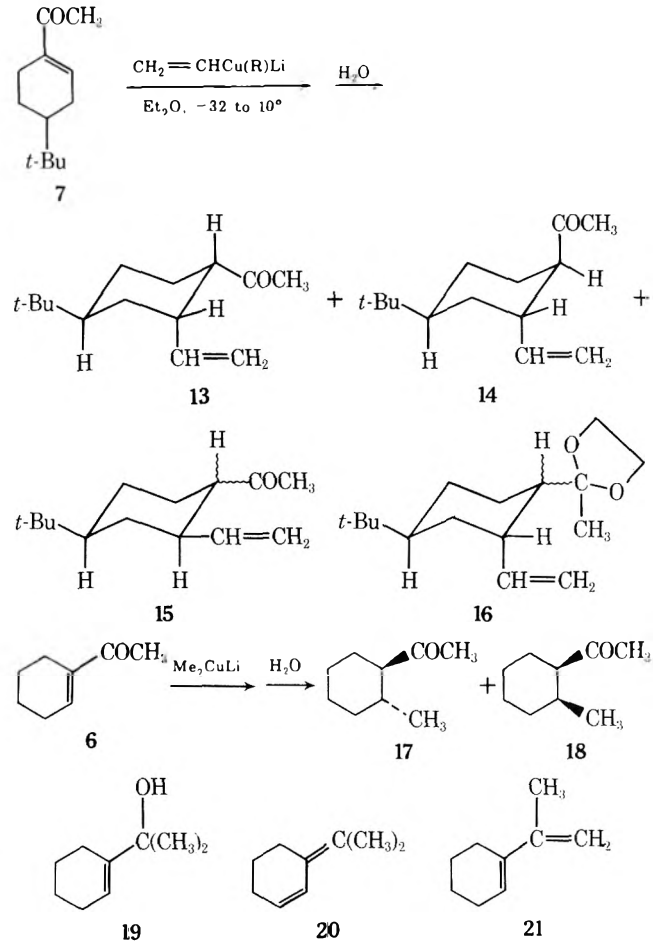
Scheme I



The effectiveness of various cuprate preparations was initially studied for the conjugate addition of vinyl groups to the unsaturated ketones **6** and **7**. From reactions of the enone **6** with $(CH_2{=}CH)(t\text{-BuC}{\equiv}C)CuLi$,[6] $(CH_2{=}CH)_2CuLi$ (from a *solution* of Me_2SCuBr), and $(CH_2{=}CH)_2CuLi$ (from a *suspension* of CuI), the yields of adducts **8** and **9** were 64, 78, and 69%, respectively. The product obtained from reaction with $(CH_2{=}CH)_2CuLi$ (from a *suspension* of CuI) was contaminated with an alcohol by-product believed to be the 1,2 adduct of the ketone **6** with CH_2=CHLi. This same type of by-product was also evident when the $(CH_2{=}CH)_2CuLi$ was generated from a *suspension* of Me_2SCuBr in Et_2O (containing no excess Me_2S). The initial mixture of ketones formed in the reactions contained ca. 80% of the cis ketone **9** and ca. 20% of the trans ketone **8** as expected from the kinetically controlled protonation of the intermediate enolate **12**.[13] After equilibration, the mixture of ketones contained ca. 15% of the cis isomer **9** and ca. 85% of the trans isomer **8** (the isomer allowing both substituents to be equatorial). Each of the ketone products was also characterized as the corresponding ketal **10** or **11**.

Reaction of the enone **7** (Scheme II) with $(CH_2{=}CH)(t\text{-BuC}{\equiv}C)CuLi$[6] or with $(CH_2{=}CH)_2CuLi$ (from a solution of Me_2SCuBr) formed a mixture of stereoisomeric adducts **13–15** in yields of 88 and 86%, respectively. The product mixture contained ca. 80% of the ketone **13**, ca. 15% of the epimeric ketone **14**, and ca. 5% of the stereoisomeric ketones **15** with equatorial vinyl substituents. Thus, the conjugate addition of a vinyl group, like the previously described[6] conjugate addition of a methyl group, to the enone **7** occurs predominantly from the direction that introduces an axial substituent.

Scheme II



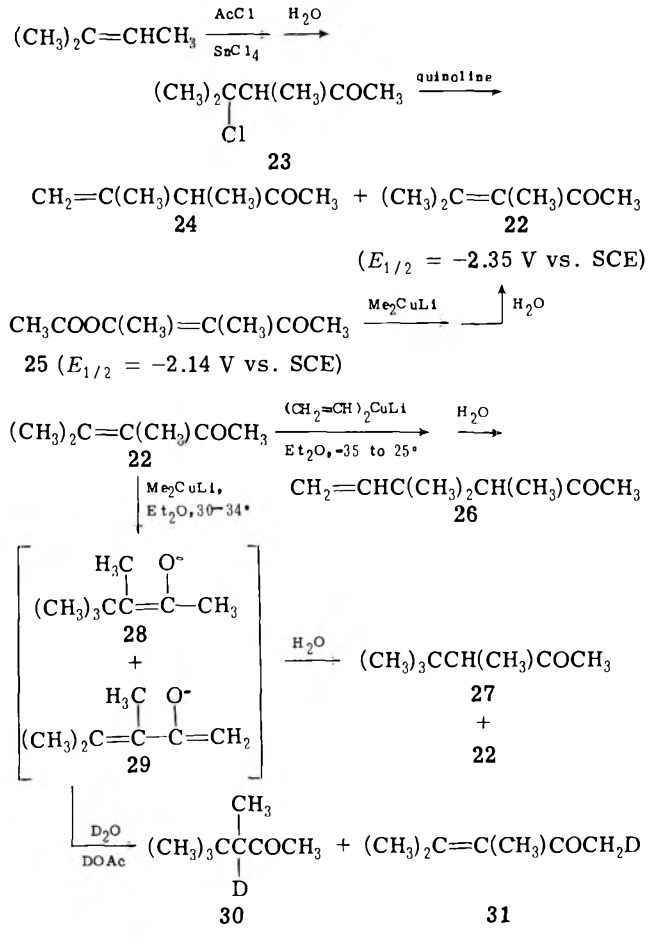
Reaction of the enone **6** with Me_2CuLi (from a *solution* of Me_2SCuBr) at 20–25° afforded a mixture of the stereoisomeric ketones **17** (21% of the mixture) and **18** (79% of the mixture) in 86% yield. Prompted by a recent report[14a] suggesting that Me_2CuLi adds in a 1,2 manner to enones at −78°, we also performed several reactions in which Me_2CuLi (*preformed at 25°*) was cooled to −78° and then treated with the enone **6**. In each of these experiments we observed the separation of only very small amounts of $(MeCu)_n$ while the reaction solutions were kept at −60 to −78° for 60–80 min. When the reaction solution was warmed to 20° before hydrolysis with aqueous NH_4Cl, an abundant precipitate of $(MeCu)_n$ separated as the solution was warmed above −20 to −10° and the adducts **17** and **18** were obtained in 70% yield. In another experiment where aqueous NH_4Cl was added to the cold (−60 to −70°) solution, the temperature rose to −20° during the hydrolysis and the adducts **17** and **18** were obtained in 11% yield. Finally, when the cold reaction solution was kept below −60° throughout

the dropwise addition of a precooled mixture of MeOH and HOAc, the yield of adducts **17** and **18** was 1.3%. In each of these experiments the only other component detected in the crude product was the unchanged enone **6** and we found no indication that the alcohol **19** (or its dehydration products **20** or **21**) was present. When we attempted to prepare the Me_2CuLi by addition of MeLi to a cold (−50 to −60°) partial solution of Me_2SCuBr, formation of the cuprate reagent was clearly incomplete, since the yellow precipitate of $(MeCu)_n$ did not dissolve as excess MeLi was added. Reaction of this reagent [presumably a mixture of Me_2CuLi, $(MeCu)_n$, and MeLi] with the enone **6** at −45 to −25° resulted in the formation of the alcohol **19** (71% yield, isolated after GLC separation as the olefins **20** and **21**) accompanied by a 16% yield of the ketones **17** and **18** and 2% recovery of the enone **16**. Thus, with the enone **6**, we see no evidence that 1,2 addition of *preformed* Me_2CuLi occurs at low temperatures. Furthermore, a preformed solution of Me_2CuLi reacts only very slowly with the enone **6** to give conjugate addition products provided that the reaction temperature is maintained in the range −60 to −78° during both the reaction period *and during subsequent hydrolysis*. In view of these results, we are somewhat uncertain about how to interpret earlier reports of reactions of substituted cyclohexenone derivatives with Me_2CuLi at −78 to −80° in which both rapid conjugate addition[2a,14b] and failure of conjugate addition accompanied by partial 1,2 addition[14a] have been reported.

A recent report[15a] of the use of the mixed cuprate, $(CH_3)(CH_2{=}CH)CuLi$, for the selective conjugate addition of a vinyl unit to a cyclopentenone derivative also prompted us to examine this reaction with the enone **6**. When a preformed ethereal suspension of $(MeCu)_n$ was cooled to −20 to −30° and treated with $CH_2{=}CHLi$, reaction clearly occurred to dissolve the polymeric $(MeCu)_n$. Reaction of this mixture with the enone **6** at −20° for 20 min followed by warming produced a mixture of the methyl ketone **18** (4% yield) and the vinyl ketones **8** and **9** (73%). Our efforts to effect the same reaction by adding MeLi to a cold (−20 to −35°) ethereal slurry of $CH_2{=}CHCu$ followed by addition of the enone **6** resulted in the formation of a complex mixture in which the alcohol **19** (isolated after GLC separation as olefins **20** and **21**) was the major product. Thus, we concluded that addition of MeLi to ethereal $CH_2{=}CHCu$ at −20 to −35° did not result in complete conversion of $CH_2{=}CHCu$ to a cuprate reagent. These results indicated that, provided formation of the cuprate reagent $(CH_3)(CH_2{=}CH)CuLi$ is complete, the transfer of a vinyl group from the mixed cuprate to the enone **6** is somewhat more rapid than the transfer of a methyl group. However, the fact that some methyl transfer is observed (to form **17** and **18**) indicates that the difference in ease of transfer of methyl and vinyl groups is much less than the difference in ease of transfer of a methyl and an alkynyl group from a mixed cuprate such as $(Me)(t\text{-}BuC{\equiv}C)CuLi$ where no alkynyl group transfer was observed.[6a]

To probe further the question of relative reactivities of vinyl and methyl groups in a mixed cuprate, we synthesized (Scheme III) the trisubstituted enone **22** that was expected[16] to have a sufficiently negative reduction potential that its reaction with Me_2CuLi would be questionable.[6a] This enone **22** was prepared either by reaction of Me_2CuLi with the enol acetate **25**[17] or more simply by the acetylation of 2-methyl-2-butene.[18] Reaction of this enone **22** with $(CH_2{=}CH)_2CuLi$ (from a *solution* of Me_2SCuBr at −25 to 25°) produced, after hydrolysis, a mixture of the conjugate adduct **26** (55% yield) and the recovered enone **22** (17% recovery). Reaction of the enone **22** with the mixed reagent,

Scheme III

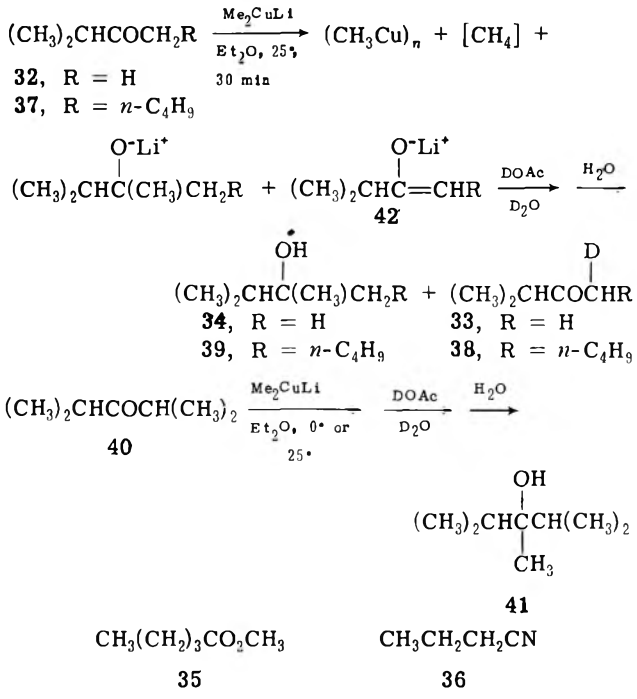


$(CH_2{=}CH)(CH_3)CuLi$, at −30 to 25° yielded a mixture of the ketones **26** (58%), **27** (2%), and **22** (13% recovery). Thus, with this acyclic enone **22**, as with the enone **6** and the previously described[15a] cyclopentenone derivatives, there is some preference for transfer of a vinyl group rather than a methyl group from the mixed cuprate, $(CH_3)(CH_2{=}CH)CuLi$. This apparent order of ease of transfer of organic ligands from mixed cuprates (vinyl > methyl ≫ alkynyl) is not what we would have expected based on an earlier study of conjugate additions of several mixed cuprates to two acyclic enones, methyl vinyl ketone and mesityl oxide, where the order alkyl > phenyl > alkynyl was suggested.[15b]

Our initial study of reaction of the enone **22** with Me_2CuLi (from either a *suspension* of CuI or a *solution* of Me_2SCuBr) led to a seemingly curious result. After an initial rapid reaction which produced, upon hydrolysis, the conjugate adduct **27** (20–35% yield) accompanied by the recovered enone **22**, no further reaction occurred even after prolonged reaction at 30–40° with excess Me_2CuLi. Further examination revealed that the initial rapid reaction was accompanied by gas evolution (presumably CH_4) to form a mixture of the adduct enolate **28** and the enolate **29** of the starting enone. Quenching this mixture with a mixture of D_2O and DOAc afforded the monodeuterated ketones **30** and **31**. Thus, with this difficultly reduced enone **22** [$E_{1/2}$ = −2.35 V (vs. SCE)] where an initial electron transfer is not energetically favorable,[19] reaction of the ketone **22** with Me_2CuLi to form an enolate **29** has clearly become a competitive reaction.[20]

Earlier studies had indicated that Me_2CuLi added only very slowly to methyl isobutyl ketone at 25°[21a] and that more than 85% of the di-*n*-butyl ketone mixed with Me_2CuLi at −10° was recovered when the reaction mixture was

Scheme IV



hydrolyzed after 15 min.[21b] The present results obtained with the enone **22** and Me_2CuLi suggested that the above results might be interpreted as conversions of saturated ketones to their enolates rather than the absence of any reaction. This idea was explored (Scheme IV) by treating Me_2CuLi solutions with several compounds having moderately acidic C–H bonds. The relatively acidic ketones **32** and **37**, having an α-methyl or an α-methylene group, clearly reacted [gas evolution and precipitation of $(MeCu)_n$] slowly during a period of 30 min with a Me_2CuLi solution at 25° to form mixtures of a lithium enolate **42** and an alkoxide. Quenching these reaction mixtures in a D_2O–DOAc mixture produced the alcohols **34** or **39** and deuterated ketones **33** or **38**. Under the same conditions, the less reactive and less acidic ester **35** and the nitrile **36** did not react in any way with a Me_2CuLi solution at 25° and were recovered unchanged after 30 min. The ketone **40**, which is less acidic than ketones **32** and **37**, reacted slowly at 25° [precipitation of $(MeCu)_n$ but no gas evolution] and, after quenching the mixture with D_2O–DOAc, the alcohol **41** (41% yield) and the nondeuterated ketone **40** were obtained. At 0° this addition reaction was much slower so that only 7–9% of the ketone **40** was converted to alcohol **41** after a 15-min reaction period.

Thus, we concluded that reaction mixtures containing saturated ketones and Me_2CuLi will undergo a slow reaction, especially if this reaction is run at 25° or is warmed to 25° before hydrolysis. With relatively acidic ketones of the types $RCOCH_3$ and $RCOCH_2R$, two competing reactions may be observed, one forming an enolate (cf. ref 14a) that is inert to further reaction and the other reaction forming an alcohol. With less acidic ketones only a slow addition to form an alcohol is observed. It should be noted that at 0° both of these reactions are very much slower than the conjugate addition of lithium organocuprate reagents to unsaturated carbonyl compounds. Thus, it is clearly possible to achieve selective addition of a cuprate reagent to an unsaturated carbonyl compound in the presence of an unconjugated carbonyl group provided one takes the precautions of not using a large excess of the cuprate reagent and of hydrolyzing the reaction mixture before it is warmed to room temperature. Finally, it should be noted that the slow conversion of relatively acidic ketones to enolate anions is apparently a reaction that is characteristic of lithium organocuprate reagents. Whether this enolate formation is facilitated by prior coordination of the carbonyl oxygen atom to the cuprate reagent is not known. However, the relatively slow reaction leading to saturated alcohol products may result, not from the slow addition of a cuprate reagent, but rather from the addition of a small concentration of an alkyllithium reagent present as a result of an equilibrium such as the following: $R_4Cu_2Li_2 \rightleftharpoons R_3Cu_2Li + RLi$.

Experimental Section[22]

Preparation of Starting Materials. Previously described procedures were used to prepare *tert*-butylacetylene[6] and to convert[6,23] 4-*tert*-butylcyclohexanone to its crude cyanohydrin (a mixture of epimers); the bulk of the material melted at 53–55° with a small amount of remaining material that melted at 63–65°. A mixture of 197.1 g (1.089 mol) of this cyanohydrin, 180 g of Ac_2O, and 12 ml of AcCl was refluxed for 5 hr, at which time TLC analysis (silica gel coating, CH_2Cl_2–Et_2O mixture as eluent) indicated complete conversion of the cyanohydrin (R_f 0.22) to its acetate **4b** (R_f 0.62). A small portion of the crude reaction mixture was partitioned between Et_2O and aqueous NaCl and the Et_2O solution was washed successively with aqueous $NaHCO_3$ and H_2O and then dried and concentrated. The crude acetate **4b**, which crystallized on standing, exhibited GLC peaks (silicone SE-52 on Chromosorb P) corresponding to 4-*tert*-butylcyclohexanone (retention time 3.9 min, ca. 2%) and the acetate **4b** (19.2 min, ca. 98%). The bulk of the crude acetate **4b** in Ac_2O solution was added dropwise to a tube packed with glass beads and heated to 550–570°.[24] A slow stream of N_2 was used to sweep the products into a cooled flask. The crude pyrolysis mixture contained (GLC, silicone SE-30 on Chromosorb P) primarily the unsaturated nitrile **5b** (retention time 7.8 min) accompanied by small amounts of 4-*tert*-butylcyclohexanone (4.2 min) and the unchanged acetate **4b** (10.9 min) as well as HOAc and Ac_2O. After the bulk of the HOAc had been removed by distillation (42–46° at 73 mm), the residue was partitioned between Et_2O and aqueous NaCl and the Et_2O solution was washed with aqueous $NaHCO_3$, dried, and concentrated. The residual unsaturated nitrile, a brown solid, was recrystallized from EtOH to separate 108 g (61%) of the nitrile **5b** as white plates, mp 45–46° (lit.[23] mp 45–46°), with ir and NMR spectra corresponding to those previously reported.[6] Reaction of nitrile **5b** with ethereal MeLi[6] yielded 65% of the ketone **7**, bp 67–81° (0.14 mm), $n^{25}D$ 1.4838–1.4842 [lit.[6] bp 141–143° (19 mm), $n^{25}D$ 1.4844], that exhibited a single GLC peak (retention time 12.8 min) on a column (silicone SE-30 on Chromosorb P) where the retention time of the starting nitrile **5b** was 9.4 min. The ir and NMR spectra of the product **7** corresponded to those previously reported.[6] Similarly, the cyanohydrin of cyclohexanone[25] was acetylated with refluxing Ac_2O containing a catalytic amount of AcCl and the crude acetate **4a** was pyrolyzed[24] by passing it through a tube heated to 575° along with a stream of N_2. An Et_2O solution of the crude pyrolysate was washed with aqueous $NaHCO_3$, dried, and distilled to separate the nitrile **5a**, bp 81–85° (14 mm), $n^{25}D$ 1.4810 [lit.[25] bp 86° (18 mm), $n^{20}D$ 1.4818].[26] After reaction of 9.54 g (89 mmol) of the nitrile **5a** with 184 mmol of MeLi in 140 ml of Et_2O for 20 min at 0–10°, the reaction mixture was poured into 500 ml of aqueous 1 *M* HCl and extracted with Et_2O. A mixture of the aqueous phase and 300 ml of hexane was refluxed for 17 hr to complete hydrolysis of the imine and then the hexane layer was separated and the aqueous phase was extracted with Et_2O. The combined organic layers were dried, concentrated, and distilled to separate 7.98 g (71%) of the ketone **6** as colorless liquid fractions, bp 88–93° (17 mm), $n^{25}D$ 1.4880–1.4894 [lit.[27] bp 63–65° (5 mm), $n^{20}D$ 1.4913]. Except for a minor low-boiling impurity in the first fraction, the product **6** exhibited a single GLC peak (retention time 8.9 min) on a column (silicone SE-30 on Chromosorb P) where the retention time for the starting nitrile **5a** was 7.4 min: ir (CCl_4) 1670 (conjugated C=O) and 1639 cm^{-1} (conjugated C=C); uv max (95% EtOH) 232 mμ (ϵ 13,900); NMR (CCl_4) δ 6.3–6.5 (1 H, m, vinyl CH) and 1.0–2.0 (11 H, m, aliphatic CH including a CH_3 singlet at 1.71).

Commercial Et_2O solutions containing about 1.6 *M* MeLi (halide free, Foote Mineral Co.) and THF solutions containing 1.6–2.1 *M* CH_2=CHLi (Lithium Corp. of America) were standardized by a double titration procedure[28] in which aliquots of the reagent, both before and after reaction with 1,2-dibromoethane, were titrated

with standard aqueous acid. All of the commercial THF solutions of CH_2=CHLi (Lithium Corp. of America) were contaminated with substantial amounts of mineral oil (presumably from the Li dispersion used) that contaminated the final product and had to be separated by fractional distillation. Commercial CuI (Fisher Scientific) was purified by solution in aqueous KI and reprecipitation.[29]

Preparation of the Me_2S Complexes of Copper(I) Halides. A. Me_2SCuBr (2).[12] To 40.0 g (279 mmol) of pulverized CuBr (Fisher Scientific) was added 50 ml (42.4 g, 682 mmol) of Me_2S (Eastman, bp 36–38°). The resulting mixture, which warmed during dissolution, was stirred vigorously and then filtered through a glass wool plug. The residual solid was stirred with an additional 30 ml (25 g, 409 mmol) of Me_2S to dissolve the bulk of the remaining solid and this mixture was filtered. The combined red solutions were diluted with 200 ml of hexane. The white crystals that separated were filtered with suction and washed with hexane until the washings were colorless. The residual solid was dried under nitrogen to leave 51.6 g (90%) of the complex **2** as white prisms that dissolved in an Et_2O–Me_2S mixture to give a *colorless* solution. For recrystallization, a solution of 1.02 g of the complex in 5 ml of Me_2S was slowly diluted with 20 ml of hexane to give 0.96 g of the pure complex **2** as colorless prisms, mp 124–129° dec. The complex **2** is essentially insoluble in hexane, Et_2O, acetone, $CHCl_3$, CCl_4, MeOH, EtOH, and H_2O. Although the complex **2** does dissolve in DMF and in DMSO, the facts that heat is evolved and the resulting solutions are green colored suggests that the complex has dissociated and that some oxidation (or disproportionation) to give Cu(II) species has occurred. A solution prepared from the complex **2** and DMSO-d_6 exhibited an NMR peak at δ 2.17 (CH_3S); a solution of Me_2S in the same solvent exhibited a peak at δ 2.05. The complex **2** would dissolve to give a colorless solution in PhH, Et_2O, MeOH, or $CHCl_3$ when excess Me_2S was added to the mixture, suggesting the reversible formation of a more soluble complex such as $(Me_2S)_2CuBr$ or $(Me_2S)_3CuBr$.

Anal. Calcd for C_2H_6BrCuS: C, 11.68; H, 2.94; Br, 38.87; S, 15.60. Found: C, 11.50; H, 2.91; Br, 38.75; S, 15.51.

B. Me_2SCuCl (1). Following the same procedure, 20 ml of Me_2S was added to a slurry of 5.00 g (50.5 mmol) of CuCl (Fisher Scientific) in 20 ml of Et_2O and the mixture was stirred for 20 min while warming to 25°. After filtration of the dark green solution, it was mixed with 50 ml of hexane and then filtered with suction and washed with hexane to leave 2.2 g (27%) of the complex **1** as a white solid. A 1.30-g portion of the material was recrystallized by dissolving it in 8 ml of Me_2S and then slowly diluting the solution with 20 ml of hexane to precipitate the complex **1** as 1.14 g of white plates, mp 118–124° dec. The complex **1** was essentially insoluble in hexane, Et_2O, acetone, $CHCl_3$, CCl_4, MeOH, EtOH, and H_2O but it did dissolve (probably with dissociation) in either DMSO or DMF to give green solutions.

Anal. Calcd for C_2H_6ClCuS: C, 14.91; H, 3.75; Cl, 22.00; S, 19.90. Found: C, 14.73; H, 3.69; Cl, 21.77; S, 19.66.

Our attempt to prepare and isolate the stable complex **3** involved a comparable reaction of 20 ml of Me_2S with a slurry of 5.00 g (26.3 mmol) of CuI (Fisher Scientific) in 15 ml of Et_2O to give a deep red solution that was filtered and diluted with 50 ml of hexane. The resulting crystalline material that separated was filtered with suction and washed with hexane to leave 5.65 g (ca. 85%) of the complex **3** as white prisms. On standing, the crystals of the complex **3** collapsed to a white powder and the sample steadily lost weight, indicating loss of Me_2S from the sample at room temperature. The sample also apparently lost Me_2S when it was heated in an attempt to obtain a melting point. When a partially decomposed sample of 1.12 g of the complex **3** was again recrystallized from 4 ml of Me_2S and 20 ml of hexane, the freshly recrystallized complex **3** (1.13 g) gained in weight and was again obtained as white prisms. The composition of a sample of the material (Anal. Found: C, 7.16; H, 1.83; S, 9.51; I, 54.14) also indicated partial loss of Me_2S from the complex **3** (Anal. Calcd for C_2H_6CuIS: C, 9.51; H, 2.39; S, 12.69; I, 50.24) even at room temperature. Like the previously described complexes **1** and **2**, the complex **3** was essentially insoluble in Et_2O, hexane, acetone, $CHCl_3$, CCl_4, H_2O, MeOH, and EtOH. It was also insoluble in DMF but did dissolve (probably with dissociation) in DMSO.

Reactions of the Enone 6. A. Addition of a Vinyl Group. A colorless solution of 3.0 g (14.6 mmol) of Me_2SCuBr (**2**), 15 ml of Me_2S, and 20 ml of Et_2O was cooled to −57° (during this cooling part of the complex **2** crystallized from the solution) and then 14.5 ml of a THF solution containing 30.5 mmol of CH_2=CHLi (Lithium Corp. of America, this reagent also contained mineral oil), was added, dropwise and with stirring, during 20 min while the temperature of the reaction mixture was maintained at −50 and −57°. To the resulting cold, light-gray solution, containing some undissolved solid, was added, dropwise and with stirring during 2 min, a solution of 1.66 g (13.4 mmol) of the enone **6** in 10 ml of Et_2O. The mixture, which warmed to −25° during the addition, was cooled to maintain the temperature in the range −25 to −40° and stirred for 10 min, and then the mixture was allowed to warm to 25° with continuous stirring during 30 min. As the temperature of the mixture rose to −25° and warmer, the reaction mixture became a dark brown or black color. The reaction mixture was diluted with Et_2O and aqueous NH_4Cl and filtered to remove suspended solids. The Et_2O extract was then separated, washed with aqueous NH_3, dried, treated with decolorizing carbon, and concentrated. An aliquot of the residual pale yellow liquid (3.51 g) containing the ketones **8** and **9** and mineral oil (from the CH_2=CHLi) was mixed with a known weight of internal standard n-$C_{15}H_{32}$ and analyzed by GLC (Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples). The mixture contained ketone **8** (retention time 7.4 min, 14% yield), ketone **9** (8.2 min, 64% yield), and n-$C_{15}H_{32}$ (6.6 min); the high-boiling mineral oil was not eluted. The crude product was distilled in a short-path still to separate 1.37 g (67%) of a mixture of ketones **8** and **9** as a colorless liquid, bp 80–95° (20 mm). A collected (GLC) sample of ketone **8** was obtained as a colorless liquid: n^{25}D 1.4650; ir (CCl_4), 1713 (C=O), 1639 (C=C), 994, and 920 cm^{-1} (CH=CH_2); uv max (95% EtOH) 282 mμ (ϵ 64); NMR (CCl_4) δ 4.6–6.0 (3 H, m, vinyl CH) and 0.9–2.4 (13 H, m, aliphatic CH including a CH_3 singlet at 1.97); mass spectrum *m/e* (rel intensity) 152 (M^+, 20), 109 (100), 95 (32), 67 (85), 55 (28), 43 (87), and 41 (26).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.85; H, 10.61.

A collected (GLC) sample of the ketone **9** was obtained as a colorless liquid: n^{25}D 1.4707; ir (CCl_4) 1712 (C=O), 1638 (C=C), 995, and 922 cm^{-1} (CH=CH_2); uv max (95% EtOH) 282 mμ (ϵ 83); NMR (CCl_4) δ 4.7–6.3 (3 H, m, vinyl CH) and 0.9–2.9 (13 H, m, aliphatic CH including a CH_3 singlet at 1.98); mass spectrum *m/e* (rel intensity) 152 (M^+, 21), 109 (85), 94 (33), 79 (24), 67 (87), 55 (28), 43 (100), and 41 (28).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.86; H, 10.62.

The reaction was repeated employing a smaller proportion of Me_2S, the quantities being 20.0 g (97.3 mmol) of Me_2SCuBr, 2 ml of Me_2S, 120 ml of Et_2O, 100 ml of a THF solution containing 210 mmol of CH_2=CHLi, and 11.0 g (88.7 mmol) of the enone **6** in 20 ml of Et_2O. Analysis (GLC) of the crude liquid product (25.4 g, a mixture of ketones **8** and **9** and mineral oil) indicated the proportions of the ketones to be ca. 15% of **8** and 85% of **9**. Short-path distillation separated 9.15 g (68%) of the mixture of ketones **8** and **9** as a colorless liquid, bp 90–110° (20 mm), n^{25}D 1.4691–1.4706. A second distillation separated 8.72 g (65%) of fractions, bp 53–55° (1.2 mm), containing (GLC) only the ketones **8** and **9**.

The reaction was also performed with no added Me_2S employing 3.00 g (14.6 mmol) of Me_2SCuBr, 25 ml of Et_2O, 14.5 ml of THF solution containing 30.5 mmol of CH_2=CHLi, and a solution of 1.66 g (13.4 mmol) of the enone **6** in 3 ml of Et_2O. The yields of the ketones (GLC analysis with added n-$C_{15}H_{32}$) were 8% of **8** and 56% of **9**. The ir spectrum (CCl_4) of this crude product exhibited substantial absorption at 3590 and 3480 cm^{-1} (OH) suggesting that the crude product, unlike the materials formed in the previous experiments, contained some alcohol derived from 1,2 addition of CH_2=CHLi to the enone **6**.

A solution of t-BuC≡CLi, from 12.1 g (147 mmol) of t-BuC≡CH and 1.48 mmol of MeLi in 106 ml of Et_2O, was added to a cold (5°) slurry of 28.0 g (147 mmol) of purified[29] CuI in 180 ml of Et_2O. The resulting orange solution of t-BuC≡CCu was cooled (during which time part of the t-BuC≡CCu separated as an orange solid) and then 63 ml of a THF solution containing 132 mmol of CH_2=CHLi was added, dropwise and with stirring, while the temperature of the mixture was maintained at −50 to −60°. The resulting dark-colored solution of the cuprate reagent was warmed to −40° and stirred for 5 min, and then a solution of 5.00 g (40.7 mmol) of the enone **6** in 100 ml of Et_2O was added, dropwise and with stirring, while the temperature was maintained at −40°. The resulting mixture was warmed to 0–10°, stirred for 90 min, and then poured into 150 ml of ethanolic 1 *M* HOAc. After this mixture had been neutralized with aqueous $NaHCO_3$, it was extracted with Et_2O and the Et_2O extract was washed successively with aqueous 28% NH_3[30] and with H_2O. The organic solution was dried, treated with decolorizing carbon, and then concentrated to leave 11.2 g of

red liquid containing the ketone product and mineral oil. Analysis (GLC of an aliquot with added n-$C_{16}H_{32}$) indicated the yields of ketone to be 30% of **8** and 34% of **9**. To examine the outcome of a reaction with no solubilizing ligand for the copper salt, a cold (−33°) slurry of 2.65 g (14.6 mmol) of purified[29] CuI in 15 ml of Et_2O was treated, dropwise and with stirring, with 14.5 ml of a THF solution containing 30.5 mmol of CH_2=CHLi while the temperature of the mixture was kept at −25 to −33°. During this addition a black precipitate formed in the reaction mixture. To the cold (ca. −30°) solution was added, dropwise and with stirring, 1.535 g (12.4 mmol) of the enone **6**. As soon as the addition was complete, the temperature of the reaction mixture was raised to −5° and the mixture was stirred at −5 to 8° for 10 min and then poured into aqueous NH_4Cl and NH_3 (pH 8). The Et_2O layer was separated and combined with the Et_2O extract of the aqueous phase. The ethereal solution was washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave 3.63 g of yellow liquid containing the ketones **8** and **9**, mineral oil, and other products. The ir (peaks at 3590 and 3490 cm^{-1}) and NMR (singlet at δ 1.30) spectra of the crude product suggested that it was contaminated with the alcohol formed by 1,2 addition of CH_2=CHLi to the enone **6**. Analysis (GLC with added n-$C_{15}H_{32}$) indicated the yield of ketone products to be 11% of **8** and 58% of **9**.

A solution of 382 mg (2.51 mmol) of a mixture of epimeric ketones (54% of **9** and 46% of **8**) and 102 mg of p-TsOH in 10 ml of $CHCl_3$ was refluxed for 2 hr and then cooled and washed with aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, analysis (GLC with added n-$C_{15}H_{32}$) indicated that the total recovery of the ketones was 88% and the mixture contained 21% of **9** and 79% of **8**. A collected (GLC) sample of ketone **8** was identified with an authentic sample by comparison of GLC retention times and NMR spectra. In a similar experiment, 544 mg (3.85 mmol) of a mixture of ketones (87% of **9** and 13% of **8**) was chromatographed on 11 g of basic alumina employing a hexane–Et_2O mixture as the eluent. The combined eluted fractions of ketone (quantitative recovery) contained (GLC) 11% of the cis ketone **9** and 89% of the trans ketone **8**. A sample of the eluted product was identified with ketone **8** by comparison of GLC retention times and ir and NMR spectra.

B. Reaction with Me_2CuLi. To a colorless solution of 3.00 g (14.6 mmol) of Me_2SCuBr in 20 ml of Me_2S and 20 ml of Et_2O was added, dropwise and with stirring while maintaining the temperature at 20–25°, 16.2 ml of an Et_2O solution containing 26.7 mmol of MeLi. The addition of MeLi was stopped at the point when the last of initially formed yellow precipitate of $(MeCu)_n$ just dissolved to form a pale yellow solution. To this solution was added 1.33 g (10.7 mmol) of the enone **6** and the resulting mixture, from which a yellow precipitate of $(MeCu)_n$ separated, was stirred at 25° for 40 min and then partitioned between Et_2O and an aqueous solution (pH 8) of NH_4Cl and NH_3. The ethereal layer was dried and concentrated to leave 1.49 g of a pale yellow liquid that contained (GLC, Carbowax 20M on Chromosorb P, n-$C_{14}H_{30}$ added as an internal standard and apparatus calibrated with known mixtures) n-$C_{14}H_{30}$ (retention time 4.9 mm), the trans ketone **17** (5.8 min, 18% yield), and the cis ketone **18** (6.8 min, 68% yield). A collected (GLC) sample of the trans ketone **17** was obtained as a colorless liquid: $n^{25}D$ 1.4471 [lit.[31] bp 64–65° (10 mm), $n^{25}D$ 1.4464]; ir (CCl_4) 1705 cm^{-1} (C=O); NMR (CCl_4) δ 2.01 (3 H, s, CH_3CO), 0.9–2.0 (10 H, m, aliphatic CH), and 0.80 (3 H, d, J = 5 Hz, CH_3); mass spectrum m/e (rel intensity) 140 (M^+, 23), 97 (45), 85 (22), 82 (22), 71 (29), 55 (100), and 43 (48). A collected (GLC) sample of the cis ketone **18** was obtained as a colorless liquid: $n^{25}D$ 1.4552 [lit.[31] bp 67–68° (10 mm), $n^{25}D$ 1.4532]; ir (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 1.0–2.7 (13 H, m, aliphatic CH including a $COCH_3$ singlet at δ 2.00) and 0.82 (3 H, d, J = 6.5 Hz, CH_3); mass spectrum m/e (rel intensity) 140 (M^+, 18), 97 (45), 55 (100), and 43 (41).

In several additional experiments the Me_2CuLi solution was formed at 25°, and then cooled to −78° before the enone **6** was added. When the reaction mixture was stirred at −78° for 80 min (during which time no reaction was apparent) and then allowed to warm to 20° with stirring during 25 min [during which time a copious precipitate of $(MeCu)_n$ separated], the crude product contained (GLC) n-$C_{14}H_{30}$ (5.0 min), the trans ketone **17** (5.9 min, 16% yield), the cis ketone **18** (6.9 min, 54% yield), and the starting enone **6** (10.6 min, 10% recovery). In a comparable experiment, the reaction solution was stirred at −60 to −70° for 1 hr and then hydrolyzed by addition of aqueous NH_4Cl and NH_3 (pH 8). After this hydrolysis procedure (which warmed the reaction mixture to −20°), the crude product contained (GLC and NMR analyses) adducts **17** (3% yield) and **18** (8% yield) accompanied by the starting enone **6** (65% recovery). The same reaction was repeated and the cold (−60 to −70°) reaction solution was hydrolyzed by the dropwise addition of a precooled mixture of MeOH and HOAc (5:1 v/v) so that the temperature of the reaction solution was kept below −60°. In this case the crude product contained (GLC and NMR analyses) only minor amounts of the adducts **17** (0.8% yield) and **18** (0.5% yield) accompanied by the unchanged enone **6** (82% recovery). When we attempted to form the cuprate reagent by adding MeLi to the Me_2SCuBr solution in Et_2O and Me_2S at −50 to −60°, formation of Me_2CuLi was clearly incomplete, since most of the yellow $(MeCu)_n$ did not dissolve when the second equivalent of MeLi was added. Addition of the enone **6** to this cold mixture was followed by reaction at −45 to −25° for 5 min and subsequent warming of the mixture to 25° during 30 min; then the usual isolation and analysis procedures were used. In this case the crude product contained (GLC, Carbowax 20M on Chromosorb P) the olefin **21** (retention time 2.8 min, 43% yield), the olefin **20** (3.3 min, 28% yield), n-$C_{14}H_{30}$ (4.6 min), the trans ketone **17** (5.4 min, 5% yield), the cis ketone **18** (6.4 min, 11% yield), and the starting enone **6** (9.6 min, 2% recovery). The two olefins **20** and **21** are presumably formed from the alcohol **19** during GLC analysis, since the ir spectrum of the crude product (CCl_4) has strong bands at 3590 and 3470 cm^{-1} (OH). A collected (GLC) sample of the olefin **21** [lit.[32a,b] bp 49–50° (7 mm)] has ir absorption at 1630, 1605 (C=C), and 885 cm^{-1} (C=CH_2) and NMR (CCl_4) peaks at δ 5.79 (1 H, broad, vinyl CH), 4.6–4.9 (2 H, m, vinyl CH), and 1.1–2.6 (11 H, m, aliphatic CH including a broad singlet at δ 1.83 attributable to an allylic CH_3 group). A collected (GLC) sample of the olefin **20** (lit.[32b,c] bp 164–165°) exhibited ir (CCl_4) weak absorption at 1672, 1638, and 1605 cm^{-1} (C=C) with NMR absorption (CCl_4) at δ 6.1–6.6, 5.4–5.8 (2 H, two multiplets, vinyl CH), and 1.1–2.4 (12 H, m, aliphatic CH including a broad singlet at δ 1.67 attributable to two allylic CH_3 groups).

C. Reaction with $Me(CH_2$=$CH)CuLi$. A solution of 3.00 g (14.6 mmol) of Me_2SCuBr in 20 ml of Me_2S and 20 ml of Et_2O was treated at 25° with 8.1 ml of an Et_2O solution containing 13.4 mmol of MeLi. The resulting slurry of yellow $(MeCu)_n$ was cooled to −30° and then 8.2 ml of a THF solution containing 13.4 mmol of CH_2=CHLi was added, dropwise and with stirring, while the temperature was maintained at −20 to −30°. To the resulting cold mixture was added, dropwise and with stirring while the temperature was maintained at −20 to −30°, a solution of 372 mg (3.00 mmol) of the enone **6** in 2 ml of Et_2O. The reaction mixture was stirred at −20° for 10 min and at 25° for 90 min and then subjected to the usual isolation and analysis procedures. The crude liquid product (1.26 g of yellow liquid) contained (GLC, Carbowax 20M on Chromosorb P, n-$C_{15}H_{32}$ added as an internal standard) ketone **18** (6.7 min, 4% yield), n-$C_{15}H_{32}$ (7.2 min), ketone **8** (9.0 min, 10% yield), and ketone **9** (10.3 min, 63% yield). Collected (GLC) samples of ketones **8** and **9** were identified with previously described samples by comparison of GLC retention time and NMR spectra and a collected (GLC) sample of ketone **18** was identified with a previously described sample by comparison of GLC retention times and mass spectra.

An attempt to form the mixed cuprate by treating a cold (−20 to −35°) solution of Me_2SCuBr in Me_2S and Et_2O, first with 1 equiv of CH_2=CHLi and then with 1 equiv of MeLi, failed to form the cuprate. After the addition of the enone **6**, the major products formed after GLC analysis were the previously described olefins **20** and **21**, indicating that the unchanged MeLi in the original reaction mixture had reacted with the enone **6** to form the alcohol **19**.

Preparation of the Ketals 10 and 11. A solution of 1.50 g (9.87 mmol) of a mixture of ketones (46% of **8** and 54% of **9**), 35 mg of p-TsOH, 20 ml of $HOCH_2CH_2OH$, and 100 ml of PhH was refluxed for 48 hr with continous separation of H_2O and then cooled and partitioned between Et_2O and aqueous $NaHCO_3$. The organic solution was dried and concentrated to leave 2.189 g of the crude product as a yellow liquid containing [GLC, Carbowax 20M on Chromosorb P, internal standard (n-$C_{15}H_{32}$) added and the apparatus was calibrated with known mixtures of authentic samples] n-$C_{15}H_{32}$ (retention time 6.0 min), the cis ketal **11** (15.6 min, 21% yield), and the trans ketal **10** (13.9 min, 57% yield).

A collected sample of the trans ketal **10** was obtained as a colorless liquid: $n^{25}D$ 1.4773; ir (CCl_4) 1632 (C=C), 991, and 903 cm^{-1} (CH=CH_2); uv (95% EtOH) end absorption with ϵ 96 at 210 mμ; NMR (CCl_4) δ 4.7–6.2 (3 H, m, vinyl CH), 3.6–3.9 (4 H, m, CH_2O), and 0.9–2.1 (13 H, m, aliphatic CH including a CH_3 singlet at 1.12); mass spectrum m/e (rel intensity) 196 (M^+, <1), 87 (100), 55 (22), and 43 (27).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.40; H, 10.28.

A solution of 27.3 mg of the ketal **10** and 1.5 ml of aqueous 1 *M* HCl in 5 ml of dioxane was stirred at 25° for 5 hr and then partitioned between Et_2O and H_2O. The Et_2O layer was washed with aqueous $NaHCO_3$, dried, and concentrated to leave a colorless liquid identified as the trans ketone **8** by comparison of GLC retention times and NMR spectra.

A collected (GLC) sample of the cis ketal **11** was obtained as a colorless liquid: $n^{25}D$ 1.4791; ir (CCl_4) 1629 (C=C), 991, and 910 cm^{-1} ($CH=CH_2$); uv (95% EtOH) end absorption with ϵ 247 at 210 mμ; NMR (CCl_4) δ 4.8–6.6 (3 H, m, vinyl CH), 3.6–3.9 (4 H, broad, CH_2O), and 1.0–2.8 (13 H, m, aliphatic CH including a CH_3 singlet at 1.13); mass spectrum *m/e* (rel intensity) 196 (M^+, <1), 181 (8), 87 (100), and 43 (10).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.45; H, 10.28.

A solution of 10 mg of the cis ketal **11** and 0.5 ml of aqueous 1 *M* HCl in 2 ml of dioxane was subjected to the previously described reaction and isolation procedures to yield a liquid product identified as the cis ketone **9** by comparison of GLC retention times and NMR spectra.

Preparation of the Vinyl Ketones 13 and 14. To a cold (0°) solution of 0.139 mol of MeLi in 80 ml of Et_2O was added 11.6 g (0.142 mol) of *t*-BuC≡CH. The resulting solution of *t*-BuC≡CLi was added to a cold (5°) slurry of 26.5 g (0.139 mol) of purified[29] CuI in 160 ml of Et_2O and the resulting mixture was warmed to 29° with stirring during 15 min to give a red-orange solution of *t*-BuC≡CCu. This solution was cooled to −50° and the resulting orange suspension was treated with a solution of 0.129 mol of CH_2=CHLi[33] in 68 ml of Et_2O while the temperature was maintained at −45 to −50°. The resulting solution, whose color changed progressively from orange to red to green, was warmed to −32° with stirring during 10 min and then treated with a solution of 7.2 g (40 mmol) of the ketone **7** in 80 ml of Et_2O. The resulting mixture was stirred at 0–10° for 1 hr and then added to 150 ml of ethanolic 1 *M* HOAc. The resulting mixture was neutralized with aqueous $NaHCO_3$ and extracted with Et_2O. After the Et_2O extract had been washed successively with aqueous 28% NH_3[30] and with H_2O, it was dried and concentrated to leave 7.94 g of liquid containing (GLC, silicone fluid QF_1 on Chromosorb P) a mixture of a component believed to be one epimer of ketone **15** (retention time 10.1 min, ca. 4%), ketone **14** (12.8 min, ca. 15%), a component believed to be the second epimer of ketone **15** (15.4 min, ca. 3%), and ketone **13** (17.5 min, ca. 78%). A 5.69-g aliquot of this crude product was distilled to separate 4.745 g of fractions, bp 69–91° (0.1–0.7 mm), containing various mixtures of the ketones **13, 14,** and **15.** A collected (GLC) sample of the major product **13** was obtained as a colorless liquid: $n^{25}D$ 1.4728; ir (CCl_4) 1710 (C=O), 1635 (C=C), and 920 cm^{-1} ($CH=CH_2$); uv max (95% EtOH) 278 mμ (ϵ 35); NMR (CCl_4) δ 4.8–6.2 (3 H, m, vinyl CH), 2.3–3.2 (1 H, m, allylic CH), 2.38 [1 H, d (J_{aa} = 10.8 Hz) of t (J_{ae} = 4.4 Hz), axial H of CHCO, exchanged with NaOMe in MeOD], 1.99 (3 H, s, CH_3CO, exchanged with NaOMe in MeOD), 0.9–1.9 (7 H, m, aliphatic CH), and 0.85 (9 H, s, *t*-Bu); the signal at δ 2.38 exhibited the same splitting pattern and *J* values when the spectrum was determined at 100 MHz with a Jeol NMR spectrometer; mass spectrum *m/e* (rel intensity) 208 (1, M^+), 152 (8), 151 (6), 109 (17), 58 (30), 57 (30), and 43 (100); calcd for $C_{14}H_{24}O$, 208.1827; found, 208.1847.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.91; H, 11.78.

A solution of 59 mg (0.28 mmol) of the pure (GLC) ketone **13** and 23 mg (0.42 mmol) of NaOMe in 3 ml of MeOH was refluxed for 38.5 hr and then partitioned between Et_2O and aqueous 1 *M* HCl. The Et_2O solution was dried and concentrated to leave 53 mg of yellow liquid containing (GLC) the ketones **14** (ca. 31%) and **13** (ca. 69%). Collected (GLC) samples of the ketone **14** from this equilibration and from the original cuprate addition reaction were identified by comparison of GLC retention times and ir and mass spectra: ir (CCl_4) 1705 (C=O), 1635 (C=C), and 920 cm^{-1} ($CH=CH_2$); mass spectrum *m/e* (rel intensity) 208 (M^+, <1), 152 (21), 109 (45), 57 (88), 43 (100), and 41 (26).

In a larger scale reaction the mixed cuprate, from 27.0 g (329 mmol) of *t*-BuC≡CH, 329 mmol of MeLi, 62.5 g (329 mmol) of purified[29] CuI, 308 mmol of CH_2=CHLi,[33] and 773 ml of Et_2O, was treated with a solution of 17.1 g (95 mmol) of the ketone **7** in 150 ml of Et_2O. After the previously described reaction and isolation procedures were followed, distillation afforded 15.70 g (88%) of colorless liquid product, bp 82–100° (0.4 mm), containing (GLC) the ketones **13** (ca. 80%) and **14** (ca. 11%) as well as two minor components (ca. 2 and 5%) believed to be the epimers of ketone **15** and a minor unidentified component (ca. 2%).

In another experiment in which the mixed cuprate was generated from ethereal CH_2=CHLi and a solution prepared from pure[6] *t*-BuC≡CCu, the same reaction and isolation procedures were followed. The crude liquid reaction product contained (GLC) the same mixture of ketones **13, 14,** and **15** formed in the previously described experiment.

A solution of 15.0 g (73.0 mmol) of Me_2SCuBr (**2**) in 75 ml of Me_2S and 100 ml of Et_2O was cooled to −50 to −57° (accompanied by partial crystallization of the complex **2**) and then 93.2 ml of a THF solution containing 153 mmol of CH_2=CHLi was added, dropwise with stirring. The resulting reddish-brown solution was warmed to −35° and a solution of 12.06 g (67.0 mmol) of the ketone **7** in 50 ml of Et_2O was added dropwise with stirring. The resulting mixture was stirred at −30 to −35° for 10 min and then allowed to warm to 25° with stirring during 1 hr. As the solution warmed from −30 to 25°, it became dark brown to black in color. The reaction mixture was partitioned between ether and aqueous NH_4Cl and NH_3 and then the ether solution was washed successively with aqueous 10% $Na_2S_2O_3$ and with aqueous 28% NH_3. The organic solution was then decolorized with carbon, dried, and concentrated to leave a pale yellow liquid (59.89 g, containing mineral oil from the CH_2=CHLi). The crude mixture contained (GLC, Carbowax 20M on Chromosorb P) the ketone **13** (retention time 17.1 min, ca. 80% of the mixture) as well as a partially resolved mixture of ketones **14** and **15** (9.9 and 12.4 min, ca. 20% of the mixture). A collected (GLC) sample of the major product, ketone **13,** was identified with the previously described sample by comparison of GLC retention times and ir and NMR spectra. Distillation of the crude product separated 11.94 g (85.7%) of a mixture of ketones **13, 14,** and **15** as fractions of colorless liquid, bp 83–87° (1.5 mm), $n^{25}D$ 1.4724–1.4730, and left the higher boiling mineral oil (from the CH_2=CHLi) in the still pot.

Preparation of the Ketal 16. A solution of 13.16 g (63.5 mmol) of the previously described mixtures of ketones **13** (ca. 80%) and **14** (ca. 11% plus minor amounts of ketones **15**), 306 mg of *p*-TsOH·H_2O, and 170 ml of ethylene glycol in 950 ml of PhH was refluxed for 68 hr with continuous separation of H_2O and then partitioned between Et_2O and aqueous $NaHCO_3$. The organic layer was dried and concentrated to leave 16.14 g of the crude ketal **16** as a pale yellow liquid containing (ir analysis) only a very minor amount of the starting ketones **13–15** and containing (GLC, silicone fluid QF_1 on Chromosorb P) two major components, the epimeric ketals **16** [retention times 13.3 (ca. 20%) and 15.1 min (ca. 80%)]. A collected (GLC) sample of the mixture of epimers **16** was obtained as a colorless liquid: $n^{25}D$ 1.4790; ir (CCl_4) 1630 (C=C) and 910 cm^{-1} ($CH=CH_2$); uv (95% EtOH) end absorption with ϵ 66 at 210 mμ; NMR (CCl_4) δ 5.8–6.2 and 4.7–5.2 (3 H, m, vinyl CH), 3.7–4.0 (4 H, m, CH_2O), 1.0–3.0 [12 H, m including two singlets at 1.23 (minor) and 1.15 (major), 3 H, CH_3 of epimers], and 0.82 (9 H, s, *t*-Bu)]; mass spectrum *m/e* (rel intensity) 252 (<1, M^+), 237 (1), 87 (100), and 43 (18).

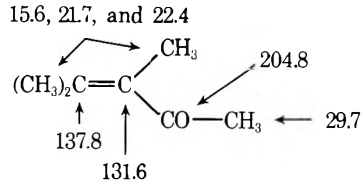
Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.24; H, 11.20.

To demonstrate the absence of C=C migration during ketalization, a 234-mg portion of the crude ketal **16** was stirred at 25° for 12.5 hr with a solution of 3 ml of aqueous 0.01 *M* HCl in 7 ml of dioxane and for 6.5 hr with 3 ml of aqueous 1 *M* HCl in 7 ml of dioxane and then partitioned between Et_2O and aqueous $NaHCO_3$. The Et_2O layer was dried and concentrated to leave 140 mg of crude product that contained (GLC, ir, and NMR analysis) the same mixture of ketones **13–15** that was used to form the ketal **16.**

Preparation of the Unsaturated Ketone 22. To a cold (4°) mixture of 20.01 g (285 mmol) of 2-methyl-2-butene and 2.55 g (9.8 mmol) of freshly distilled $SnCl_4$ (bp 114°) was added, dropwise and with stirring, 26.8 g (341 mmol) of AcCl.[18] After the addition was complete, the yellow reaction solution was allowed to warm to 25° (accompanied by formation of a red-brown color) and then the mixture was stirred at 25–27° for 3.5 hr. After the reaction mixture had been poured onto ice and extracted with Et_2O, the ethereal solution was washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. The crude residual liquid was distilled to separate 19.05 g of fractions, bp 43–80° (44 mm), $n^{25}D$ 1.4401–1.4449, that contained (ir and NMR analysis) a mixture of the unsaturated ketones **22** and **24** and the chloro ketone **23.** A mixture of this crude product (12.05 g) with 16.53 g (128 mmol) of freshly distilled quinoline [bp 87–91° (0.35 mm)] was heated under reflux (ca. 140°) for 2.5 hr and then cooled and partitioned between Et_2O and H_2O. The ethereal layer was dried and

concentrated and the residual liquid was distilled to separate 12.15 g (38%) of fractions, bp 73.5–75.5° (20 mm), that contained (GLC, TCEP on Chromosorb P) ca. 12–33% of the unconjugated ketone **24** (retention time 4.5 min) and 67–88% of the conjugated ketone **22** (9.1 min). A mixture of these ketones **22** and **24** (12.15 g) and 120 mg of *p*-TsOH was heated to 140° for 20 min and then cooled and partitioned between Et_2O and aqueous $NaHCO_3$. The ethereal solution was dried and concentrated to leave a ketone mixture containing (GLC) ca. 19% of ketone **24** and ca. 81% of ketone **22**.

The mixture was fractionally distilled at atmospheric pressure with a 55-cm Teflon spinning-band column to separate the pure ketone **24**, bp 125°, n^{25}D 1.4201, followed by fractions containing (GLC) mixtures of ketones **22** and **24**, and finally the pure ketone **22**, bp 146°, n^{25}D 1.4500 (lit. bp 146°,[34] 149.5°,[18] n^{24}D 1.4473[15]). The ketone **24** exhibited ir peaks (CCl_4) at 1718 (C=O), 1641 (C=C), and 890 cm^{-1} (C=CH_2) with NMR peaks (CCl_4) at δ 4.7–5.0 (2 H, m, vinyl CH), 3.15 (1 H, q, J = 7 Hz, allylic CH), 2.01 (3 H, s, CH_3CO), 1.65 (3 H, partially resolved multiplet, allylic CH_3), and 1.10 (3 H, d, J = 7 Hz, CH_3). The ketone **22** has the following spectroscopic properties: ir (CCl_4) 1684 (conjugated C=O) and 1615 cm^{-1} (conjugated C=C); uv max (95% EtOH) 247 mμ (ε 6000); NMR (CCl_4) δ 2.12 (3 H, s, $COCH_3$), 1.80 (6 H, s, CH_3), and 1.73 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 112 (M^+, 100), 97 (64), 69 (93), 53 (22), 43 (63), 41 (81), and 39 (30). A 0.017 *M* solution of the enone **17** in DMF containing 0.5 *M* *n*-$Bu_4N^+BF_4^-$ at 25° exhibited a polarographic[35] $E_{1/2}$ value of −2.35 V (vs. SCE), n = 1.1. Measurement by cyclic voltammetry[35] indicated a half-life of ca. 0.01 sec for the anion radical derived from the enone **22**. The natural-abundance ^{13}C NMR spectrum of the enone **22**, measured in $CDCl_3$ with added Me_4Si, is summarized in the following formula.



In an alternative preparation,[36] 130.4 g (1.30 mol) of 2,4-pentanedione was methylated with 228 g (1.61 mol) of CH_3I and 168 g (1.22 mol) of anhydrous K_2CO_3 in 500 ml of acetone to yield 100.4 g (68%) of 3-methyl-2,4-pentanedione: bp 75.5–76.5° (25 mm); n^{25}D 1.4375 [lit. bp 60–65° (13 mm),[37] 75° (30 mm),[38] n^{20}D 1.4443[37]]; ir (CCl_4) 1725 and 1695 cm^{-1} (C=O); NMR (CCl_4) δ 16.75 (ca. 0.35 H, s, enol OH), 3.70 (ca. 0.65 H, q, J = 7 Hz, CH_3 of keto form), 2.13, 2.07 (6 H, two singlets, CH_3CO of enol and keto forms). This product contained (GLC, silicone QF_1 on Chromosorb P) about 95% of the monomethylated product (retention time 5.3 min) accompanied by a minor component thought to be the dialkylated product (6.1 min). A solution of 5.71 g (50 mmol) of this diketone, 27.6 g (270 mmol) of Ac_2O, and 0.034 ml of aqueous 70% $HClO_4$ in 60 ml of CCl_4 was allowed to stand at 25° for 3 hr and then partitioned between pentane and aqueous $NaHCO_3$. The organic layer was dried, concentrated, and distilled to separate 6.05 g (77%) of the crude enol acetates **25**, bp 85.5–86.5° (10 mm) [lit.[39] bp 115–117° (30 mm)], which contained (GLC, silicone QF_1 on Chromosorb P) the stereoisomeric enol acetates **25** [retention times 13.3 (ca. 67%) and 16.1 min (ca. 33%)] as well as a small amount of the starting diketone (5.4 min). A collected (GLC) sample of the more rapidly eluted (13.3 min) isomer **25a** was obtained as a colorless liquid: n^{25}D 1.4518; ir (CCl_4) 1755 (enol ester C=O), 1697 (conjugated C=O), and 1626 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 156 (M^+, <1), 114 (M − CH_2=C=O, 17), 99 (47), and 43 (100); NMR (CCl_4) δ 2.22 (3 H, s, CH_3CO_2), 2.12 (3 H, s, CH_3CO), 2.07 (3 H, q, J = 1.5 Hz, allylic CH_3), and 1.77 (3 H, q, J = 1.5 Hz, allylic CH_3); uv max (95% EtOH) 237 mμ (ε 7630) with a shoulder at 290 mμ (ε 185). A 0.009 *M* solution of this enol acetate **25a** in DMF containing 0.5 *M* *n*-$Bu_4N^+BF_4^-$ at 24° exhibited a polarographic[35] $E_{1/2}$ value of −2.14 V (vs. SCE), n = 1.2.

A collected (GLC) sample of the more slowly eluted (16.1 min) enol acetate **25b** was obtained as a colorless liquid: n^{25}D 1.4559; ir (CCl_4) 1757 (enol ester C=O), 1695 (conjugated C=O), 1665, and 1647 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 114 (M − CH_2=C=O, 3), 99 (7), and 43 (100); NMR (CCl_4) δ 2.12 (6 H, s, CH_3CO and CH_3CO_2), ca. 2.07 (3 H, broad, allylic CH_3), and 1.80 (3 H, broad, allylic CH_3); uv max (95% EtOH) 234.5 mμ (ε 8330) with a shoulder at 286 mμ (ε 160). A 0.0088 *M* solution of this enol acetate **25b** in DMF containing 0.5 *M* *n*-$Bu_4N^+BF_4^-$ at 26° exhibited a polarographic[35] $E_{1/2}$ value of −2.13 V (vs. SCE), n = 1.1.

Following a previously described general procedure,[17] a cold (−40°) solution of Me_2CuLi, from 2.99 g (15.7 mmol) of purified[29] CuI and 31.5 mmol of MeLi in 30 ml of Et_2O, was added to a cold (−75°) solution of 2.46 g (15.7 mmol) of the enol acetate **25** in 10 ml of Et_2O. The reaction mixture, from which a red-brown precipitate separated, was allowed to stand for 30 min and then partitioned between Et_2O and aqueous NH_4Cl and NH_3 (pH 8). The organic layer was washed with aqueous $Na_2S_2O_3$, dried, and concentrated to leave 1.00 g of crude liquid product. Distillation in a short-path still separated 0.61 g (35%) of the crude enone **22** as a yellow liquid containing (GLC, silicone QF_1 on Chromosorb P) primarily the enone **22** (retention time 6.2 min) accompanied by a small amount of unchanged enol acetates **25** (13.3 and 16.1 min). A collected (GLC) sample of the enone **22** was identified with the previously described material by comparison of ir and NMR spectra and GLC retention times.

Reactions with the Enone 22. A. Addition of Me_2CuLi. To a solution of Me_2CuLi, prepared by the addition of 17 ml of an Et_2O solution containing 28.1 mmol of MeLi to a solution of 3.0 g (14.6 mmol) of Me_2SCuBr in 15 ml of Me_2S and 15 ml of Et_2O, was added 1.12 g (10.0 mmol) of the enone **22**. The resulting solution, from which $(MeCu)_n$ separated, was stirred at 30–34° for 1.7 hr and then partitioned between Et_2O and aqueous (pH 8) NH_4Cl and NH_3. The ethereal layer was washed successively with aqueous 28% NH_3 and with aqueous NaCl and then dried and concentrated to leave 1.10 g of residual yellow liquid containing (GLC, Carbowax 20M on Chromosorb P) the ketone **27** (retention time 5.1 min, ca. 23% of the mixture) and the starting enone **22** (8.7 min, ca. 77% of the mixture). A collected (GLC) sample of the enone **22** was identified with an authentic sample by comparison of GLC retention times and ir and NMR spectra. A collected (GLC) sample of the pure ketone **27** was obtained as a colorless liquid: n^{25}D 1.4162 [lit. bp 148–154° (760 mm),[40] 78–79.5° (77 mm),[41] n^{25}D 1.4161[41]]; ir (CCl_4) 1711 cm^{-1} (C=O); NMR (CCl_4) δ 2.42 (1 H, q, J = 7 Hz, CHCO), 2.15 (3 H, s, CH_3CO), and 0.9–1.1 (12 H, CH_3 including a singlet at δ 0.96 attributable to *t*-Bu); mass spectrum *m/e* (rel intensity) 128 (M^+, 2), 97 (12), 85 (29), 72 (81), 57 (70), 43 (100), 41 (64), and 39 (26).

In various similar experiments at other concentrations, temperatures, and reaction times, the composition of crude product remained within the ranges 15–30% of the ketone **27** and 70–85% of the recovered enone **22**. The composition of the reaction mixture was established in less than 5 min and did vary with longer reaction periods; during this intial 5-min reaction period, gas evolution (presumably CH_4) was evident in the reaction mixture. The reaction was repeated with 10.0 mmol of the enone **22** employing a reaction time of 50 min at 25° and then a solution of 58 mmol of DOAc in 10 ml of D_2O was added and the mixture was extracted with hexane. The hexane extract was washed successively with aqueous $NaHCO_3$, aqueous 28% NH_3, and aqueous NaCl and then dried and concentrated to leave 1.48 g of colorless liquid containing (GLC) ca. 25% of the ketone **30** and ca. 75% of the enone **31**. A collected (GLC) sample of the ketone **30** contained (mass spectral analysis) 12% d_0 species, 85% d_1 species, and 3% d_2 species; NMR (CCl_4) differs from the spectrum of ketone **27** in lacking CHCO absorption centered at δ 2.42 and in a collapse of the partially resolved CH_3 doublet at ca. δ 0.98 to a signal partially resolved from the *t*-Bu singlet at δ 0.96. A collected sample of the enone **31** contained (mass spectral analysis) 12% d_0 species, 74% d_1 species, 13% d_2 species, and 1% d_3 species; NMR (CCl_4) differs from the spectrum of the enone **22** in that the CH_3CO singlet at δ 2.12 appears as a three-line signal (J_{H-D} = 1.1 Hz) of diminished intensity.

B. Addition of $(CH_2$=$CH)_2CuLi$. A solution of 3.00 g (14.6 mmol) of Me_2SCuBr in 15 ml of Me_2S and 20 ml of Et_2O was cooled to −57° and then 17 ml of a THF solution containing 27.6 mmol of CH_2=CHLi was added, dropwise and with stirring, while the temperature was kept at −49 to −59°. The resulting mixture was warmed to −40° and a solution of 1.25 g (11.1 mmol) of the enone **22** in 2 ml of Et_2O was added. After the resulting mixture had been stirred for 10 min at −35 to −25°, it was warmed to 25°, stirred for 50 min, and then partitioned between Et_2O and aqueous NH_4Cl and NH_3. The ethereal layer was washed successively with aqueous 28% NH_3 and with aqueous NaCl and then dried and concentrated. The residual yellow liquid (3.72 g, contained mineral oil) was mixed with an internal standard (*n*-$C_{11}H_{24}$) and analyzed by GLC (silicone SE-30 on Chromosorb P). The mixture contained the starting enone **22** (retention time 3.4 min, 17% recovery, collected sample identified by comparison of NMR spectra and GLC retention times), the ketone **26** (4.9 min, 55% yield), and *n*-$C_{11}H_{24}$ (10.7 min). A collected (GLC) sample of the ketone **26** was ob-

tained as a colorless liquid: n^{25}D 1.4371; ir (CCl_4) 1711 (C=O), 1635 (C=C), and 910 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.7–6.2 (3 H, m, vinyl CH), 2.45 (1 H, q, J = 7 Hz, CHCO), 2.04 (3 H, s, CH_3CO), and 0.9–1.1 [9 H, two lines corresponding to a doublet (J = 7 Hz) at δ 0.96 superimposed on a singlet at δ 1.01]; mass spectrum m/e (rel intensity) 140 (M^+, 2), 125 (30), 97 (31), 72 (66), 69 (100), 55 (59), 53 (24), 43 (63), 41 (78), and 39 (39).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.06; H, 11.52.

To examine the reaction with the mixed cuprate, (CH_2=CH)(CH_3)CuLi, a solution of 3.00 g (14.6 mmol) of Me_2SCuBr in 10 ml of Me_2S was treated with 8.0 ml of an ether solution containing 14.3 ml of MeLi and the resulting slurry was cooled to −30 to −40° and treated with 8.8 ml of a THF solution containing 14.3 mmol of CH_2=CHLi. To the resulting cold (−22 to −30°) mixture was added, dropwise and with stirring, 1.12 g (10.0 mmol) of the enone **22**. The reaction mixture was then allowed to warm to 25° with stirring during 30 min and then subjected to the usual isolation and analysis procedures. The crude product contained (GLC, silicone SE-30 Chromosorb P) the ketone **27** (retention time 4.1 min, 2% yield), the enone **22** (4.5 min, 13% recovery), the ketone **26** (6.3 min, 58% yield), and n-$C_{11}H_{24}$ (13.6 min, internal standard). A collected (GLC) sample of the enone **22** was identified by comparison of NMR spectra and GLC retention times and a collected (GLC) sample of the ketone **26** was identified by comparison of ir and NMR spectra and GLC retention times.

Reaction of Me_2CuLi with Some Nonconjugated Compounds. To a 25° solution of Me_2CuLi, prepared from 3.00 g (14.6 mmol) of Me_2SCuBr, 28.6 mmol of MeLi, 16 ml of Et_2O, and 10 ml of Me_2S, was added 1.00 g (11.6 mmol) of the ketone **32**. An immediate reaction occurred as indicated by the evolution of gas and the separation of a yellow precipitate. The reaction mixture was stirred at 25° for 30 min and then poured into a solution of 59 mmol of DOAc in D_2O. The resulting mixture was extracted with Et_2O and the ethereal extract was washed successively with aqueous $NaHCO_3$, aqueous 28% NH_3, and aqueous NaCl and then dried and concentrated by fractional distillation. The crude liquid product (0.94 g) contained (GLC, Carbowax 20M on Chromosorb P) n-C_8H_{18} (retention time 2.2 min, internal standard), the ketone **33** (3.9 min, 49% yield), and the alcohol **34** (8.4 min, 16% yield). A collected (GLC) sample of the alcohol **34** was identified with an authentic sample by comparison of ir and NMR spectra and GLC retention times. A collected (GLC) sample of ketone **33** exhibited NMR absorption (CCl_4) at δ 2.53 (1 H, m, CH), 2.03 (ca. 2 H, $COCH_2D$), and 1.06 (6 H, d, J = 7 Hz, CH_3); mass spectrum 45% d_0 species, 34% d_1 species, 20% d_2 species, and 1% d_3 species.

When comparable cold (−2 to 2°) solutions containing 14 mmol of Me_2CuLi were treated with either 1.16 g (10 mmol) of the ester **35** or 0.69 g (10 mmol) of the nitrile **36**, no evidence of reaction was observed. Each solution was warmed to 25° and stirred for 30 min with no evidence of reaction. After each reaction solution had been quenched in a mixture of DOAc and D_2O, the crude organic products were recovered and found to contain (GLC) only the starting material **35** or **36**. Collected samples (GLC) of each compound were identified and shown to contain no appreciable quantity of deuterium by NMR analysis. When a solution of 14.3 mmol of Me_2CuLi was treated with 1.42 g (10 mmol) of the ketone **37** at 25°, a reaction was evident (gas evolution, temperature rise, separation of a yellow precipitate). The mixture was stirred for 30 min at 25–32° and then quenched in a mixture of DOAc and D_2O and subjected to the usual isolation procedure. The crude neutral product (1.46 g of yellow liquid) contained (GLC, silicone SE-30 on Chromosorb P) n-C_9H_{20} (2.2 min, added internal standard), the ketone **38** (3.8 min, 21% yield), and the alcohol **39** (5.9 min, 55% yield). A collected (GLC) sample of the ketone **38** contained (mass spectral analysis) 25% d_0 species and 75% d_1 species and exhibited a 2 H NMR (CCl_4) multiplet in the region δ 2.0–2.8 where the starting ketone **37** has a 3 H multiplet (>$CHCOCH_2$–). The mass spectrum of the ketone **38** exhibited an abundant fragment peak at m/e 100 (n-$C_4H_9CHDC{\equiv}O^+$) rather than the peak at m/e 99 (n-$C_4H_9CH_2C{\equiv}O^+$) found in the mass spectrum of the starting ketone **37**. A collected (GLC) sample of the alcohol **39** was identified with an authentic sample by comparison of GLC retention times and ir and NMR spectra. An authentic sample of the alcohol **39**, obtained by reaction of the ketone **37** with MeLi, was obtained as a colorless liquid: bp 104–105° (15 mm); n^{25}D 1.4371 [lit.[42] bp 69–70° (5 mm), n^{25}D 1.4380]; ir (CCl_4) 3580 and 3470 cm^{-1} (OH).

When 1.14 g (10 mmol) of the ketone **40** was added to 21 ml of an Et_2O solution containing 14.3 mmol of Me_2CuLi at 25–27°, no gas evolution was observed but a yellow precipitate of $(MeCu)_n$ began to separate after about 2 min. After this mixture had been stirred at 25–27° for 30 min, it was quenched in a DOAc–D_2O mixture and then subjected to the usual isolation procedure. The crude product contained (GLC, Carbowax 20M on Chromosorb P, n-$C_{11}H_{24}$ added as internal standard) the unchanged ketone **40** (retention time 2.2 min, 34% recovery), n-$C_{11}H_{24}$ (3.3 min), and the alcohol **41** (5.6 min, 41% yield). Collected (GLC) samples of each component **40** and **41** were identified with authentic samples by comparison of GLC retention times and ir and NMR spectra. The recovered ketone **40** contained (NMR analysis) no appreciable amount of deuterium. An authentic sample of the alcohol **41**, prepared by reaction of the ketone **40** with ethereal MeLi, was obtained as a colorless liquid, n^{25}D 1.4336 (lit.[43] n^{25}D 1.4326). In additional experiments cold (0°) ethereal solutions of 2.9 mmol of Me_2CuLi (prepared either from a solution of Me_2SCuBr and Me_2S or from a slurry of CuI) were treated with 2.0-mmol samples of the ketone **40**. After these solutions had been stirred for 15 min at 0°, aliquots were removed and subjected to the usual isolation and analysis procedures. These mixtures contained 91–93% of the unchanged ketone **40** and 7–9% of the alcohol **41**. When one of these reaction solutions was allowed to warm to 25° with stirring during 15 min [during which time separation of $(MeCu)_n$ indicated that a slow reaction was occurring], the resulting crude product contained 52% of the unchanged ketone **40** and 48% of the alcohol **41**.

Registry No.—**1**, 54678-22-7; **2**, 54678-23-8; **3**, 54678-24-9; **4a**, 32379-37-6; **4b**, 54678-03-4; **5a**, 1855-63-6; **5b**, 7370-14-1; **6**, 932-66-1; **7**, 37881-09-7; **8**, 54678-07-8; **9**, 54678-08-9; **10**, 54678-09-0; **11**, 54678-10-3; **13**, 54678-11-4; **14**, 54678-12-5; **15** epimer 1, 54678-13-6; **15** epimer 2, 54678-14-7; **16** epimer 1, 54678-15-8; **16** epimer 2, 54678-16-9; **17**, 5222-61-7; **18**, 5222-62-8; **20**, 6248-81-3; **21**, 6252-18-2; **22**, 684-94-6; **24**, 54678-04-5; **25a**, 54678-17-0; **25b**, 54678-18-1; **26**, 54678-05-6; **27**, 5340-45-4; **32**, 563-80-4; **33**, 54678-06-7; **35**, 624-24-8; **36**, 104-74-0; **37**, 923-28-4; **38**, 54678-19-2; **40**, 565-80-0; 4-*tert*-butylcyclohexanone, 98-53-3; CuBr, 7787-70-4; Me_2S, 75-18-3; CuCl, 7758-89-6; CuI, 7681-65-4; CH_2=CHLi, 917-57-7; *t*-BuC≡CLi, 37892-71-0; Me_2CuLi, 15681-48-8; Me(CH_2=CH)CuLi, 54678-20-5; $HOCH_2CH_2OH$, 107-21-1; 2-methyl-2-butene, 513-35-9; 2,4-pentanedione, 123-54-6; 3-methyl-2,4-pentanedione, 815-57-6; $(CH_2{=}CH)_2CuLi$, 22903-99-7.

References and Notes

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(2) For recent reviews, see (a) G. Posner, *Org. React.*, **19**, 1 (1972); (b) G. Posner, *ibid.*, in press; (c) H. O. House, Proceedings of the XVII Robert A. Welch Foundation Conference, Houston, Tex., Nov 5–7, 1973, pp 101–149.

(3) Potential side reactions arising from thermal decomposition to form CuH derivatives are noted elsewhere; see H. O. House and J. C. DuBose, *J. Org. Chem.*, **40**, 788 (1975), and references cited therein.

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Stereoselective Organometallic Alkylation Reactions. IV. Organolithium and Organoaluminum Addition to Trimethyl-, Triphenyl-, and Trichloroaluminum Complexes of 4-*tert*-Butylcyclohexanone and 2-Methylcyclopentanone[1]

Eugene C. Ashby*[2] and Joseph T. Laemmle

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

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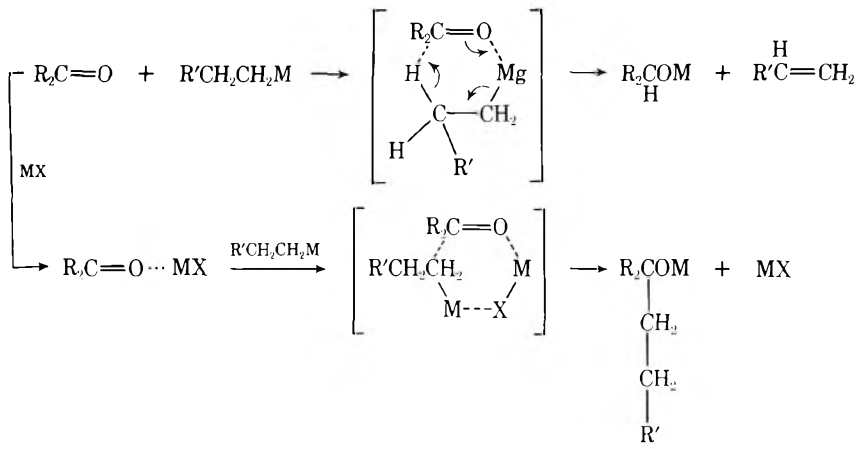
Reaction of $(C_2H_5)_3Al$ with 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$ complex gave significant percentages of ethylation, methylation, and reduction. The similarity between this reaction and the addition of $(CH_3)_3Al$ and $(C_2H_5)_3Al$ in 1:1 ratio to 4-*tert*-butylcyclohexanone as well as the similarity of the predominant isomer (equatorial alcohol) arising from methylation and ethylation in both cases indicates that in the first case redistribution of the alkyl groups between $(C_2H_5)_3Al$ and ketone–$Al(CH_3)_3$ is much faster than alkylation. Triethylaluminum addition to ketone–$AlCl_3$ complex leads to ethyl entry predominantly from the axial side (compression effect) accompanied by a much larger percentage of reduction than $(C_2H_5)_3Al$ addition to uncomplexed ketone. Compounds of the type $(C_2H_5)_nAlX_{3-n}$ give larger ethylation:reduction ratios than $(C_2H_5)_3Al$ when X is electron donating (CH_3) and smaller ratios when X is electron withdrawing (Cl). Attempts to introduce *n*-butyl groups into 4-*tert*-butylcyclohexanone and 2-methylcyclopentanone from the more hindered side by reaction of *n*-butyllithium with ketone–AlR_3 and ketone–$AlCl_3$ complexes were not successful. Alkylation of these complexes gave about the same ratio of isomeric alcohols as did *n*-butyllithium. Analysis of the results of these latter reactions indicates that the reactions did not occur via the corresponding ate complexes, $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n*, since the latter gave a significantly larger percentage of methylation and reduction, respectively.

One of the more potentially fruitful recent developments in the area of stereoselective alkylation of ketones has been the discovery that reaction of $(CH_3)_3Al$ with alicyclic ketones in 2:1 ratio in hydrocarbon solvent causes attachment of the methyl group at the carbonyl site predominantly (90%) from the most hindered side.[3,4] Unfortunately, the method is limited in those cases where the organoaluminum reagent possesses β hydrogens in that reduction products are formed.

The present work involves a study of reactions of $(C_2H_5)_3Al$ and *n*-C_4H_9Li with aluminum alkyl and aluminum chloride complexes of 4-*tert*-butylcyclohexanone and 2-methylcyclopentanone (ketones displaying a large compression effect)[3c] in order to investigate the possibility of bonding groups other than methyl or phenyl, particularly those that possess a β hydrogen, to the more hindered side of the ketones in high yield. The object of adding the RLi or R_3Al compounds to a complexed ketone was not only to direct the R group to the most hindered side of the carbonyl group (compression effect), but also to hinder the possibility of reduction by the ethyl or butyl group via β-hydrogen transfer. In addition, the potential of compounds such as $(CH_3)_nAl(C_2H_5)_{3-n}$, $(CH_3)_nAlCl_{3-n}$, and $(C_2H_5)_n$-$AlCl_{3-n}$ were investigated as stereoselective alkylating agents. In each case, special attention was given to the total percentages of the various possible alkylation–reduction products as well as to the ratio of isomeric alcohols obtained from alkylation and reduction.



Experimental Section

Materials. Trimethylaluminum and triethylaluminum were obtained from Texas Alkyls, Inc., and distilled through a 12-in. glass helix packed column at reduced pressure. *n*-Butyllithium, obtained from Foote Mineral Co. as a clear hexane solution, was used without further purification. 2-Methylcyclopentanone, obtained from Chemical Samples Co., was dried over activated 4-A molecular sieve prior to use. Frinton Laboratories 4-*tert*-butylcyclohexanone and Fisher reagent grade anhydrous aluminum chloride were sublimed under nitrogen prior to use. Fisher Certified thiophene-free benzene was distilled from $NaAlH_4$ prior to use.

Apparatus and Procedure. Transfers of materials used in this study were carried out in a glove box described elsewhere.[5] Calibrated syringes equipped with stainless steel needles were used for transfer of reagents. Deliveries could be reproduced to better than ±0.5%. Solutions of ketones were prepared by weighing out a known amount of ketone in a calibrated volumetric flask and diluting to the mark with benzene. Solutions of ketone–$AlCl_3$ complexes were prepared by adding an appropriate amount of ketone solution in benzene to a weighed amount of $AlCl_3$ in a volumetric flask and diluting to the mark with benzene.[3c] These solutions were used within 24 hr of preparation in every case. Solutions of organoaluminum compounds were prepared by diluting known amounts of the standard reagents with benzene. The concentrations of organoaluminum solutions were determined by hydrolysis of an aliquot followed by aluminum analysis which was carried out by EDTA–zinc acetate titration at pH 4 using dithizone as an indicator. Solutions of *n*-butyllithium were hydrolyzed and lithium analysis was carried out by flame photometry.

Preparations. "Mixed aluminum alkyls" [$(C_2H_5)_2AlCH_3$, $(CH_3)_3Al_2(C_2H_5)_3$, etc.] were prepared by mixing appropriate volumes of standard trimethyl- and triethylaluminum solutions in a volumetric flask and diluting to the mark.[6] Dimethylaluminum *n*-propoxide was prepared by addition of an appropriate amount of *n*-propyl alcohol to standard $(CH_3)_3Al$ solution. Alkylaluminum chlorides were prepared by adding an appropriate amount of standard aluminum alkyl solution to a weighed amount of $AlCl_3$ in a volumetric flask and diluting to the mark. Reaction was indicated by the fact that all the aluminum chloride dissolved. $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n* were prepared by adding an appropriate amount of *n*-butyllithium in hexane to the standard solution of aluminum alkyl in benzene. Ate complex formation was indicated by the immediate appearance of a white precipitate.

Reactions. All reactions were carried out in 6 × 0.625 in. test tubes equipped with 12/30 ground glass joints and stoppers. The test tubes were flamed, taken under vacuum through the glove box entry port, and flushed with high-purity nitrogen once inside the glove box.

In those cases involving the addition of alkylating agent to ketone–$Al(CH_3)_3$ and ketone–$Al(C_6H_5)_3$ complexes, the following procedure was used. An appropriate amount of ketone was placed in the test tube followed by addition of a sufficient amount of complexing agent to yield a 1:1 ketone–aluminum alkyl complex. The test tube was shaken briefly to ensure mixing and an appropriate amount of alkylating agent was added. The time elapsed between addition of the complexing agent and addition of the alkylating agent was about 10–15 sec and never more than 25 sec.

In those reactions involving addition of alkylating agents to ketone or ketone–$AlCl_3$ complex, appropriate amounts of alkylating agent were added to the ketone or ketone–$AlCl_3$ when a 1:1 ratio was desired and ketone or ketone–$AlCl_3$ was added to alkylating agent when a 2:1 or greater alkylating agent:substrate ratio was desired.

All reaction mixtures were immediately stoppered after addition of reagents and although the addition process generally resulted in thorough mixing, the tubes were shaken. In those reactions involving a solid alkylating agent, i.e., $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n*, and in those in which a precipitate immediately formed, i.e., additions of *n*-C_4H_9Li to ketone–$Al(CH_3)_3$, ketone–$Al(C_6H_5)_3$, and ketone–$AlCl_3$ complexes, continuous stirring was accomplished via a Teflon stirring bar. All reaction mixtures were allowed to stand stoppered overnight in the glove box and were removed and hydrolyzed about 20 hr after mixing. The solvent in all reactions was benzene except those involving organolithium compounds, when the solvent was benzene–hexane.

Product Analysis. All reactions were hydrolyzed with distilled water and after hydrolysis 3,3,5-trimethylcyclohexanone was added as an internal standard. Those mixtures involving alkylations of 4-*tert*-butylcyclohexanone were all analyzed by GLC employing a 22 ft × 0.125 in. stainless steel column of 10% FFAP on Diatoport-Sat (115°). The following order of emergence of the standard and all possible products occurs under these conditions: 3,3,5-trimethylcyclohexanone (standard) > axial alcohol (methylation) > 4-*tert*-butylcyclohexanone > equatorial alcohol (methylation) > axial alcohol (reduction) > axial alcohol (ethylation) > equatorial alcohol (reduction) > equatorial alcohol (ethylation) > axial alcohol (butylation) > equatorial alcohol (butylation). The axial alcohols from reduction and ethylation and the equatorial alcohols from reduction and ethylation do not completely separate under these conditions, although the separation is good. In order to estimate the area associated with each alcohol, a straight line was dropped from the trough between the two peaks perpendicular to the base line and was considered to be the separation point of the peaks. Overlap between the two butylation isomers is even more serious. The butylation products take an extremely long time to emerge under these conditions (about 6 hr) and have very long frontside slopes which drop rapidly to the base line after the peak is reached. The area corresponding to each butylation isomer was estimated in the following fashion. The total area for both isomers was measured. The forward slope corresponding to the equatorial alcohol (second peak) was extrapolated to the base line and the area measured. This area was considered to be the area corresponding to the equatorial alcohol. Substraction of this area from the total area then gave the area corresponding to the axial alcohol. A sample of the butylation isomers obtained by reaction of 4-*tert*-butylcyclohexanone with *n*-butyllithium was analyzed by both GLC and NMR in DMSO-d_6. In the NMR, the equatorial OH protons and the axial OH protons are completely separated with the axial OH protons absorbing at higher field.[3] The isomer percentage obtained by NMR and the GLC method described agreed within 2%. All remaining samples involving butylation of 4-*tert*-butylcyclohexanone were analyzed by GLC.

Those mixtures involving alkylation of 2-methylcyclopentanone were analyzed by GLC employing a 15 ft × 0.125 in. stainless steel column of 10% diglycerol on Chromosorb W at 80°. The order of emergence of the standard and all products analyzed is the following: 2-methylcyclopentanone > cis alcohol (methylation) > 3,3,5-trimethylcyclohexanone (standard) > trans alcohol (methylation) = cis alcohol (reduction) > trans alcohol (reduction) > cis alcohol (butylation) > trans alcohol (butylation). Since it was impossible to separate the cis alcohol (reduction) from the trans alcohol (methylation), the total amount of both methylation and re-

duction is reported in those reactions where both occurred; however, no isomer ratios are given (Table VI). The isomeric butylation products gave broad peaks under the conditions cited but separated completely from all other products and from one another.

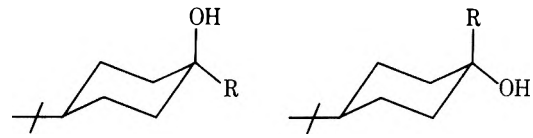
The material balances for all reactions reported were essentially 100% except for those reactions involving alkylaluminum chlorides or alkylations of 4-*tert*-butylcyclohexanone–$AlCl_3$ complexes. In the latter cases, the material balances were ~80% and a number of small unidentified peaks appeared in the GLC. No attempt was made to measure isomer ratios due to phenylation of the ketones because of decomposition of these alcohols under GLC conditions.

Results and Discussion

Table I reports on the results of the reaction of trimethylaluminum with 4-*tert*-butylcyclohexanone and 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$ complex. Two possible paths were envisioned for the latter reaction. Path I assumes that only ethylation would be observed if (1) alkyl exchange between $(C_2H_5)_3Al$ and the ketone–$Al(CH_3)_3$ is slow compared to ethylation and (2) methylation via intramolecular rearrangement of the $R_2C{=}O{\cdots}Al(CH_3)_3$ complex is slow compared to ethylation.[7] Reduction should not be possible via this scheme, since the organoaluminum compound possessing the β hydrogens is not complexed to the carbonyl oxygen.[8]

The results in Table I indicate that redistribution of alkyl groups between $(C_2H_5)_3Al$ and ketone–$Al(CH_3)_3$ complex occurs much faster than alkylation. In these reactions methylation, ethylation, and reduction all occur to a significant extent and in about the same ratios as alkylations with the corresponding $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds.

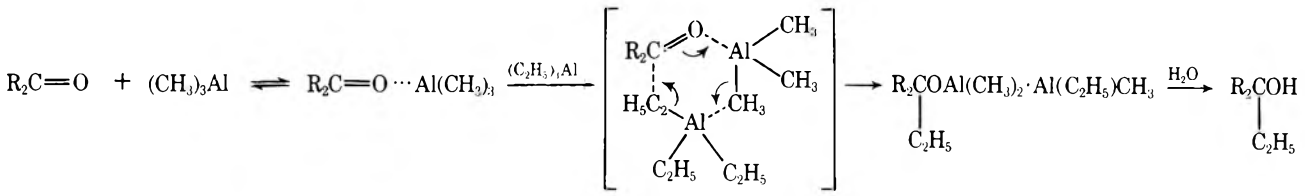
Several other interesting facts are demonstrated by the data in Table I. First, in all cases of alkylation (methylation and ethylation) where the ratio of organoaluminum compound to ketone was 1:1, the predominant attack was from the equatorial side to give predominantly the axial alcohol (steric approach control), whereas when excess organoaluminum compound was employed the preferred attack was from the more hindered axial side, giving predominantly equatorial alcohol (compression effect). Second, while



axial alcohol equatorial alcohol

methyl and ethyl groups are transferred at about the same rate from $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds, statistical correction of the data to account for the methyl:ethyl ratio indicates that ethyl groups are transferred more rapidly than methyl groups when the organoaluminum:ketone ratio is 1:1, whereas methyl groups are transferred more rapidly than ethyl groups when excess organoaluminum compound is used. Third, the ethylation:reduction ratio is somewhat higher in alkylations with $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds than with triethylaluminum itself. For example, in a 1:1 reactant ratio, the ratio of ethylation to reduction is 1.7:1 for triethylaluminum and averages 2.3:1 for $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds, whereas employing excess organoaluminum compound the ethylation:reduction ratio is 2.8:1 for triethylaluminum and averages 3.6:1 for $(CH_3)_nAl(C_2H_5)_{3-n}$ compounds. Finally, it should be pointed out that the ratio of axial to equatorial alcohol for the reduction reaction does not change significantly regardless of the organoaluminum compound employed. This re-

Path I. Redistribution Slow Compared to Ethylation



Path II. Redistribution More Rapid Than Ethylation

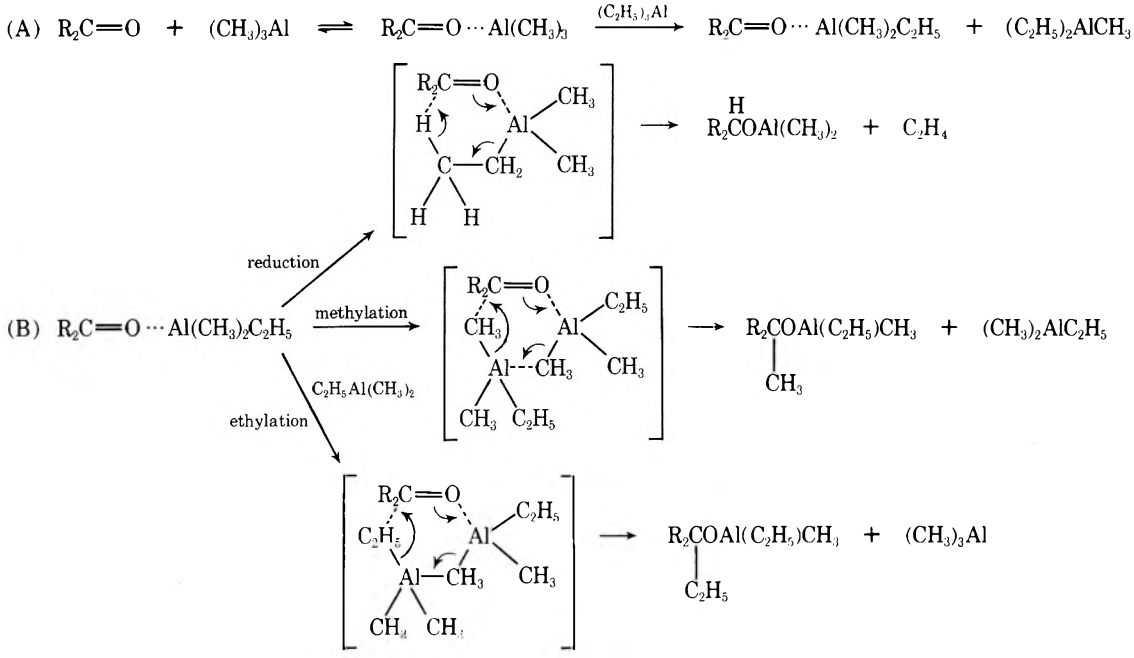


Table I
Reaction of $(C_2H_5)_3Al$ with 4-*tert*-Butylcyclohexanone and 4-*tert*-Butylcyclohexanone–$Al(CH_3)_3$ Complex.[a] Reaction of $(C_2H_5)_3Al_2(CH_3)_3$, $(C_2H_5)_2AlCH_3$, and $C_2H_5Al(CH_3)_2$ with 4-*tert*-Butylcyclohexanone

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Methylation %			Ethylation %			Reduction %			Recovered[d] ketone, %
				Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial alcohol	
$(C_2H_5)_3Al$	Ketone	0.179	1.0				64	79	21	36	19	81	46
$(C_2H_5)_3Al$	Ketone	0.204	2.9				74	12	88	26	25	75	0
$(C_2H_5)_3Al$	Ketone–$Al(CH_3)_3$	0.094	1.0	54	31	71	37	35	65	9	23	77	6
$(C_2H_5)_3Al$	Ketone–$Al(CH_3)_3$	0.151	2.9	26	23	77	53	12	88	21	27	73	2
$(C_2H_5)_3Al_2(CH_3)_3$	Ketone	0.050	0.5	35	79	21	42	79	21	23	21	79	51
$(C_2H_5)_3Al_2(CH_3)_3$	Ketone	0.098	1.5	50	11	89	38	12	88	12	22	78	0
$C_2H_5Al(CH_3)_2$	Ketone	0.170	1.0	58	80	20	29	71	29	13	24	76	39
$C_2H_5Al(CH_3)_2$	Ketone	0.191	3.0	66	12	88	27	12	88	7	24	76	0
$(C_2H_5)_2AlCH_3$	Ketone	0.174	1.0	21	73	27	60	79	21	19	26	74	48
$(C_2H_5)_2AlCH_3$	Ketone	0.198	3.1	30	11	89	56	10	90	14	23	77	0

[a] Complexes formed by $(CH_3)_3Al$ addition to ketone followed in 10–20 sec by addition of $(C_2H_5)_3Al$. [b] Normalized as % methylation alcohols + % ethylation alcohols + % reduction alcohols = 100%. [c] Normalized as % axial alcohol + % equatorial alcohol = 100%. [d] Normalized as % total alcohol + % ketone = 100%.

Table II
Reaction of $(CH_3)_3Al$ with 4-*tert*-Butylcyclohexanone and 4-*tert*-Butylcyclohexanone–$AlCl_3$ Complex. Reaction of $(CH_3)_3Al_2Cl_3$, $(C_2H_5)_3Al_2Cl_3$, $(CH_3)_2AlCl$, and $(C_2H_5)_2AlCl$ with 4-*tert*-Butylcyclohexanone

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Alkylation %			Reduction %			Recovered[c] ketone, %
				Total[a]	Axial[b] alcohol	Equatorial[b] alcohol	Total[a]	Axial[b] alcohol	Equatorial[b] alcohol	
$(CH_3)_3Al$	Ketone–$AlCl_3$	0.182	0.98	100	10	90	0			76
$(CH_3)_3Al$	Ketone–$AlCl_3$	0.202	1.94	100	11	89	0			11
$(C_2H_5)_3Al$	Ketone–$AlCl_3$	0.193	1.00	0			100	19	81	56
$(C_2H_5)_3Al$	Ketone–$AlCl_3$	0.214	2.00	17	20	80	83	28	72	8
$(CH_3)_3Al_2Cl_3$	Ketone	0.113	0.50	100	54	46	0			77
$(CH_3)_3Al_2Cl_3$	Ketone	0.127	1.00	100	13	87	0			52
$(CH_3)_2AlCl$	Ketone	0.217	1.00	100	56	44	0			69
$(CH_3)_2AlCl$	Ketone	0.244	2.00	100	9	91	0			15
$(C_2H_5)_3Al_2Cl_3$	Ketone	0.115	0.50	35	57	43	65	27	73	80
$(C_2H_5)_3Al_2Cl_3$	Ketone	0.121	0.93	43	23	77	57	17	83	32
$(C_2H_5)_2AlCl$	Ketone	0.223	1.00	31	65	35	69	20	80	31
$(C_2H_5)_2AlCl$	Ketone	0.250	2.00	41	27	73	59	26	74	6

[a] Normalized as % alkylation alcohols + % reduction alcohols = 100%. [b] Normalized as % axial alcohol + % equatorial alcohol = 100%. [c] Normalized as % total alcohol + % ketone = 100%.

sult is consistent with the cyclic six-center transition state proposed for the reduction reaction.[8]

Table II illustrates the reactions of $(CH_3)_3Al$ and $(C_2H_5)_3Al$ with 4-*tert*-butylcyclohexanone–$AlCl_3$ complex as well as the reactions of methyl- and ethylaluminum chloride with 4-*tert*-butylcyclohexanone. Addition of the organoaluminum compounds to the ketone–$AlCl_3$ complex leads to predominantly axial attack, indicating operation of the compression effect, as expected.

Compounds such as $(CH_3)_nAlCl_{3-n}$ and $(C_2H_5)_nAlCl_{3-n}$ alkylate with little discrimination in 1:1 aluminum alkyl: ketone ratio (steric approach control); however, alkylation takes place predominantly from the axial side in 2:1 ratio. The percentage of equatorial attack in 1:1 ratio is considerably less than that formed from the corresponding aluminum alkyls, whereas the percentage of axial attack in a 2:1 ratio is about the same as that formed from the corresponding aluminum alkyls.

One striking observation (Table II) is the large percentage of reduction product formed in reactions involving $(C_2H_5)_nAlCl_{3-n}$ compounds as compared to $(C_2H_5)_3Al$ (see Table I). This is consistent with the observation by Mole that in alkylation of benzophenone, the ethylation:reduction ratio greatly decreases when $(C_2H_5)_2AlC_6H_5$ is employed rather than $(C_2H_5)_3Al$.[6a] Thus, it appears that in compounds of the type $(C_2H_5)_nAlX_{3-n}$, the ethylation is enhanced when X is electron donating (CH_3), thus increasing the reactivity of the Al–C_2H_5 bond, whereas reduction is enhanced when X is electron withdrawing (Cl) as expected for groups that decrease the reactivity of the Al–C_2H_5 bond. Another interesting observation is that the addition of 2 mol of $(C_2H_5)_3Al$ to 1 mol of ketone–$AlCl_3$ complex gave 83% reduction. This result is sufficiently different from the addition of 2 mol of $(C_2H_5)_2AlCl$ to 1 mol of ketone (59% reduction) that a clear choice between paths I and II cannot be made in these cases.

Table III illustrates the reaction of $(CH_3)_3Al$ *with* 4-*tert*-butylcyclohexanone in the presence of $(CH_3)_2AlOC_3H_7$-*n*. Since dimethylaluminum alkoxides are formed during the course of alkylation of ketones by $(CH_3)_3Al$, it was of interest to observe the effect of this type of compound on the steric course of alkylation when present initially. Surprisingly, $(CH_3)_2AlOC_3H_7$-*n* alkylated the ketone in very small yield with predominantly equatorial attack (85%). Isomer ratios obtained from alkylations in the presence of $(CH_3)_2AlOC_3H_7$-*n* were essentially the same as those obtained with $(CH_3)_3Al$ alone. This result may appear surprising in view of the reports that $(CH_3)_2AlOR$ compounds

Table III
Reaction of $(CH_3)_2AlOC_3H_7$-*n* with 4-*tert*-Butylcyclohexanone. Reaction of $(CH_3)_3Al$ with 4-*tert*-Butylcyclohexanone in the Presence of $(CH_3)_2AlOC_3H_7$-*n* and with 4-*tert*-Butylcyclohexanone–$Al(C_6H_5)_3$ Complex

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Product isomer ratio[a]		Relative % yield[b]
				Axial alcohol	Equatorial alcohol	
$(CH_3)_2AlOC_3H_7$-*n*	Ketone	0.158	1.0	85	15	5.2
$(CH_3)_2AlOC_3H_7$-*n*		0.172	2.0	86	14	10
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.088	1.0	78	32	49
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.122	2.0	14	86	100
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.141	3.0	10	90	100
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.044	1.0	36	64	0.6[c]
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.072	2.0	27	73	2.2[c]

[a] Methylation product. [b] Normalized as % ketone + % alcohols = 100%. [c] Methylation % as determined by an internal standard. The major product of these reactions is apparently phenylation.

Table IV
Reaction of $(CH_3)_2AlOC_3H_7$-*n* with 2-Methylcyclopentanone. Reaction of $(CH_3)_3Al$ with 2-Methylcyclopentanone in the Presence of $(CH_3)_2AlOC_3H_7$-*n* and with 2-Methylcyclopentanone–$Al(C_6H_5)_3$ Complex

Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Product[a] of		Relative % yield[b]
				Trans attack	Cis attack	
$(CH_3)_2AlOC_3H_7$-*n*	Ketone	0.185	1.0	Trace[c]		0
$(CH_3)_2AlOC_3H_7$-*n*	Ketone	0.187	2.0	Trace[c]		0
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.096	1.0	53	47	50
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.129	2.0	34	66	75
$(CH_3)_3Al$	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.147	3.0	18	82	100
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.046	1.0	32	68	2.7[d]
$(CH_3)_3Al$	Ketone–$Al(C_6H_5)_3$	0.074	2.0	9	91	11[d]

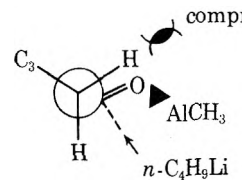
[a] Methylation or phenylation product. [b] Normalized as % alcohol + % ketone = 100%. [c] Cis alcohol predominates. [d] Methylation % as determined by an internal standard. The major product of these reactions is apparently phenylation.

form stable complexes with $(CH_3)_3Al$ of the type $(CH_3)_2AlOR{\cdot}Al(CH_3)_3$,[8,9] which renders $Al(CH_3)_3$ relatively unreactive.[8] However, Mole has pointed out that these complexes are formed in high yield only by addition of $(CH_3)_3Al$ to ketone in 2:1 ratio and are formed in very low yield by addition of $(CH_3)_3Al$ to a solution of $(CH_3)_2AlO$-R.[9a] Also, $(CH_3)_2AlOC_3H_7$-*n* may have less tendency to complex $(CH_3)_3Al$ compared to those alkoxides previously studied.[9]

Table III also illustrates the reaction of $(CH_3)_3Al$ with 4-*tert*-butylcyclohexanone–$Al(C_6H_5)_3$ complex. In these reactions the equatorial alcohol (methylation) predominates (compression effect). The extremely small yield of methylation product indicates rapid exchange with ketone–$Al(C_6H_5)_3$ to give compounds of the type $(CH_3)_n$-$Al(C_6H_5)_{3-n}$ (path II). Mole has shown that reaction of $(CH_3)_2AlC_6H_5$ with benzophenone yields triphenylcarbinol as the exclusive product;[6a] thus the major product of the reaction via path II is expected to arise via phenylation.

Table IV illustrates the results of the reaction of 2-methylcyclopentanone with the same reagents employed in Table III. The results are analogous.

Table V illustrates the reactions of *n*-butyllithium with 4-*tert*-butylcyclohexanone and with 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$, –$Al(C_6H_5)_3$, and –$AlCl_3$ complexes in hydrocarbon solvent. It was expected that attack on the complexes might lead to a compression effect, yielding a high



degree of axial attack by the butyl group. Reaction of *n*-butyllithium with 4-*tert*-butylcyclohexanone in all ratios in the presence or absence of $(CH_3)_2AlOC_3H_7$-*n* gave about 66% equatorial attack (steric approach control).

Reaction of *n*-butyllithium with 4-*tert*-butylcyclohexanone–$Al(CH_3)_3$ and –$Al(C_6H_5)_3$ complexes at 1:1 and 3:1 lithium alkyl:complex ratios gave about 80% equatorial attack. Thus, contrary to expectation, axial attack was even less favored in the presence of the complexing agents. These reactions were characterized by the immediate formation of a precipitate upon addition of the *n*-C_4H_9Li solution to the complex, suggesting that the reaction may have proceeded via ate complex formation ($LiAlR_3C_4H_9$-*n*) followed by alkylation of the ketone. However, the results shown in Table V indicate that this explanation cannot be the case. For example, when *n*-C_4H_9Li was added to $(CH_3)_3Al$–ketone complex in a 1:1 ratio the methylation: butylation ratio was 18:82 and the percent axial alcohol (butylation) was 79%, whereas when a suspension of $LiAl(CH_3)_3C_4H_9$-*n* was stirred overnight with ketone in a

Table V

Reaction of *n*-Butyllithium with 4-*tert*-Butylcyclohexanone and 4-*tert*-Butylcyclohexanone-$AlCl_3$, -$Al(CH_3)_3$, and -$Al(C_6H_5)_3$ Complexes[a] in Benzene-Hexane. Reaction of $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n* with 4-*tert*-Butylcyclohexanone in Benzene-Hexane

				Methylation %			Butylation %			Reduction %			
Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Total[b]	Axial[c] alcohol	Equatorial[c] alcohol	Recovered[d] ketone, %
n-C_4H_9Li	Ketone	0.149	1.04				100	67	33	0	0	0	8.2
n-C_4H_9Li	Ketone	0.369	3.02				100	63	37	0	0	0	1.3
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.149	1.04	1.5	75	25	98.5	70	30	0	0	0	10.5
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.369	3.02	1.1	80	20	98.9	65	35	0	0	0	4.1
n-C_4H_9Li	Ketone-$Al(CH_3)_3$	0.155	1.03	18	53	47	82	79	21	Trace			8.0
n-C_4H_9Li	Ketone-$Al(CH_3)_3$	0.382	3.03	9.7	68	32	90.3	81	19	0	0	0	5.5
n-C_4H_9Li	Ketone-$Al(C_6H_5)_2$	0.053	0.96					81	19	0	0	0	*d*
n-C_4H_9Li	Ketone-$Al(C_6H_5)_3$	0.155	3.04					77	23	0	0	0	*d*
n-C_4H_9Li	Ketone-$AlCl_3$	0.263	1.00				35	67	33	65	40	60	42
n-C_4H_9Li	Ketone-$AlCl_3$	0.452	1.97				60	65	35	40	33	77	16
$LiAl(CH_3)_3C_4H_9$-*n*	Ketone	0.156	1.05	86	43	57	14	65	35	Trace	0	0	37
$LiAl(C_6H_5)_3C_4H_9$-*n*	Ketone	0.052	1.06					65	35		34	66	*d*

[a] Complexes formed by organoaluminum reagent to ketone followed in 10–20 sec by addition of n-C_4H_9Li. [b] Normalized as % methylation alcohols + % butylation alcohols + % reduction alcohols = 100%. [c] Normalized as % axial alcohol + % equatorial alcohol = 100%. [d] Normalized as % total alcohol products + % ketone = 100%. % phenylation not directly determined.

Table VI

Reaction of *n*-Butyllithium with 2-Methylcyclopentanone and Complexes[a] of 2-Methylcyclopentanone with $(CH_3)_3Al$ and $(C_6H_3)_3Al$ in Benzene-Hexane. Reaction of $LiAl(CH_3)_3C_4H_9$-*n* and $LiAl(C_6H_5)_3C_4H_9$-*n* in Benzene-Hexane

					Butylation %			
Reagent	Substrate	Reagent concn, *M*	Reagent: substrate ratio	Total[b]	Trans[c] attack (cis alcohol)	Cis[c] attack (trans alcohol)	Methylation + reduction %	Recovered[d] ketone, %
n-C_4H_9Li	Ketone	0.172	1.05	100	87	13		18
n-C_4H_9Li	Ketone	0.416	3.04	100	78	22		6.2
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.172	1.05	100	82	18	Trace	12.0
n-C_4H_9Li	1:1 ketone + $(CH_3)_2AlOC_3H_7$-*n*	0.416	3.04	100	80	20	0	20.0
n-C_4H_9Li	Ketone-$Al(CH_3)_3$	0.179	1.03	95.7	86	14	4.3	17
n-C_4H_9Li	Ketone-$Al(CH_3)_3$	0.432	3.02	100	79	21	0	0.5
n-C_4H_9Li	Ketone-$Al(C_6H_5)_3$	0.056	.97		76	24	Trace redn	*d*
n-C_4H_9Li	Ketone-$Al(C_6H_5)_3$	0.155	3.02		77	23		*d*
$LiAl(CH_3)_3C_4H_9$-*n*	Ketone	0.177	1.04	90.3	78	22	9.7	50
$LiAl(CH_3)_3C_4H_9$-*n*	Ketone	0.058	1.00		80	20	Measurable redn	*d*

[a] Complexes formed by rapid addition of organoaluminum reagent to ketone followed by addition in 10–20 sec of n-C_4H_9Li. [b] Normalized as % methylation alcohol + % butylation alcohol + % reduction alcohol = 100%. [c] Normalized as % cis alcohol + % trans alcohol = 100%. [d] Normalized as % total alcohol products + % ketone = 100%. % phenylation not directly determined.

1:1 ratio the methylation:butylation ratio was 86:14 and the percent axial alcohol (butylation) was 65%. These results are far too different to suggest that alkylation occurred via the ate complex in both cases. Since the mechanism of addition of n-C_4H_9Li to ketone-AlR_3 complexes is not known, no judgment can be made as to why the observed isomer ratio is obtained.

Addition of n-C_4H_9Li to 4-*tert*-butylcyclohexanone-$AlCl_3$ complex gives large amounts of reduction as well as butylation. This result is presumably due to redistribution via path II to produce $(C_4H_9)_nAlCl_{3-n}$ compounds, which would be expected to react predominantly as reducing agents. This was the only case where a significant amount of reduction occurred except for addition of $LiAl(C_6H_5)_3C_4H_9$-*n* to ketone. These reactions all give the same ratio of axial to equatorial alcohol (butylation) as did simple addition of n-C_4H_9Li to ketone. Reactant ratio did not appear to be a factor in the observed isomer ratio obtained in any of these reactions.

Table VI illustrates the reaction of 2-methylcyclopentanone with the reagents described in Table V. In every case the percent axial alcohol formed was ~80%. Thus, n-C_4H_9Li attacking ketone or complex and ate complex attacking ketone gave essentially identical results. It is interesting that in the reaction of $LiAl(CH_3)_3C_4H_9$-*n*, 90% of the reaction proceeds via butylation and <10% via methylation, whereas in the case of reaction with 4-*tert*-butylcyclohexanone, 86% methylation and only 14% butylation were observed.

Registry No.—$(C_2H_5)_3Al$, 97-93-8; $(C_2H_5)_3Al_2(CH_3)_3$, 54617-81-1; $(C_2H_5)_2AlCH_3$, 13197-84-7; $C_2H_5Al(CH_3)_2$, 13197-83-6; $(CH_3)_3Al$, 75-24-1; $(CH_3)_3Al_2Cl_3$, 15455-52-4; $(C_2H_5)_3Al_2Cl_3$, 12075-68-2; $(CH_3)_2AlCl$, 1184-58-3; $(C_2H_5)_2AlCl$, 96-10-6;

$(CH_3)_2AlOC_3H_7$-*n*, 54549-33-6; $LiAl(CH_3)_3C_4H_9$-*n*, 54549-40-5; $LiAl(C_6H_5)_3C_4H_9$-*n*, 54549-45-0; 4-*tert*-butylcyclohexanone, 98-53-3; 2-methylcyclopentanone, 1120-72-5; *n*-butyllithium, 109-72-8; 4-*tert*-butylcyclohexanone-$Al(CH_3)_3$, 54549-41-6; 4-*tert*-butylcyclohexanone-$Al(C_6H_5)_3$, 54549-44-9; 2-methylcyclopentanone-$Al(C_6H_5)_3$, 54549-43-8; 4-*tert*-butylcyclohexanone-$AlCl_3$, 54549-39-2; 2-methylcyclopentanone-$Al(CH_3)_3$, 54549-42-7.

References and Notes

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(2) To whom correspondence should be addressed.
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Abnormal Products Obtained during an Attempted Substitution of 3α,5-Cyclo-6β-methoxy-5α-23,24-bisnorcholan-22-ol Tosylate with a Grignard Reagent Involving γ,γ-Dimethylallyl Bromide

Sunil K. Dasgupta and Marcel Gut*

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

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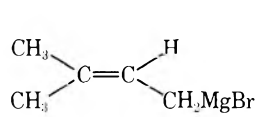
Attempted coupling of 6β-methoxy-3α,5-cyclo-5α-23,24-bisnorcholan-22-yl tosylate (**2a**) with γ,γ-dimethylallyl bromide (**1**) in the presence of magnesium leads to the formation of 22,22′-bis-6β-methoxy-3α,5-cyclo-5α-bisnorcholanyl (**6**), a novel disteroid, and 3α,5-cyclo-5α-23,24-bisnorcholan-6β-yl methyl ether (**5**) rather than to the expected desmosterol derivatives. The formation of these products has been attributed to a common 22-bisnorcholanylmagnesium bromide intermediate which undergoes Wurtz-type coupling or is hydrolyzed to an alkane during work-up.

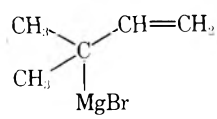
In our recently reported synthesis of desmosterol,[1] we tested the utility of allylic organometallics as synthons for construction of the steroid side chain. Recent communications[2,3] along similar lines prompted us to report the results of our experiments.

The chemistry of allyl Grignard and allyllithium reagents has been well documented.[4,5] Notable problems associated with the use of these reagents are self-coupling and allylic rearrangements of the Grignard reagents, which leads to mixtures of isomeric products. Unsymmetrical allylic Grignard reagents react with unhindered electrophilic substrates, such as carbonyl compounds[6] and epoxides,[7,8] to afford branched products. Less branched carbinols are preferentially formed, however, in reactions with relatively hindered ketones. This phenomenon, as suggested by Felkin and coworkers,[9,10] is due to the differences in the steric strain in the two possible allylic transition states.

A NMR study of γ,γ-dimethylallylmagnesium bromide[11] has indicated that the reagent exists as a rapidly equilibrating pair of classical structures (**1a** and **1b**) with the



1a



1b

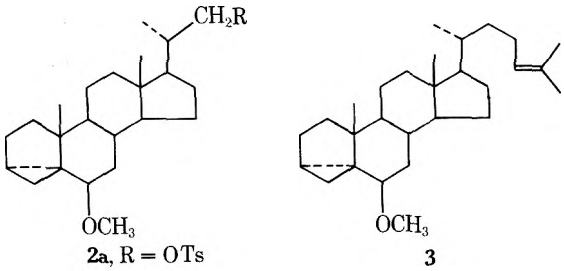
equilibrium well on the side of form **1a**. Reaction of **1** with carbon dioxide[12] and with cyclohexanone[5] has been reported to give a tertiary acid and a tertiary carbinol, respectively, suggesting the predominance of form **1b**. γ,γ-Dimethylallyllithium, however, when treated with an equimolar amount of the allylic bromide in a cross-coupling reaction, gives rise to mixtures[5] of direct and transposed products with allylic transposition limited to the allylic portion derived from either **1a** or **1b**.

It was therefore of interest to determine whether 3α,5-cyclo-22-tosyloxy-5α-23,24-bisnorcholan-6β-ol 6-methyl ether (**2a**) could be successfully substituted with the allyl Grignard reagent **1**. Coupling of aryl Grignard reagents with alkyl sulfates and sulfonates is well known and has been reviewed by Kharasch.[13] Earlier, it was observed that the tosylate **2** could be easily displaced with sodium iodide[1,3] or with sodium salts of activated methylene compounds.[14] Recently it has been also shown[3] that the tosylate **2** undergoes a smooth nucleophilic displacement with the lithium salt of 3-methyl-1-butyn-3-ol tetrahydropyranyl ether. Our specific interest in the attempted allyl Grignard reaction, however, was to examine the reaction products for the presence of compound **3** and the product of allylic transposition **4**. The latter was envisaged as a key intermediate for the preparation of 23,23-dimethylcholesterol, a substance desirable to us for biological oxidation studies.

The coupling experiment was carried out under the conditions described by Seyferth[15,16] for magnesium-induced condensation of triphenyltin chloride with allyl bromide. The reaction mixture was separated by column chromatography, but none of the products could be identified as the expected structures **3** or **4**. Instead, two crystalline steroidal products differing in their respective mobility on thin layer chromatography were isolated.

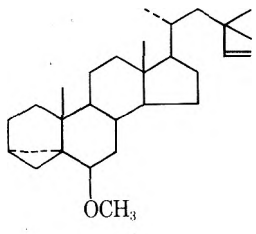
The less polar product showed infrared spectral bands at 1090, 1010, and 970 cm^{-1}, indicating the presence of a 6-methoxy *i*-steroid moiety. This was supported by the appearance of signals at 3.32 (3 H), 2.77 (1 H), and broad multiplets at 0.33–0.67 ppm in the NMR spectrum, confirming the presence of a methyl ether residue, 6α-H, and cyclopropyl hydrogens, respectively. The other characteristic methyl proton signals, besides the two singlets at 0.72 (3 H) and 1.01 (3 H) ppm due to 18- and 19-methyls, were three sharp peaks at 0.78, 0.89, and 0.99 ppm (J = 6 Hz, 6 H). The latter three signals would seem to represent a pair of overlapping doublets for two methyls which could be due to 21 and 22 secondary methyls. This speculation was con-

firmed by the NMR spectrum of **7**, which also exhibited three sharp signals at 0.78, 0.89, and 0.99 ppm (J = 6 Hz, 6 H) in addition to the singlets for 18- and 19-methyls see Experimental Section). The mass spectrum of the less polar product (m/e 330, M^+) and the other spectral data are in reasonable agreement with the proposed structure **5**. This structure was confirmed by comparison of its ir and NMR spectra and mixture melting point with those of an authentic sample of **5**. Its preparation will be described later.



2a, R = OTs
b, R = Br

3



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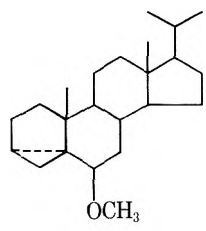

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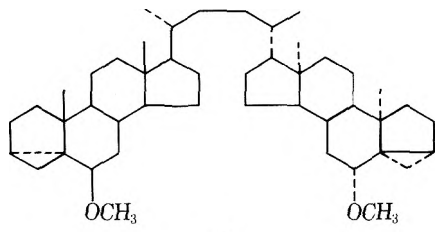

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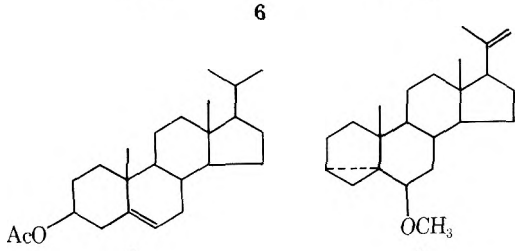
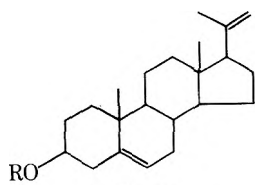


7 **8**



9a, R = H
b, R = Ac
c, R = Ts
d, R = Me

The more polar steroidal product also exhibited the usual ir and NMR signals associated with a 3,5-cyclo-6-methoxy moiety described above. The NMR spectra further revealed the presence of 18- and 19-methyls as denoted by two singlets at 0.70 and 1.01 ppm, respectively. However, the characteristic signals at 0.78, 0.88, and 0.98 ppm assigned to the 21 and 22 secondary methyls of structure **5** were conspicuously absent. A vinylic methyl group and the ABX pattern[17] of the olefinic $-CH=CH_2$ protons were absent as well, thus proving that the dimethylallyl residue had not been coupled in either of its two forms, **1a** or **1b**. The mass spectrum exhibits a molecular ion at m/e 658, suggesting that the product results from the coupling of the two C_{22} steroid units, derived from the 22-tosylate **2a**. On the basis of the spectral evidence, and from mechanistic considerations (see later), structure **6** has been assigned to the more polar product. It is likely that a common intermediate is involved in the generation of **5** and **6** during the Grignard reaction. Since the composition[18] of the Grignard solution may involve the Schlenk[19] equilibrium, i.e., $2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons R_2Mg \cdot MX_2$, both R_2Mg and MgX_2 could compete for reaction with electrophilic substrates. The 22-tosylate **2a** is readily converted to the 22-bromide (**2b**) under conditions of a Grignard reaction.[3] The bromide **2b** could then form an organomagnesium derivative which, on decomposition with water, would result in the formation of the hydrocarbon **5**. Moreau et al.[2] observed the formation of a hydrocarbon derivative from an analogous 22-bromide during a coupling with γ,γ-dimethylallyl bromide in the presence of magnesium, but attributed the process to a reductive elimination involving a cyclic seven-membered transition state. In our opinion, the facile decomposition of Grignard reagents with water to yield hydrocarbons is too well known[20,21] to warrant any other explanation. The disteroid **6**, however, was formed by a Wurtz-type coupling of the organomagnesium derivative.

An authentic sample of **5** was prepared by lithium aluminum hydride reduction of the tosylate **2a**, as well as by catalytic reduction of the 20-methylene derivative **8**. The latter was prepared by the solvolysis of the tosyl derivative **9c** of the previously described 3-hydroxy compound **9a** in the presence of pyridine and methanol. Compound **7** was prepared by controlled catalytic reduction of **9b** in the presence of 5% Pd on calcium carbonate.

Experimental Section

Melting points are uncorrected. NMR spectra, reported in parts per million, were obtained in deuteriochloroform solution on a 60-MHz Varian Associates DA-60 spectrometer using tetramethylsilane as an internal reference. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Attempted Coupling of 3α,5-Cyclo-22-tosyloxy-5α-23,24-bisnorcholan-6β-yl Methyl Ether (2a) with γ,γ-Dimethylallyl Bromide in the Presence of Magnesium. In a flask were placed 150 mg of magnesium shavings, 3 ml of anhydrous ether, and a trace of iodine. A drop of γ,γ-dimethylallyl bromide was added and the mixture was stirred under nitrogen at 20°. After a few minutes the brown color of the iodine began to fade to a cloudy yellow. A solution of 0.45 g of γ,γ-dimethylallyl bromide, previously distilled under reduced pressure, and 1 g of 3α,5-cyclo-6β-methoxy-5α-23,24-bisnorcholan-22-ol tosylate (**2a**) in 4 ml of anhydrous tetrahydrofuran was added with stirring to the gently refluxing magnesium suspension during 5 hr. After the addition was complete, 5 ml of dry benzene was added and the reaction mixture was heated to reflux for an additional 5 hr. The complex was decomposed by cautious addition of ice-cold saturated ammonium chloride solution. The mixture was transferred to a separatory funnel and extracted with ether. The ether extract was washed repeatedly with saturated brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, leaving behind a gum which was dissolved in hexane and chromatographed on 45 g of alumina. The hexane eluates furnished 250 mg of an oil which was further purified by preparative layer chromatography on 1 mm thick silica gel plates developed with benzene–hexane (1:1). There was obtained 150 mg of 3α,5-cyclo-5α-23,24-bisnorcholan-6β-yl methyl ether (**5**): mp 61–63° (acetone); ir 1090, 1010, and 970 cm^{-1} (6-OMe-i); NMR 0.72 (18-CH_3), one pair of overlapping doublets 0.78, 0.89, 0.99 (J = 6 Hz, 21-, 22-methyls), 1.01 (19-CH_3), 3.32 (6β-OCH_3), broad multiplets at 0.33–0.67 (cyclopropyl hydrogens) and 2.77 ppm (6α-H); mass spectrum m/e 330 (M^+), 315 (M − CH_3), 298 (M − CH_3OH), 283 [M − (CH_3OH + CH_3)], 272 [M −

(CH_3 + $(CH_3)_2CH$)], 268 [M − (MeOH + $2CH_3$)], 255 [M − (MeOH + $(CH_3)_2CH$)].

Anal. Calcd for $C_{23}H_{38}O$: C, 83.57; H, 11.59. Found: C, 83.80; H, 11.64.

Eluates combining 5–10% benzene in hexane furnished 200 mg of a glass, which on purification by preparative layer chromatography on 1 mm thick silica gel plates, developed with 10% hexane–benzene, gave 125 mg of 22,22′-bis-6β-methoxy-3α,5-cyclo-5α-23,24-bisnorcholanyl (**6**): mp 95° (acetone); ir 1090, 1010, and 965 cm^{-1} (6-OMe-*i*); NMR 0.70 (18-CH_3), 1.01 (19-CH_3), 3.32 (6β-OCH_3), broad multiplets at 0.33–0.67 (cyclopropyl hydrogens) and 2.77 ppm (6α-H); mass spectrum *m/e* 658 (M^+), 643 (M − 15), 626 (M − CH_3OH), 611 [M − (MeOH + CH_3)].

Anal. Calcd for $C_{46}H_{74}O_2$: C, 83.82; H, 11.32. Found: C, 83.85; H, 11.38.

23,24-Bisnorchol-5-en-3β-ol Acetate (7). A solution of 200 mg of 20-methylenepregn-5-en-3β-ol acetate (**9b**)[23] in 10 ml of ethyl acetate was magnetically stirred under an atmosphere of hydrogen in the presence of 80 mg of 5% palladium on calcium carbonate. Uptake of the calculated amount of hydrogen was over in 30 min. The ethyl acetate suspension was filtered through Celite. Evaporation of the filtrate furnished a solid which was recrystallized from a methylene chloride–methanol solution to give 185 mg of the 20-methyl derivative **7**: ir 1720 cm^{-1} (CH_3COO–); NMR 0.67 (18-CH_3), one pair of overlapping doublets 0.78, 0.89, 0.99 (J = 6 Hz, 21-, 22-methyls), 1.01 (19-CH_3), 2.02 (acetate methyl), 4.64 (3α-H), and 5.36 ppm (6 H).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.51; H, 10.83.

3α,5-Cyclo-5α-23,24-bisnorcholan-6β-yl Methyl Ether (5) by the Lithium Aluminum Hydride Reduction of 6β-Methoxy-3α,5-cyclo-5α-23,24-bisnorcholan-22-ol Tosylate (2a). A solution of 500 mg of the tosylate **2a**[1] in 10 ml of anhydrous tetrahydrofuran was added slowly to a stirred slurry of 200 mg of lithium aluminum hydride in 10 ml of tetrahydrofuran. After the addition was complete, the mixture was refluxed for 6 hr. It was decomposed by the cautious addition of 2 *N* sodium hydroxide solution. The tetrahydrofuran solution was filtered through Celite. Concentration of the filtrate gave a residue which was dissolved in hexane and filtered through a short column of alumina. The hexane eluates furnished 250 mg of **5**, which was recrystallized from acetone, mp 61–63°, melts unchanged on admixture with the less polar product obtained from the previously described coupling experiment; ir and NMR were found to be identical.

23,24-Bisnorchola-5,20-dien-3β-ol Tosylate (9c). A solution of 2 g of 23,24-bisnorchola-5,20-dien-3β-ol (**9a**)[22] and 2.6 g of *p*-toluenesulfonyl chloride in 32 ml of dry pyridine was left standing for 18 hr at 5°. Cold water was added dropwise while stirring and the resulting precipitate was filtered off and washed with a large excess of water. Crystallization from hexane furnished 1.8 g of **9c**: mp 95–99°; ir 1180 and 1145 (tosylate), 890 cm^{-1} (=CH_2).

Anal. Calcd for $C_{29}H_{40}O_3S$: C, 74.36; H, 8.55. Found: C, 74.38; H, 8.59.

3α,5-Cyclo-5α-23,24-bisnorchol-20-en-6β-yl Methyl Ether (8). A solution of 1.8 g of the tosylate **9c** in 13 ml of anhydrous pyridine and 190 ml of dry methanol was heated on a steam bath for 2 hr, after which time the methanol was removed by distillation in vacuo. After the addition of water the mixture was extracted with ethyl acetate. The organic extract was washed with 2 *N* acetic acid. Then the extract was washed with water, saturated bicarbonate solution, and again with water. It was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was dissolved in hexane and chromatographed over 60 g of alumina. Careful elution with hexane furnished 400 mg of an oil which showed a single spot on TLC. An analytical sample was crystallized from methanol: mp 41–42°; ir 1090, 1010, and 965 (6-OMe-*i*), 891 cm^{-1} (=CH_2); NMR 0.63 (18-CH_3), 1.02 (19-CH_3), 1.75 (21 olefinic methyl), 3.33 (6β-OCH_3), broad multiplets at 0.33–0.67 (cyclopropyl hydrogens), 2.77 (6α-H), multiplets at 4.69–4.86 ppm (terminal methylene).

Anal. Calcd for $C_{23}H_{36}O$: C, 84.08; H, 11.05. Found: C, 84.36; H, 10.82.

23,24-Bisnorchola-5,20-dien-3β-yl Methyl Ether (9d). The eluates with 10% benzene in hexane of the above-mentioned chromatography furnished 150 mg of crystalline **9d**: mp 88–89° (MeOH); NMR 0.58 (18-CH_3), 1.00 (19-CH_3), 3.33 (3β-OCH_3), 1.75 (21 olefinic methyl), multiplets at 4.69–4.86 (22 terminal methylene) and 5.34 ppm (6 H).

Anal. Calcd for $C_{23}H_{36}O$: C, 84.08; H, 11.05. Found: C, 83.90; H, 10.96.

3α,5-Cyclo-5α-23,24-bisnorcholan-6β-yl Methyl Ether (5) from 8. A solution of 100 mg of 8 was dissolved in 5 ml of ethyl acetate and stirred under an atmosphere of hydrogen in the presence of 50 mg of 5% palladium on calcium carbonate. Uptake of hydrogen was complete in 30 min. The ethyl acetate solution was filtered through Celite and concentrated to dryness. The residue, on crystallization from acetone, furnished 90 mg of **5**, mp 61–63°, not depressed by admixture with the other samples described previously.

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Registry No.—**2a**, 51231-24-4; **5**, 54446-73-0; **6**, 54446-74-1; **7**, 33168-84-2; **8**, 54446-75-2; **9a**, 17879-91-3; **9b**, 38388-16-8; **9c**, 54446-76-3; **9d**, 54446-77-4; γ,γ-dimethylallyl bromide, 870-63-3; *p*-toluenesulfonyl chloride, 98-59-9.

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(23) This compound was prepared by the acetylation of **9a**[22] with pyridine and acetic anhydride and gave mp 128–131°; ir 1720, 1230 (CH_3COO–), 1615, 887 cm^{-1}; NMR 0.58 (18-CH_3), 1.03 (19-CH_3), 1.78 (olefinic 21-methyl), 2.03 (acetate methyl), 4.73–4.87 (terminal methylene), and 5.41 ppm (6 vinylic proton).

Substituent Effects on Rates and Equilibria for Benzaldehyde–Benzaldehyde Dimethyl Acetal Interconversion[1]

T. S. Davis,[2] P. D. Feil,[2] D. G. Kubler,*[3] and D. J. Wells, Jr.[2]

Department of Chemistry, Furman University, Greenville, South Carolina 29613

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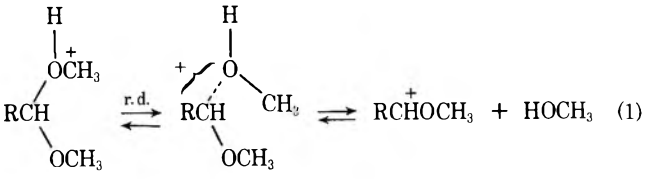
The rates of formation and the rates of hydrolysis of para-substituted benzaldehyde dimethyl acetals have been determined in 95% methanol–5% water at 15, 25, and 35°. Equilibrium constants, thermodynamic constants (ΔG, ΔH, and ΔS) and activation parameters (E_a, $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) have been calculated from the rate data. The mechanistic implications of these results are discussed.

The evidence supporting the accepted mechanism for the hydrolysis of acetals is substantial and has been reviewed critically by Cordes.[4] To the extent that this accepted mechanism is correct, one can have considerable confidence, via microscopic reversibility, that the mechanism for the formation of acetals is just the reverse of the hydrolytic mechanism. The rate-determining step for the hydrolysis of acetals in water is considered to be the formation of the alkoxycarbonium ion from the protonated acetal. Mechanism studies of the formation reaction are sparse and the studies of the hydrolytic reaction have revealed little about the nature of the steps beyond the formation of the alkoxycarbonium ion. However, it is just these steps in which we must be most interested for understanding the mechanism for the formation of acetals.



(1)

Most studies of the hydrolysis of acetals have been performed in water or in dioxane–water. There are a number of comments in the literature which suggest, but do not substantiate, that alcohol–water mixtures are undesirable for the study of the hydrolysis of acetals.[4,5,6] There are good reasons for avoiding the use of primary alcohols in a mixture with water if one is interested only in the hydrolysis of acetals and if one wishes to completely repress the formation reaction.

If one wishes to study the formation of acetals from aldehydes and alcohols, then alcohols are the solvent(s) of choice, but if one wishes to study both acetal formation and acetal hydrolysis under identical conditions, then alcohol–water mixtures are necessary.

In previous studies from this laboratory, we reported the equilibrium constants for the formation of dimethyl acetals of aromatic aldehydes, cyclic ketones, and acyclic ketones in methanol–water mixtures.[7] Based upon these data we estimated that a solvent mixture of 95% methanol–5% water would give sufficient reaction in both directions to permit us to study the rates of acetal formation and of acetal hydrolysis without changing the solvent composition. We have verified this estimate and have completed a study of substituent effects and of temperature effects on the hydrolysis of and on the formation of dimethyl acetals of benzaldehydes in 95% methanol–5% water. The results and conclusions are reported herein.

Experimental Section

Preparation and Purification of Reagents. Methanol (Union Carbide Chemicals Co.) was purified in 3-l. batches by the method of Lund and Bjerrum.[8] Each batch was distilled on a 1.5 × 45 cm protruded metal-packed column until the transmittance was 97% or better against a specially purified sample of water at 256 mm (Beckman DU spectrophotometer). In all cases the water content (Karl Fischer) was less than 0.01% (usually 0.005% or less).

95% methanol–5% water 0.100 *m* sodium perchlorate was prepared in kilogram lots in the following manner. A 2-l. flask was tared on a solution balance (±0.2 g) and 950 g of spectral grade methanol was added followed by 50.00 ml (pipet) of spectral grade water (distilled and deionized) and 12.245 g of sodium perchlorate (G. Frederick Smith Co. reagent grade). The sodium perchlorate was used as received except for drying in a 110° oven. The pH of each batch of sodium perchlorate was measured as a function of concentration in water and did not change from that of the water.

Perchloric acid solution was prepared by adding 2–3 ml of concentrated perchloric acid (J. T. Baker) to about 500 ml of 95% methanol–5% water that was 0.1 *m* in sodium perchlorate. The acid solution was standardized by titration with aqueous KOH solution (phenolphthalein end point.) The acid and base solutions were standardized biweekly.

Aldehydes. Benzaldehyde (J. T. Baker), *p*-tolualdehyde, furfural, and *p*-anisaldehyde (all from Columbia Organic Chemicals Co.) were each washed three times with 5% sodium bicarbonate and once with water, dried over sodium bicarbonate, and distilled under vacuum. The aldehydes were collected in melting point capillary tubes and sealed under vacuum. This procedure was necessary because even the minimal exposure of the aldehydes to air by the rapid sample transfer with a nitrogen flush caused sufficient oxidation of the aldehydes to prevent attainment of reproducible extinction coefficients and reproducible rate constants.

The distillation system (Ace micro Vigreux assembly) had a four-armed "cow" attached and two of these arms supported small flasks to receive the forerun and afterrun. The other two arms each supported a receiver constructed from a 24/40 female joint sealed at the end and having a small side arm at an angle near the bottom. The side arm was sealed with a silicone rubber septum cap. The melting point capillary tube was sealed on one end, washed with spectral grade methanol, and weighed on an analytical balance. The open end was inserted through the septum cap. When sufficient middle-cut aldehyde had distilled into the receiver, the capillary tube was dipped below the surface of the liquid and a slight increase in pressure was applied to the system by nitrogen. When sufficient liquid (0.05–0.08 g) was in the tube, the end was removed from the surface of the liquid and slight nitrogen pressure was used to push the liquid to the closed end. With the system still under vacuum the tube was sealed off and the tube was pulled off at the seal point. The two parts of the tube were weighed to obtain the weight of the contained aldehyde. Repeated weighings of blank tubes demonstrated a high reproducibility of the weighing procedure.

The weighed, sealed tubes were crushed under the surface of the solvent in a volumetric flask. The flask was filled to the mark with solvent. The aldehyde solution was used for dilution for the kinetic runs and for dilutions to check the extinction coefficients. Repeated preparations of the solutions by the sealed-tube method throughout this work gave extinction coefficients which varied by less than ±1%.

p-Bromobenzaldehyde and *p*-chlorobenzaldehyde were purified by recrystallization from hexane and then vacuum sublimed. These solid aldehydes gave the same extinction coefficients by this handling procedure as we obtained using the sealed-tube method. Apparently these solid aldehydes are much less susceptible to air oxidation than are the liquid aldehydes. The observed properties of the aldehydes are summarized in Table I.

Table I
Physical Properties of Aromatic Aldehydes

Aldehyde	Bp (mmHg)[a] or mp, °C	nD (temp, °C)	ϵ, M^{-1} cm^{-1}	λ_{max}, nm	Registry no.
p-Anisaldehyde	92 (4)	1.5693 (25)	16,700	283.5	123-11-5
Benzaldehyde	39 (5)	1.5450 (15)	1,250	281	100-52-7
p-Bromobenzaldehyde	57–59		15,200	258	1122-91-4
p-Chlorobenzaldehyde	47–48		1,100	289[b]	104-88-1
Furfural	29 (4)	1.5241 (20)	14,900	271	98-01-1
p-Tolualdehyde	55 (4)	1.5430 (20)	14,600	262	104-87-0

[a] The boiling points (melting points) and nD values of these well-known compounds all compare closely with those found in handbooks. [b] This wavelength is not λ_{max} but a shoulder and was used because the corresponding dimethyl acetal absorbed sufficiently at λ_{max} to interfere in the analysis.

Table II
Properties of Dimethyl Acetals of Aromatic Aldehydes[a,b]

Dimethyl acetal of	Bp, °C (mmHg)	n^{25}D	Registry no.
p-Anisaldehyde	86 (1.6)	1.5029	2186-92-7
Benzaldehyde	73 (10)	1.4898	1125-88-8
p-Bromobenzaldehyde	94 (3.3)	1.5296	24856-58-4
p-Chlorobenzaldehyde	90 (6)	1.5076	3395-81-1
Furfural	56 (12)	1.4488	1453-62-9
p-Tolualdehyde	54 (1.1)	1.4916	3395-83-3

[a] All of these acetals had molar extinction coefficients of less than 200 at λ_{max} for the corresponding aldehyde except for *p*-chlorobenzaldehyde. Because of this fact, the molar absorption of the acetal solution never exceeded 0.05 at the start of a hydrolysis run for the concentrations used. [b] Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and satisfactory values (±0.4% for C and H) were found for all compounds.

Dimethyl acetals of the aromatic aldehydes were prepared by mixing 0.1 mol of aldehyde, 0.15 mol of trimethyl orthoformate, 15 ml of methanol, and 2 drops of concentrated hydrochloric acid. The solutions were maintained at room temperature for 1 or 2 days and made basic to test paper by the addition of potassium hydroxide in methanol. The low-boiling materials were removed at a water aspirator at room temperature and the residue was fractionated on a Nester-Faust platinum spinning band column having about 25 theoretical plates. An infrared spectrum and a refractive index were obtained for each fraction. Those fractions having the same refractive index (±0.0003) and showing no carbonyl absorption in the infrared were combined. The acetals were stored in the dark in brown bottles and redistilled (micro Vigreux column) just before use in the kinetic experiments. Freshly prepared solutions (methanol–water) for the acetals were used to show the absence or near absence of absorption at the wavelength used for the kinetic studies. The properties measured for these acetals are recorded in Table II.

Rate Measurements. The rate at which aldehyde disappeared (acetal formation) or at which aldehyde appeared (acetal hydrolysis) was followed by monitoring the carbonyl absorption (at the wavelength specified in Table I) with a Beckman DU spectrophotometer as a function of time. The special cell holder and temperature regulation system has been described elsewhere.[9] With this system the temperature can be controlled to at least ±0.025° (widest variation between any two places in the three quartz cells over a period of several hours) over the range of at least 10–45°. Temperatures were monitored in the cell holder throughout the kinetic runs by means of a Hewlett-Packard Model 2801A quartz thermometer (relative readings to ±0.001° and absolute readings to ±0.02°). The readings in the cells were calibrated relative to the readings in the cell holder and the quartz thermometer was calibrated with ice (made from distilled water). All temperature readings reported are those in the light path in the cell and are corrected.

A volume of standard perchloric acid solution (0.06–0.08 M) sufficient to give a final $[H_3O^+]$ of about 10^{-4} M (but of known value) was pipetted into a 100-ml volumetric flask and diluted to the mark with the solvent. Various amounts of acid were used depending upon the rate of reaction of the particular aldehyde or acetal being studied. The aldehydes (or acetal) were added to the reaction system as diluted solutions in the solvent. These solutions were prepared by weighing the aldehyde (or acetal) just prior to beginning the kinetic experiments and the concentration ranges were 10^{-2}–10^{-3} M.

Exactly 1 ml of the diluted perchloric acid solutions was added to each of three 10-ml volumetric flasks by means of a 5-ml buret (±0.001 ml readings). Eight milliliters (buret) of the solvent was added to each of two flasks. The third flask was diluted to the mark (temperature bath) with solvent and served as the reference solution. The two flasks reserved for reaction mixtures were equilibrated in the temperature bath and the reaction was initiated by the addition (pipet) of 1 ml of the aldehyde or acetal solution (timer started). The solutions were transferred to the spectrophotometer cells and readings were usually started within about 2 min of mixing. Absorbance readings were taken at 1–1.5-min intervals over the 15–35-min reaction period. Generally about 20 absorbance readings were recorded. As the system began to approach equilibrium (taken to be an absorbance change of less than 0.002 over 2–3 min), the second run was started. The solutions were maintained in stoppered volumetric flasks in the constant-temperature bath and after about 10–12 half-lives the equilibrium absorbances were read and then checked 1 hr later. Most often these readings were made after the solutions remained in the constant-temperature bath overnight.

Calculations. The first-order reaction rate constants were calculated for the equilibration

$$RCHO + 2CH_3OH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} RCH(OCH_3)_2 + H_2O \qquad (2)$$

by means of standard expressions[10] modified for our analytical system. These expressions for reversible first-order processes follow.

(a) For acetal formation corrected for the hydronium ion concentration

$$k_1 = \frac{-(\text{slope})(A_0 - A_\infty)}{60\,A_0[H_3O^+]}\,M^{-1}\ \text{sec}^{-1} \qquad (3)$$

$$k_1 + k_2 = \frac{-(\text{slope})}{60[H_3O^+]}\,M^{-1}\ \text{sec}^{-1} \qquad (4)$$

with slope = ln $(A - A_\infty)$ vs. time (minutes).

(b) For acetal hydrolysis corrected for hydronium ion concentration

$$k_2 = \frac{-(\text{slope})[\text{aldehyde}]_\infty}{60[\text{acetal}]_0[H_3O^+]}\,M^{-1}\ \text{sec}^{-1} \qquad (5)$$

with slope = ln $(A_\infty - A)$ vs. time (minutes), and the $(k_1 + k_2)$ expression is the same as for acetal formation. A, A_0, and A_∞ are the measured absorptions at time t, at zero time, and at infinite time, respectively. All data were plotted to eliminate gross errors and calculations of the rate constants were made by the method of least squares on an IBM 1130 computer.

The activation parameters E_a, $\Delta H^\ddagger$, $\Delta S^\ddagger$, and $\Delta G^\ddagger$ were calculated by least-squares treatment of the rate constant-temperature data in the usual manner.[11] The error analyses for the values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ were calculated by the procedure recommended by

Table III
Rate and Equilibrium Data for the Formation and Hydrolysis of Dimethyl Acetals of Aromatic Aldehydes[a]

Aldehyde	Temp, °C	Acetal formation[b] k_1	Acetal formation[b] k_2[c]	Acetal hydrolysis[d] k_2	Acetal hydrolysis[d] k_1[c]	Average of all $(k_1 + k_2)$ values[e]	k_1[f]/k_2	$K_e \times 10^3$
p-Anisaldehyde	15.02	3.92	7.56	7.13	3.99	11.4 ± 0.2 (8)	0.550	2.01
	25.39	9.06	21.7	21.3	9.50	30.7 ± 0.6 (4)	0.426	1.56 (1.5)[g]
	35.04	15.7	46.6	46.2	17.5	63.0 ± 0.7 (4)	0.340	1.26
p-Tolualdehyde	15.02	2.09	1.11	1.07	2.18	3.21 ± 0.04 (9)	1.95	7.12
	25.39	4.82	3.26	3.30	4.92	8.16 ± 0.08 (4)	1.46	5.37 (6.6)
	35.04	9.60	7.31	7.96	9.36	17.1 ± 0.2 (5)	1.21	4.47
Benzaldehyde	15.02	0.782	0.150	0.152	0.765	0.924 ± 0.007 (4)	5.14	18.8
	20.00	1.13	0.247	0.257	1.10	1.37 ± 0.013 (6)	4.40	16.1
	25.39	1.74	0.495	0.510	1.80	2.26 ± 0.04 (6)	3.41	12.5 (14.2)
	30.04	2.64	0.858	0.897	2.70	3.55 ± 0.05 (4)	2.94	10.8
	35.04	3.68	1.42	1.36	3.60	5.02 ± 0.08 (4)	2.71	10.0
Furfural	15.02	0.363	0.164	0.158	0.370	0.527 ± 0.003 (4)	2.30	8.38
	25.39	0.841	0.504	0.513	0.814	1.34 ± 0.01 (4)	1.64	6.02 (7.4)
	35.04	1.64	1.22	1.38	1.69	2.94 ± 0.1 (5)	1.19	4.41
p-Chlorobenzaldehyde	15.02	0.303	0.033	0.032	0.314	0.340 ± 0.005 (5)	9.47	34.5
	25.39	0.761	0.106	0.116	0.762	0.872 ± 0.005 (4)	6.53	24.1
	35.04	1.74	0.285	0.360	1.70	2.04 ± 0.02 (6)	4.83	17.9
p-Bromobenzaldehyde	15.02	0.269	0.027	0.028	0.276	0.302 ± 0.006 (6)	9.61	35.0
	35.39	0.693	0.105	0.103	0.694	0.796 ± 0.002 (9)	6.73	24.7 (28.7)
	35.04	1.56	0.283	0.315	1.55	1.85 ± 0.01 (4)	4.95	18.4

[a] The reactions were conducted in 95% methanol–5% water with 0.1 *m* $NaClO_4$ and $HClO_4$ catalyst. [b] These data were determined by following spectrophotometrically the disappearance of the carbonyl absorbance (uv) for the reaction of the aldehyde with methanol to form the dimethyl acetal. k_1 values were calculated by eq 3 and $(k_1 + k_2)$ values by eq 4; k's in M^{-1} sec^{-1}. [c] Calculated from $(k_1 + k_2)$ data and the opposite rate constant. [d] These data were determined by following spectrophotometrically the appearance of the carbonyl absorbance (uv) for the reactions of the dimethyl acetal with water to form the aldehyde. k_2 values were calculated by eq 5 and $(k_1 + k_2)$ values by eq 4; k's in M^{-1} sec^{-1}. [e] This is the average of all $(k_1 + k_2)$ from forward and reverse measurements at each temperature. The number in parentheses is the number of values. [f] This ratio of rate constants is not K_e. The ratio is multipled by the factor $[H_2O]/[CH_3OH]^2$ to yield K_e. [g] The values in parentheses are the equilibrium constants measured by a static method which we previously reported.[7]

Wiberg.[12] The thermodynamic values, ΔH, ΔS, and ΔG, were calculated from the equilibrium constant–temperature data in the usual manner using the method of least squares.

Results

Rate and equilibrium constants at 15.02, 25.39, and 35.04° were calculated for the acid-catalyzed hydrolysis of the dimethyl acetals of *p*-anisaldehyde, benzaldehyde (also at 20.00° and 30.04°), *p*-bromobenzaldehyde, *p*-chlorobenzaldehyde, furfural, and *p*-tolualdehyde. The reactions were conducted in 95% methanol–5% water which was 0.100 *m* in sodium perchlorate with perchloric acid as the catalyst. Under identical conditions the rate constants and equilibrium constants were calculated for the acid-catalyzed formation of the dimethyl acetals from the corresponding aldehydes. The hydrolysis reaction (k_2) is first order each in the concentration of acetal and of hydronium ion. The formation reaction (k_1) is first order each in the concentration of aldehyde and of hydronium ion. Because of the solvent composition the system is swamped with the concentrations of methanol and of water and the order for these substances has not been determined. The rate law of constant salt concentration is of the form

$$k_{obsd} = k_{H_3O^+}[H_3O^+]$$

and all rate constants reported are those of $k_{H_3O^+}$ for unit concentration of hydronium ion. All of the rate constants are average values of at least two experiments and usually of three and four experiments. Values generally agreed to within ±1%. Discordant data were eliminated by the Q test.[13]

The rate constants at the specified temperatures are given in Table III for acetal formation and for acetal hydrolysis with the aldehydes listed in order of decreasing reactivity. Table III also includes the sums and ratios of the formation and hydrolysis rate constants as well as the equilibrium constants for acetal formation.

The acetal formation rate constants, k_1, were calculated from the net forward data by the use of eq 3 and the values of $k_1 + k_2$ were calculated by means of eq 4. The hydrolytic rate constants, k_2, were obtained directly from these forward rate values by the difference. The hydrolytic rate constants, k_2, were calculated from the net hydrolytic data by means of eq 5 and the values of $k_1 + k_2$ were calculated by means of eq 4. Again the opposite rate constants, k_1, were obtained by difference.

The forward and reverse reaction studies give an additional test of reproducibility of the data. One may compare the k_1 and the k_2 values for the formation data to those of the hydrolytic data and can see that these values are quite reproducible. A better evaluation is the average of the $k_1 + k_2$ values, forward and reverse, for a given aldehyde and its acetal at a given temperature. As may be seen in Table III, this gives at least four experiments for each aldehyde and its acetal and up to as many as nine experiments in some cases. The greatest deviation observed was a 3.4% average deviation for furfural at 35° and the least deviation was 0.3% average deviation for *p*-bromobenzaldehyde at 25°. The average of the average deviations for all of these values was 1.2%.

Calculations of the ratios of the rate constants (k_1/k_2) provided values which did not correspond with the equilibrium constants we had previously reported for acetal formation.[7] When these ratios of rate constants were multiplied by the factor $[H_2O]/[CH_3OH]^2$, the equilibrium constants did correspond with those we had previously mea-

Table IV
Activation and Reaction Parameters for the Formation and Hydrolysis of Dimethyl Acetals of Aromatic Aldehydes

Aldehyde or the dimethyl acetal	Formation reaction[a]				Hydrolysis reaction[b]				Calcd from activation values[c]			Calcd from equil – T data[d]		
	E_a, kcal mol^{-1}	$\Delta G^{\ddagger}_{298}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	E_a, kcal mol^{-1}	$\Delta G^{\ddagger}_{298}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	ΔG_{298}, kcal mol^{-1}	ΔH, kcal mol^{-1}	ΔS, eu	ΔG_{298}, kcal mol^{-1}	ΔH, kcal mol^{-1}	ΔS, eu
p-Anisaldehyde	12.4	20.0	11.8 ± 0.2	−27.5 ± 0.8	16.4	16.2	15.8 ± 0.2	−1.3 ± 0.6	3.8	−4.0	−26.2	3.8	−4.0 (−3.8)	−26.2 (−26)
p-Tolualdehyde	13.6	20.4	13.0 ± 0.2	−24.8 ± 0.5	17.5	17.3	16.9 ± 0.2	−1.2 ± 0.6	3.1	−3.9	−23.6	3.1	−4.0 (−5.2)	−23.8 (−28)
Benzaldehyde	14.3	20.9	13.7 ± 0.1	−24.3 ± 0.4	20.4	18.4	19.9 ± 0.2	+5.0 ± 0.9	2.5	−6.2	−29.3	2.6	−5.9 (−5.7)	−28.0 (−28)
Furfural	13.2	21.4	12.6 ± 0.1	−29.6 ± 0.2	18.8	18.4	18.2 ± 0.2	−0.44 ± 0.08	3.0	−5.7	−29.2	3.1	−5.6 (−5.6)	−29.0 (−29)
p-Bromobenzaldehyde	15.6	21.5	15.0 ± 0.1	−21.9 ± 0.3	21.2	19.3	20.0 ± 0.2	+4.2 ± 0.8	2.2	−5.6	−26.1	2.2	−5.8 (−4.7)	−26.8 (−23)
p-Chlorobenzaldehyde	15.4	21.5	14.8 ± 0.1	−22.4 ± 0.1	21.2	19.2	20.6 ± 0.1	+4.5 ± 0.5	2.2	−5.8	−26.9	2.2	−6.0	−27.4

[a] Calculated using $k_1 = k_{H_3O^+}/[CH_3OH]^2$. [b] Calculated using $k_2 = k_{H_3O^+}/[H_2O]$. [c] Calculated from formation parameters minus hydrolysis parameters. [d] Calculated from log K_e vs. $1/T$ data.

sured or with those which could be independently calculated for the rate systems from the initial and equilibrium concentrations. These equilibrium constants are of the same degree of reliability as the rate constants (better than ±2% average deviation), since they are derived from the rate constants and the concentrations of both the methanol and water are known to a greater accuracy than are the concentrations of the aldehydes and acetals. The values in Table IV in parentheses in the equilibrium column are those equilibrium constants we previously measured at 25°.[7] The agreement between the two methods is seen to be reasonably good but we consider the values reported for the kinetic study as being more reliable.

The activation parameters for acetal formation and for acetal hydrolysis are summarized in Table IV. Calculation of these parameters for forward and reverse reactions by the use of $k_{H_3O^+}$ variations with temperature provided values which did not sum exactly to the thermodynamic parameters calculated from the equilibrium constants variation with temperature. For this reason, we multiplied the forward rate constant, k_1, by the factor $1/[CH_3OH]^2$ and the reverse rate constant, k_2, by the factor $1/[H_2O]$. The values in Table IV in parentheses under the ΔH and ΔS columns for equilibrium are those we reported previously.[7] The earlier values, which agree reasonably with those reported here, are not as reliable because they were obtained from equilibrium constants measured at only two temperatures.

Discussion

Examination of the kinetic results summarized in Table IV reveals a number of interesting effects. The most evident effect of structural changes seen is that both the forward rate constants and the reverse rate constants increase as the electron-donating ability of the para substituent is increased. The effect holds over the temperature range studied. In contrast to this effect on rates, it is seen that the equilibrium constants for acetal formation show just the reverse effect with structure.

For all substituents except the *p*-methoxy, the forward rate constant is greater than the reverse rate constant for the temperatures studied. Both the forward and reverse rate constants increase with an increase in temperature but the reverse rates increase to a greater extent. This result means that the ratio k_1/k_2 decreases as the temperature increases, which is another statement that the equilibrium constants decrease with an increase in temperature. The fact that the acetal formation reaction is exothermic requires that the equilibrium constant decrease with an increase in temperature. However, the complete tautologism requires the statement that the kinetic reason for the change in equilibrium with temperature is that the enthalpy of activation is greater for the hydrolysis reaction for all substrates studied than is the enthalpy of activation for the acetal formation reaction.

The activation parameters for acetal formation were calculated from the rate constants in the form $k_1' = k_1/[CH_3OH]^2$. The activation parameters for acetal hydrolysis were calculated from the rate constants in the form $k_2' = k_2/[H_2O]$. If one wishes to compare energies of activation for the forward reaction with those for the reverse reaction or with the $\Delta H^{\ddagger}$ values or with the ΔH values, then these corrected rate constants are not necessary (except for slightly different slope values of E_a and $\Delta H^{\ddagger}$ owing to changes in concentrations of methanol and water as the temperature changes). However, these correction terms make significant differences in the values of $\Delta G^{\ddagger}$ and these, in turn, affect the values of $\Delta S^{\ddagger}$. Once the correction terms are made, the ratio $k_1'/k_1' = K_e$, and the activation parameters can be directly compared to the reaction parameters. As may be seen from Table IV, the reaction parameters calculated from the activation parameters agree quite closely (as they must) with those obtained from ln K_e vs. $1/T$ plots.

Entropies of activation have been used as mechanistic criteria to distinguish A-1 from A-2 reactions.[4,14] Reactions which proceed with unimolecular decomposition of a protonated substrate (A-1) are presumed to have entropies of activation near zero or somewhat positive. On the other hand, those reactions which proceed with nucleophilic attack of the solvent on the protonated substrate (A-2) are presumed to have entropies of activation which are large and negative. All evidence obtained to date indicates that acetal hydrolyses in water proceed by an A-1 mechanism in spite of certain ambiguities[4] and details of the mechanism seem to be fairly well understood.[15]

The entropies of activation for the hydrolysis of the six acetals (Table IV) are all near zero or slightly positive in

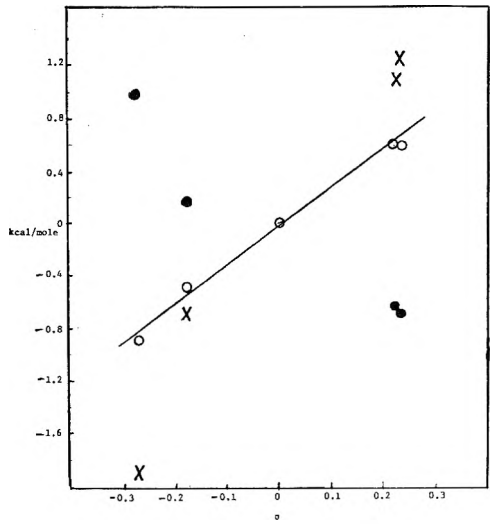


Figure 1. Plot of activation parameters for the acetal formation reaction vs. Hammett's σ: O, values for $\Delta\Delta G^{\ddagger}$; X, values for $\Delta\Delta H^{\ddagger}$; ●, values for $-T\Delta\Delta S^{\ddagger}$; only the $\Delta\Delta G^{\ddagger}$ point is placed on zero but both the $\Delta\Delta H^{\ddagger}$ and $-T\Delta\Delta S^{\ddagger}$ values are superposed.

95% methanol–5% water. This result clearly agrees with the results of other workers for acetal hydrolysis in various solvents and particularly in water. While the results for water may indicate an A-1 mechanism for acetal hydrolysis, that conclusion is not appropriate for 95% methanol–5% water. Methanol and water have about equal reactivities for the alkoxycarbonium ion based upon Cordes' work[4] and upon our unpublished results for methanol–water mixtures of 0.2–0.8 mol fraction methanol. On this basis it is probably not meaningful to speak of a rate-determining step for this reaction in either direction for the solvent used. The significance of the entropies of activation for acetal formation and for acetal hydrolysis for this solvent is not immediately evident.

Quantitative correlations of the data of Table III by means of the Hammett linear free energy equation have been made for all three temperatures. Fair correlations were obtained for all three temperatures for the forward data, the reverse data, and the equilibrium data. The values are given in Table V along with the correlation coefficients. The correlations were made by a least-squares treatment of log k/k_0 (benzaldehyde reference) vs. σ or of log K/K_0 (benzaldehyde reference) vs. σ. Plots of the data revealed slight but real curvatures for all nine correlations in spite of the fact that the correlation coefficients were all 0.95 or better. Utilization of other σ's did not improve significantly the correlations.

The particular features of these results to be noted are that the ρ values are significantly negative over the temperature range studied for both directions and that $\rho_e = \rho_1 -$

Table V
Hammett ρ Values for the Acetal Reaction for Rates and Equilibria[a]

	ρ values		
Calculated from	15°	25°	35°
Formation rate constants, k_1	−2.24 (0.997)	−2.15 (0.994)	−1.95 (0.995)
Reverse rate constants, k_2	−4.47 (0.982)	−4.29 (0.981)	−4.00 (0.979)
Equilibrium constants, K_e	2.25 (0.957)	2.14 (0.957)	2.05 (0.952)

[a] The numbers in parentheses are the correlation coefficients, r.

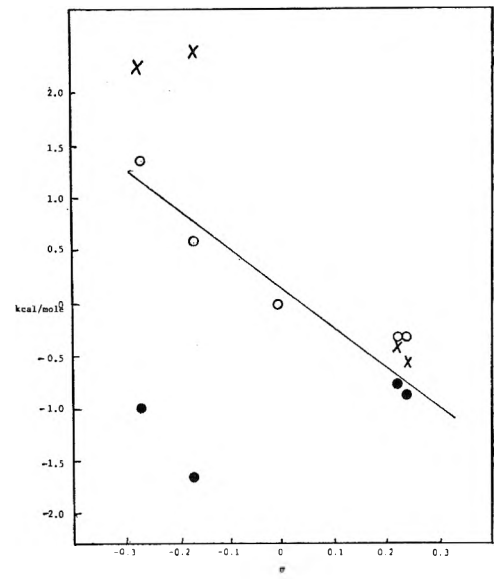


Figure 2. Plots of the equilibrium parameters for acetal formation vs. Hammett's σ: O, values for $\Delta\Delta G$; X, values for $\Delta\Delta H$; ●, values for $-T\Delta\Delta S$; only the $\Delta\Delta G$ point is placed on zero but both the $\Delta\Delta H$ and $-T\Delta\Delta S$ values are superposed.

ρ_2 (as it must from $K_e = k_1'/k_2'$). To the extent that one can rely upon the sign of ρ as an indicator of the charge quality of the transition state,[4,16] then these results suggest that this transition state is the developing (or reacting) alkoxycarbonium ion. However, one cannot be very sure of this conclusion for the reasons given in our discussion of entropies of activation.

For a plot of the activation parameters vs. σ (Figure 1) for the benzaldehydes in acetal formation we observe that the $\Delta\Delta G^{\ddagger}$ vs. σ is a sensibly linear plot but both $\Delta\Delta H^{\ddagger}$ and particularly $-T\Delta\Delta S^{\ddagger}$ vs. σ show considerably more scatter. The hydrolysis data provide similar correlations. In Figure 2 are shown similar plots for the equilibrium. In this case the $\Delta\Delta G$ vs. σ shows curvature but is made up of the two parts, $\Delta\Delta H$ vs. σ and $-T\Delta\Delta S$ vs. σ, both of which are largely scatter diagrams. For the rates in both directions, the slopes of the Hammett plots (see Figure 1) are determined predominantly by the changes in $\Delta H^{\ddagger}$ with structure. However, for equilibrium the slope of the Hammett plot (see Figure 2) is determined mainly by the changes in $-T\Delta S$ rather than by ΔH.[17]

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(1) Grateful acknowledgment is given to the National Institutes of Health for a grant (R01-AM-1124) in support of this work.
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Large Enhancement of Apparent Isomerization Rates in Endo vs. Exo Precursors for Trifluoromethanesulfonic Acid Catalyzed Tricycloundecane Rearrangements

Naotake Takaishi, Yoshiaki Inamoto,* and Koji Aigami

Industrial Research Laboratories, Kao Soap Company, Ltd., Wakayama 640-91, Japan

Eiji Osawa

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan

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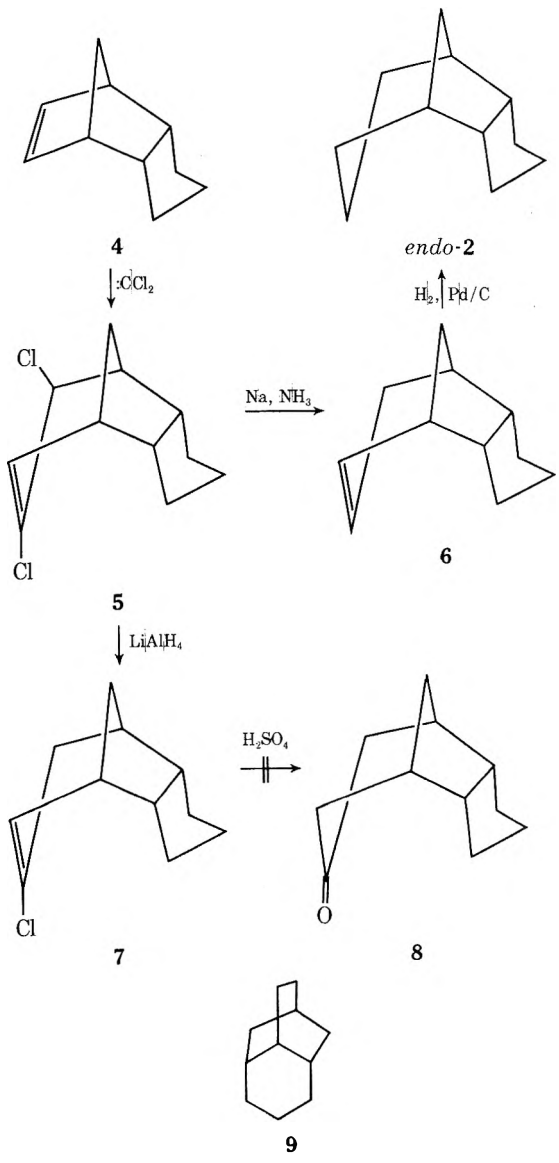
The rate of the trifluoromethanesulfonic acid catalyzed rearrangement of 2,3-*endo*-tetramethylenenorbornane (*endo*-**1**) and that of 6,7-*endo*-trimethylenebicyclo[3.2.1]octane (*endo*-**2**) were found to be 10^4 times larger than those of the corresponding exo isomers. 2,3-Trimethylenebicyclo[2.2.2]octane (**3**) was also as reactive as the endo compounds. 6,7-*endo*-Trimethylenebicyclo[3.2.1]octane (*endo*-**2**) was synthesized for the first time and the structure was established unambiguously by ^{13}C NMR spectroscopy. Product analysis for the isomerizations of endo precursors revealed some new aspects of the tricycloundecane rearrangement which have never been seen so far in the studies of the reactions of exo isomers.

Schleyer and his group[1] demonstrated that the pathway of the adamantane rearrangement of either *exo*- or *endo*-trimethylenenorbornane, (*exo*-**10** or *endo*-**10**) was such that these reactants at first gave an equilibrium mixture consisting of both isomers which then rearranged to adamantane via several steps. In contrast to this, no endo isomer (*endo*-**1**) was detected in the rearrangement of 2,3-*exo*-tetramethylenenorbornane (*exo*-**1**).[2-8] The difference between the behavior of the C_{10} and the C_{11} tricyclic hydrocarbons may be ascribed to either (or both) of two reasons: either that the equilibrium is further shifted to the exo isomer in C_{11} than in C_{10} precursors, or that *endo*-**1** is so reactive that it is present in too low a concentration to be detected. Measurement of the equilibrium between *endo*-**1** and *exo*-**1** in the presence of palladium on alumina catalyst[9] showed that the absence of *endo*-**1** during the rearrangement could not be accounted for by thermodynamic reasons. Fast disappearance of *endo*-**1**, if it is formed at all, is a remaining possibility which explains its absence. This prompted us to examine the rate of the isomerization of *endo*-**1**. Preparation and aluminum chloride catalyzed rearrangement of *endo*-**1** was reported by Whiting.[5] However, they did not find any difference between the reactivities of *endo*-**1** and *exo*-**1**, nor make any kinetic measurements.

6,7-*exo*-Trimethylenebicyclo[3.2.1]octane (*exo*-**2**), together with 4-homoisotwistane (tricyclo[5.3.1.$0^{3,8}$]undecane) (**9**)[6-8,10] and homoadamantane, was discovered by us[8] to be an intermediate in adamantane rearrangements of *exo*-**1** and 2,3-trimethylenebicyclo[2.2.2]octane (**3**).[11] Here again, no 6,7-*endo*-trimethylenebicyclo[3.2.1]octane (*endo*-**2**) was detected during the rearrangement, suggesting a high reactivity of *endo*-**2**. Since *endo*-**2** has never been prepared before, an unequivocal synthesis had to be established before the kinetic measurement.

Determination of the rate of the isomerization of these precursors was accomplished in refluxing methylene chloride solvent in the presence of trifluoromethanesulfonic acid, which was recently discovered by us[8] to be a very effective catalyst for the rearrangement. The system is homogeneous and, therefore, particularly suitable for use as the medium for the rate measurement.

Synthesis of 6,7-*endo*-Trimethylenebicyclo[3.2.1]octane (*endo*-2). A synthesis of *endo*-**2** was achieved by the application of the method of De Selms and Comb.[12] 3,4-Dichloro-6,7-*endo*-trimethylenebicyclo[3.2.1]oct-2-ene (**5**), obtained by dichlorocarbene ring expansion[13] of 5,6-*endo*-trimethylenenorborn-2-ene (**4**),[14] was reduced with metallic sodium in liquid ammonia[12] to 6,7-*endo*-trimethylenebicyclo[3.2.1]oct-2-ene (**6**), which on catalytic hydrogenation over palladium on charcoal gave *endo*-**2**. It is interesting



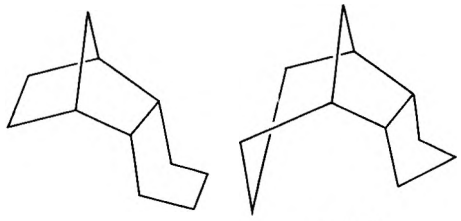
that sulfuric acid hydrolysis[13] of 3-chloro-6,7-*endo*-trimethylenebicyclo[3.2.1]oct-2-ene (**7**) (obtainable by lithium aluminum hydride reduction of **5**) did not give the hoped-for 6,7-*endo*-trimethylenebicyclo[3.2.1]octan-3-one (**8**) but only tarry materials, whereas acid hydrolysis was successfully applicable to 3-chloro-6,7-*exo*-trimethylenebicyclo-[3.2.1]oct-2-ene for the preparation of 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-3-one,[8] the exo isomer of **8**.

endo-**2** prepared in this way showed correct elemental analysis and a mass spectrum, and its total and off-resonance proton-decoupled ^{13}C NMR spectra[15] were consistent with the structure of *endo*-**2**. The compound was distinctively different from *exo*-**2** as indicated by the comparison of various spectral as well as physical properties.

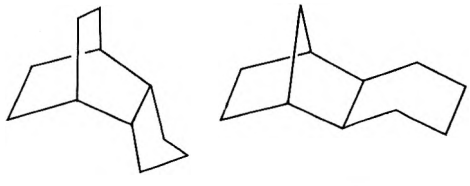
Kinetics. Rate measurements were made on *endo*-**1**, *exo*-**1**, *endo*-**2**, *exo*-**2**, and **3**. The disappearance of the reactants was followed approximately to 50%, during which five to eight determinations on the concentration of reactants were done by the use of VPC.

Reactions of *endo*-**1**, *exo*-**1**, *endo*-**2**, and **3** proceeded with reasonable rates by using 1 molar equiv of trifluoromethanesulfonic acid, but *exo*-**2** isomerized so slowly with this amount of the catalyst that the rate measurement was impracticable. Therefore the reaction of *exo*-**2** was run in the presence of 4 *M* catalyst. The rate of *exo*-**1** was also measured under the same conditions, and the ratio $k_{exo\text{-}1}/k_{exo\text{-}2}$ for 4 *M* catalyst was used to calculate $k_{exo\text{-}2}$ for 1 *M* catalyst with the assumption of an equality between two relative rates. The treatment is justified by the fact that both $k_{exo\text{-}1}$ and $k_{exo\text{-}2}$ are proportional to the fifth power of the catalyst concentration taken within the range from 0.4 to 6.0 molar equiv. All the reactants showed fairly good first-order kinetics when followed by VPC. The calculated rate constants and relative rates are listed in Chart I.

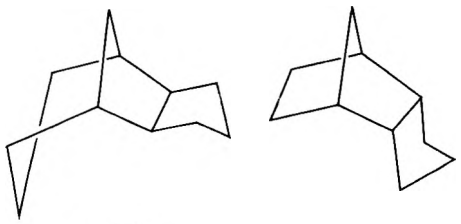
Chart I



	endo-**1**	*endo*-**2**
10^6 *k*, min^{-1}	4.6×10^5	4.1×10^4
Rel rate	3×10^5	2×10^4



	3	*exo*-**1**
10^6 *k*, min^{-1}	5.8×10^4	6.9×10^1
Rel rate	4×10^4	4×10^1



	exo-**2**	*endo*-**10**
10^6 *k*, min^{-1}	1.9	(7.7×10^3)
Rel rate	1	(4×10^3)

As is evident from these results, an interesting difference was discovered between the reactivities of endo and exo isomers. Rate constants for endo isomers are about 10^4 times larger than those of the corresponding exo isomers. Compound **3**, where endo and exo isomers are identical, reacted at a similar rate to those of *endo*-**1** and *endo*-**2**. Rate enhancement of one of the epimers vs. the other is rather familiar, e.g., in solvolysis reactions, but the phenomenon does not seem to have been recognized in the adamantane rearrangement of hydrocarbons.

Product analysis (Table I) for the rearrangement of *endo*-**1** revealed another interesting feature of the reaction: no *exo*-**1** was detected throughout the reaction. An interpretation of this may be that in *endo*-**1** the Wagner–Meerwein rearrangement to *exo*-**1** would occur much more slowly than the pathway leading to 4-homoisotwistane (**9**). The direct measurement of the rates of the interconversions between *endo*-**1** and *exo*-**1** is obviously impossible, since the reaction of *endo*-**1** does not give rise to any *exo*-**1** at all, and vice versa. Therefore the rate of the isomerization of 2,3-*endo*-trimethylenenorbornane (*endo*-**10**) to its exo isomer (*exo*-**10**) was measured in order to have a rough idea about the rate of the Wagner–Meerwein rearrangement of the bicyclo[2.2.1]heptane system under the present reaction conditions. The first-order rate constant for *endo*-**10** was found to be 10^2 times smaller than that for the isomerization of *endo*-**1** (Chart I).

Products. Golay (capillary) column VPC was used to determine the product compositions. Product analysis was done at appropriate stages of the rearrangements to establish time-conversion relationships. Identification of each product was made on a mass spectrometer connected to the Golay VPC instrument.

endo-**1** and *endo*-**2** isomerized to the products listed in Table I. The combined yields of the products were almost quantitative, as was the case for other tricycloundecane precursors so far studied (*exo*-**1**, *exo*-**2**, **3**, and **9**).[8] Although the structure of seven products designated by letters A–E[16] still remained unknown, they were all tricycloundecanes as determined by mass and ^1H NMR spectroscopy. Thus the reaction under study was really a rearrangement without being accompanied by any appreciable disproportionations and decompositions.

All the endo reactants including **3** was found to give none of homoadamantane and methyladamantanes. The result is easily understood if we consider that these products are formed from **9**.[8] Indeed **9** was quite unreactive in the presence of only 1 molar equiv of the catalyst, and gave none of homoadamantane and methyladamantanes in short reaction time (run 61) during which extensive reaction of endo compounds had been effected (runs 1–4 and 31–33).

Unknown A was not found in earlier stages of the reaction of any precursors, while it was detected in longer reaction of every reactant and also of **9**. Unknown B_3 arose only in the reaction of *endo*-**1** and *exo*-**1** (runs 1–5 and 11, Table I). Considerable amount of B_2 was formed in the reaction of *endo*-**1** and *exo*-**1** (runs 1–5, 11, and 21–23), although a little was formed in the case of *exo*-**2**, **3**, and **9** on prolonged reaction. B_1 presented itself in the reaction of all the reactants including **9**. It may be noted that B_1 did not appear at the early stage of the reaction of *endo*-**1**, *exo*-**1**, and *endo*-**2** (runs 1–4, 11, and 31), whereas it did in the reaction of **3** from the beginning (run 51).

No *exo*-**2** was obtained at all at early stages of the reaction of *endo*-**1** (runs 1–4), but a little was formed from *endo*-**2** and **3** from the beginning (runs 31, 32, and 51). Unknown D was always accompanied by **9**, which suggested that D arose from and was in equilibrium with **9**. Unknown

Table I
Products of Tricycloundecane Rearrangements under Trifluoromethanesulfonic Acid Catalysis[a]

Run	Reactant (amt of catalyst)[b]	Reaction time, hr (min)[c]	Product[d] yield, %[e] A	1-Me-Ad	B_1	B_2	B_3	C	2-Me-Ad	*exo*-2	9	D	E	Homoad
1	*endo*-1	(1)				4.0	3.5	2.8			21.8	2.1		
2	(1.0)	(2)				8.8	6.2	4.8			42.1	4.7		
3		(4)				15.4	8.2	5.6			59.4	5.1		
4		(17)				15.5	7.7	5.9			58.1	5.0		
5		2	1.5		0.3	14.3	6.8	5.9			57.8	5.0		0.3
11	*exo*-1 (1.0)	24				1.5	0.3	1.0			10.4	1.5		0.3
21	*exo*-1	1	1.2	0.5	8.4	10.9		13.2	0.6	1.0	52.6	4.2		2.0
22	(4.0)	24	6.1	3.5	11.9	7.0		15.6	6.0	6.8	35.2	4.9		1.3
23		48	8.0	9.2	11.0	5.1		14.1	8.4	5.0	29.5	4.3		1.8
31	*endo*-2	(10)						0.5		0.6	40.2	1.8		
32	(1.0)	1			0.2			1.1		0.7	58.1	3.4		
33		8	1.0		1.3			4.2		0.8	80.4	4.5		
41	*exo*-2	1			1.8			1.9		84.4	11.8			
42	(4.0)	8	2.2	2.2	9.1	0.8		8.9	3.4	45.6	23.1	3.1		1.4
43		38	1.8	10.0	12.6	1.1		11.9	11.6	18.8	26.6	2.0		1.5
51	3	1			2.8			5.0		1.5	29.2	21.5	20.2	
52	(1.0)	24	2.2	1.6	17.6	1.7		16.6	2.4	5.4	46.9	3.2		2.2
61	9 (1.0)	6			1.1			8.1		0.3	80.5	4.3		
71	9	1	0.5	1.6	9.3	1.0		19.6	3.2	4.1	51.8	4.5		2.3
72	(4.0)	6	1.0	4.4	14.4	1.3		18.9	4.6	6.2	41.1	3.6		2.6
73		24	2.4	5.3	18.0	1.6		16.8	5.8	6.5	36.3	2.8		1.8
74		100	10.0	20.3	11.6	0.9		8.0	25.2	5.5	15.0	1.3		1.2

[a] Reactant (200 mg, 1.33 mmol) and CF_3SO_3H (200 mg, 1.33 mmol, or 800 mg, 5.33 mmol) in refluxing CH_2Cl_2 (10 ml). [b] In molar equivalents to the reactant. [c] Reaction time in parentheses is expressed in minutes. [d] Combined yields of the products were always almost quantitative, the balance being unreacted starting materials. Products are aligned in the order of increasing retention times. Abbreviations: A–E refer to compounds of unknown structure;[8,16] 1-Me-Ad and 2-Me-Ad, 1- and 2-methyladamantane, respectively; Homoad, homoadamantane. [e] Calculated from VPC peak areas.

E was detectable only at early stages of the reaction of **3** (run 51). This, coupled with the formation of an unusually large amount of D, was taken[8] as an evidence for the pathway from **3** to E to D to **9**.

exo-**10** was the only product from *endo*-**10**. Neither adamantane nor any other intermediates[1] were detectable under the present reaction conditions.

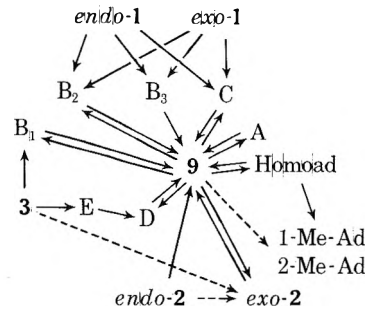
Discussion

It is shown in this work that endo precursors isomerize with much greater apparent rates than those of exo isomers. Adamantane rearrangements of polycyclic hydrocarbons consist of a very complex network of hydride transfer and isomerization reactions that occur competitively and consecutively.[1,17] The distribution of intermediates is controlled not only kinetically but also thermodynamically. It is quite difficult, therefore, to decide to which elementary reaction the observed rate enhancement should be ascribed.

Some speculations, however, may be made concerning the process of the rate enhancement. The first and at the same time rate-determining step in the adamantane rearrangement of *endo*-**10** or *exo*-**10** is, according to Schleyer,[1] hydride abstraction at a tertiary carbon atom and 1,2-alkyl shift to 1,7-trimethylenenorbornane. If a similar scheme applies to 2,3-tetramethylenenorbornanes (**1**), abstraction of 2-exo hydride in *endo*-**1** might be accompanied by the participation of the 6-methylene group. This same process should be unfavorable for the 2-endo hydride. Thus 6-methylene participation in *endo*-**1** may lead to the formation of the bridged ion[18] that lowers the activation energy. Similar mechanisms involving the abstraction of angular exo hydride with neighboring methylene participation in *endo*-**2** and **3** may account for the high reactivities of these compounds. Alternatively, the difference between the ground-state energies of endo and exo isomers may be a predominating factor that determines the activation energy difference. No definite interpretation of the phenomenon can be made at the present.

Examination of the change in product distributions with reaction time in endo precursors clarified a more precise rearrangement scheme (Chart II) than that in exo reactants

Chart II



did.[8] A conclusion in the previous studies[6–8,10] that **9** was a stable,[7] common intermediate to methyladamantanes from a various kind of precursor was further confirmed here. As is summarized in Chart II, *endo*-**1** first isomerizes to B_2, B_3, and C. Of these three, only B_3 is irreversibly isomerized to **9**, while B_2 and C are in equilibrium with **9**, because these

two arose from other precursors on prolonged reaction (runs 42, 43, and 52) and also from **9** (runs 71–74). It seems certain that there is no direct route from *endo*-**1** to A and B_1 (cf. run 5), since they were obtainable also in the reaction of various precursors as well as of **9** and, therefore, must arise from **9**.

Immediate isomerization products from *exo*-**1** are B_2, B_3, and C (run 11), the same as from *endo*-**1**. Interconversion between *endo*-**1** and *exo*-**1** was not realized starting from either isomer side under the present reaction conditions. In view of the rate of the Wagner–Meerwein rearrangement of *endo*-**10**, conversion of *endo*-**1** to *exo*-**1** would be much slower than isomerization of *endo*-**1** to unknown B's and C (cf. Chart I). On the other hand, any *endo*-**1**, if ever formed from *exo*-**1**, must react very fast compared to its formation.

No intermediate was detectable in the rearrangement of either *endo*-**2** or *exo*-**2** to **9**. The result for *endo*-**2**, together with the highest yield of **9** (80.4%), might suggest a somewhat selective pathway from *endo*-**2** to **9**. The large proportion of B_1 and C in the rearrangement of *exo*-**2** (runs 42 and 43) is evidently a consequence of the long reaction time required for the compound. It can also be taken as a confirmation of the scheme that B_1 and C are formed from and in equilibrium with **9**.

Hydrocarbon **3** was found to give B_1, together with E, as a primary product of isomerization. Thus, contrary to our former view,[8] the isomerization of **3** consisted of at least two competitive reaction pathways. Formation of a little *exo*-**2** from *endo*-**2** (0.6%, run 31) and **3** (1.5%, run 51) may be noteworthy. The amounts are considered too large to be formed only from **9** in the short reaction times (cf. run 61). Therefore the result may suggest direct formation of *exo*-**2** from *endo*-**2** and **3** in spite of the former conclusion,[8] based on the rearrangement of **3**, that *exo*-**2** was formed only from **9**. Indeed these three compounds have closely related structures which could be interconverted via Wagner–Meerwein rearrangement with assisted ionization.[19]

Unknown A was not formed directly from any of the fast-reacting precursors (runs 1–4, 31, 32, and 51). The stable intermediate **9** seems to be an immediate precursor to A, and this could not be disclosed in the previous study of slow-reacting compounds.[8]

It would be appropriate here to mention the aluminum chloride catalysis results of Petrov[4] and Whiting,[5] which relate to the rate differences found in this work. Petrov[4] obtained similar rates of rearrangement for *exo*-**1** and 6,7-trimethylenebicyclo[3.2.1]octane (**2**) of unspecified configuration,[8] and Whiting[5] noticed that *endo*-**1** and *exo*-**1** behaved indistinguishably. The discrepancy between their results and ours is only superficial, and can be easily explained, because they measured the rate of formation of methyladamantanes. Under the drastic reaction conditions they applied, rearrangement of precursors to **9** is very quick. Thus they determined the rate of the conversion of **9** to methyladamantanes, that led them to find the same isomerization rate for all the various reactants.

Experimental Section

All melting and boiling points are uncorrected. Instruments for the measurements of spectra and for conventional as well as capillary column VPC were the same as were used in the previous work.[8] Deuteriochloroform was used as the solvent for NMR spectroscopy. Chemical shifts are reported in δ for protons and in parts per million downfield from the internal Me_4Si standard for ^{13}C nuclei. All the ir spectra were taken on neat samples. Trifluoromethanesulfonic acid was a commercial product of 3M Co. Methylene chloride was dried over anhydrous calcium chloride and distilled immediately before use.

2,3-*endo*-Tetramethylenenorbornane (*endo*-**1**) was prepared according to Whiting[5] from cyclopentadiene and *p*-benzoquinone through Diels–Alder addition and subsequent hydrogenation and Wolff–Kishner reduction, and was freed from contaminating *exo*-**1** by purification by preparative VPC. 6,7-*exo*-Trimethylenebicyclo[3.2.1]octane (*exo*-**2**)[8] and 2,3-trimethylenebicyclo[2.2.2]octane-(**3**)[8,11] were synthesized in the previous work.

3,4-Dichloro-6,7-*endo*-trimethylenebicyclo[3.2.1]oct-2-ene (5). To a solution of 33.5 g (0.25 mol) of 5,6-*endo*-trimethylenenorborn-2-ene[14] in 200 ml of petroleum ether was added 54 g (1.0 mol) of sodium methoxide. Ethyl trichloroacetate (153 g, 0.8 mol) was added dropwise to the above mixture with stirring in a period of 4 hr while the reaction mixture was kept below 0° by being immersed into an ice–salt bath. The reaction mixture was stirred for a further 2 hr at 0°, and then allowed to warm up to ambient temperature, where it was kept overnight with continuous stirring. The mixture was poured onto 250 g of cracked ice–water, the separated aqueous layer being extracted four times with each 60 ml of ether. The aqueous layer was then made weakly acidic with the addition of 10% hydrochloric acid, and again extracted twice with each 60 ml of ether. The combined organic layer and ether extracts were washed with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. Fractional distillation of the solution gave 41.9 g (77% yield) of **5**: bp 123–124° (2 mm); $n^{22.5}D$ 1.5447; ir 2950, 2870, 1630, 1445, 1335, 1055, 960, 773, 718 cm^{-1}; ^1H NMR δ 1.0–3.0 (complex m, 12), 4.37 (d, 1, J = 3.0 Hz, CHCl), 6.05 (d, 1, J = 7.0 Hz, C=CH); mass spectrum *m/e* (rel intensity) 218 (6), 216 (9), 181 (17), 115 (17), 114 (10), 113 (45), 112 (14), 79 (11), 77 (32), 69 (100), 68 (18), 67 (23), 41 (12).

Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50; Cl, 32.65. Found: C, 61.10; H, 6.34; Cl, 32.13.

6,7-*endo*-Trimethylenebicyclo[3.2.1]oct-2-ene (6). Freshly cut sodium (35.4 g, 1.54 g-atoms) was added during a period of 30 min to 300 ml of liquid ammonia cooled in a Dry Ice–acetone bath, and the reaction mixture was stirred for a further 30 min at about −50°. A solution of 17.4 g (0.08 mol) of **5** in 50 ml of dry ether was added dropwise to the above mixture under efficient stirring in 35 min while the temperature was kept below −50°, stirring being continued for a further 30 min after the addition. Dry ether (300 ml) was dropped into the reaction mixture without external cooling, while ammonia was allowed to evaporate. To the residue were added carefully a methanol–ether mixture and then methanol to decompose any unreacted sodium. The reaction mixture was poured onto 1 l. of cold water, and the organic layer was separated. The aqueous layer was extracted twice with 200-ml portions of ether. The combined organic layer and ether extracts were washed with a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and fractionally distilled under diminished pressure to give 4.54 g (38% yield) of **6**: bp 76° (5 mm); $n^{22.5}D$ 1.5093; ir 3040, 3020, 2920, 2850, 2830, 2670, 1720, 1640, 1470, 1440, 1390, 1290, 1000, 935, 895, 755, 690 cm^{-1}; ^1H NMR δ 1.0–2.92 (complex m, 14), 5.24–5.98 (complex m, 2); mass spectrum *m/e* (rel intensity) 148 (27, M^+), 94 (16), 91 (15), 81 (11), 80 (40), 79 (100), 78 (72), 77 (12), 67 (14), 66 (11).

Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. FOUND: C, 88.89; H, 11.01.

6,7-*endo*-Trimethylenebicyclo[3.2.1]octane (*endo*-2). In a 100-ml autoclave were placed 3.1 g (0.012 mol) of **6**, 40 ml of ether, and 90 mg of palladium on charcoal catalyst (containing 5% palladium). Hydrogen was charged at an initial pressure of 6 kg/cm^2, and the reaction mixture was shaken for 1 hr at ambient temperature. The catalyst was filtered off from the reaction mixture, and the filtrate was concentrated to give 3.0 g (95% yield) of crude *endo*-**2** (95% purity). Fractionation by preparative VPC gave a pure sample: mp 41–42° (in sealed tube); ir 2950, 2900, 2840, 2660, 1460, 1450, 1440, 1320, 1300, 1270, 1230, 1200, 1070, 1040, 960, 890, 870, 850, 770, 720, 660 cm^{-1}; ^1H NMR δ 1.1–2.2 (complex m, 16), 2.3–2.8 (complex m, 2); ^{13}C NMR (multiplicity, rel intensity) 18.7 (t, 1), 24.9 (t, 2), 28.2 (t, 2), 32.3 (t, 1), 35.7 (d, 2), 45.1 (t, 1), 47.5 (d, 2); mass spectrum *m/e* (rel intensity) 150 (100, M^+), 108 (30), 93 (25), 82 (90), 81 (40), 80 (28), 79 (32), 67 (81).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.84; H, 12.19.

3-Chloro-6,7-*endo*-trimethylenebicyclo[3.2.1]oct-2-ene (7). A solution of 20.6 g (0.095 mol) of **5** in 20 ml of tetrahydrofuran was added dropwise with efficient stirring to a suspension of 6.45 g (0.17 mol) of powdered lithium aluminum hydride in 150 ml of ether and 450 ml of tetrahydrofuran, the addition being so regulated that a gentle reflux was maintained. It took 20 min for the addition, after which the reaction mixture was heated under reflux for 24 hr. Unreacted lithium aluminum hydride was decomposed by wet ether, and the resulting mixture was poured onto ice water.

The organic layer was separated and the aqueous layer was acidified with 10% hydrochloric acid. The aqueous layer was extracted five times with 100-ml portions of ether. The combined organic layer and ether extracts were washed three times with a saturated sodium chloride solution and dried over anhydrous sodium sulfate. Fractional distillation of the solution gave 10.6 g (61% yield) of **7**: bp 67° (0.4 mm); $n^{21.5}$D 1.5286; ir 3040, 2940, 2860, 1640, 1470, 1450, 1440, 1430, 1350, 1330, 1260, 1210, 1040, 960, 850, 680, 670 cm^{-1}; ^1H NMR 1.2–2.83 (complex m, 14), 5.83 (d, 1, J = 7.0 Hz, ClC=CH); mass spectrum m/e (rel intensity) 184 (11), 183 (4), 182 (31), 147 (20), 115 (35), 114 (47), 113 (100), 112 (96), 94 (14), 91 (21), 79 (57), 78 (12), 77 (43), 69 (27), 67 (26), 41 (18).

Anal. Calcd for $C_{11}H_{15}Cl$: C, 72.32; H, 8.28; Cl, 19.40. Found: C, 72.09; H, 8.04; Cl, 19.19.

Acid Hydrolysis of 3-Chloro-6,7-*endo*-trimethylenebicyclo[3.2.1]oct-2-ene (7). **7** (3.7 g, 0.02 mol) was mixed with 50 ml of 98% sulfuric acid cooled in an ice bath, and the mixture was stirred at ambient temperature overnight. The reaction mixture was poured onto cracked ice and extracted three times with 100-ml portions of ether. The ether extracts were washed three times with cold water and dried over anhydrous sodium sulfate. After evaporation of ether, the residue was subjected to distillation, which caused the contents of the distillation flask to suddenly polymerize at about 90°. Ether extract of the polymerized mass gave a little (ca. 0.5 g) organic material of which 6,7-*exo*-trimethylenebicyclo[3.2.1]octan-3-one[8] was the only volatile compound detected by VPC.

Rearrangements of Tricycloundecanes. Kinetic Measurement and Product Analysis. Rearrangement reactions were run in the same equipment as was used in the previous study.[8] Aliquots taken out of the reaction mixtures were quenched by cold water, and the methylene chloride layers were analyzed on the Golay column VPC. In kinetic measurements, each reaction was followed up to about 50% completion, during which five to eight determinations of the concentration of the reactants were made. At least three repetitions were done for each reactant. First-order rate constants were calculated from these kinetic data, and the reproducibility of the rate constants within a run as well as among repeated runs was fairly good, with standard deviations of ±10–15% of the respective arithmetic mean. Identification of products with known structure was made by comparison of VPC retention times and mass spectra with those of authentic samples. Identities of unknown compounds originated from different precursors were established also by Golay GC–MS.

Acknowledgment. We thank Professor P. v. R. Schleyer for helpful discussions.

Registry No.—*endo*-**1**, 54676-30-1; *exo*-**1**, 32789-29-0; *endo*-**2**, 54676-38-9; *exo*-**2**, 53495-28-6; **3**, 38255-97-9; **4**, 10466-50-9; **5**, 54643-92-4; **6**, 54643-93-5; **7**, 54643-94-6; **9**, 43000-53-9; ethyl trichloroacetate, 515-84-4; trifluoromethanesulfonic acid, 1493-13-6.

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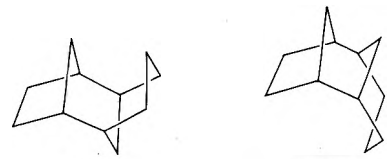
(15) Consisting of seven absorptions [t (rel intensity, 1), t (2), t (2), t (1), d (2), t (1), and d (2)]. The spectrum is also consistent with unknown 2,4-*exo*- and -*endo*-ethanobicyclo[3.2.1]nonane (*exo*-**11** and *endo*-**11**, respectively). However, *exo*-**11** was synthesized recently by us from 2-*endo*-hydroxymethyl-2,3-*exo*-trimethylenenorbornane through a ring expansion–hydride transfer reduction, and found to be different from *endo*-**2**: N. Takaishi, Y. Inamoto, and K. Aigami, *J. Chem. Soc., Perkin Trans. 1*, in press. Ketones with the skeleton of **11** were prepared recently via an independent route: R. Schmid and H. Schmid, *Helv. Chim. Acta*, **57**, 1883 (1974).



exo-11 *endo*-11

(16) Actually A and C are not single tricycloundecanes but mixtures, while B_1, B_2, B_3, D, and E are individual isomers no longer separable on the capillary VPC columns used. Letters A–E were originally assigned to unidentified fractions separated on conventional VPC columns. Fractions A, B, and C were later found further separable into three, three, and four components, respectively, on Golay columns. Since the roles of each compound in A and C in the rearrangement reactions have been left unclarified, we refrain from referring to these components in the text more precisely than by A and C in order to avoid unnecessary complications in the statement of the results.
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β-Alkylalkanedioic Acids from Cycloalkenones via Michael Alkylation–Methoxycarbonylation

Robert G. Salomon* and Mary F. Salomon

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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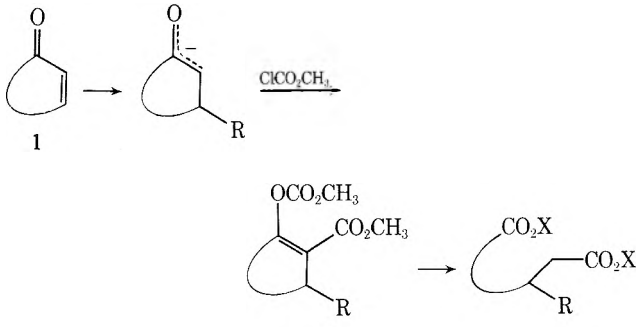
A synthesis of β-alkylalkanedioic acids is described which involves methoxycarbonylation of enolates produced by 1,4 addition of lithium dialkylcuprates to α,β-unsaturated ketones. Introduction of the methoxycarbonyl group serves both to complete the carbon skeleton and to activate an intermediate, the enol carbonate of a cyclic β-keto ester, toward further transformations. Thus, the enol carbonates are converted by a retro-Dieckmann cleavage into β-alkylalkanedioic acids or esters. The success of the method depends on the proclivity of the enolates toward acylation at carbon rather than oxygen, and upon the propensity of methyl chloroformate to acylate the carbonionic center of the ambident enolate ions. The new synthetic method is simple, convenient, and highly stereoselective. The method's scope is delineated by a study of the C- to O-acylation ratio for a series of substituted 2-cyclohexen-1-ones.

There is no short and convenient synthesis of β-alkylalkanedioic acids. Moreover, such compounds, in particular β-benzyladipic acid derivatives, are key intermediates for the synthesis of tetracyclines which are physiologically active and medicinally useful natural products.[1] We now report a new synthetic procedure for β-alkylalkanedioic acids which is not only simple and convenient, but which is also *highly stereoselective when applied to the synthesis of polysubstituted alkanedioic acids.* Our synthesis exploits Michael alkylation of α-enones coupled with reaction of the product enolates with a carbon electrophile in one combined step.[2] This procedure is particularly effective, since it allows rapid assembly of complex carbon networks in which new carbon–carbon bonds are created at both the α and β positions of the enone precursor. Use of a methoxycarbonyl group as electrophile serves both to complete the carbon skeleton and to activate the product toward further chemical modification.

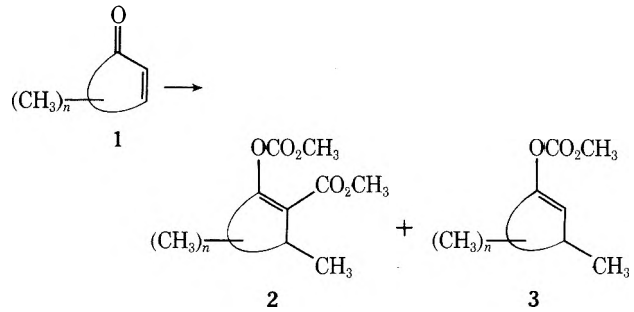
We find that methoxycarbonylation of enolates produced by 1,4 addition of lithium dialkylcuprates to 2-cycloalken-1-ones (1) yields enol carbonates (2) in a single combined step. The carbonates give alkanedioic acids or esters in high yields upon treatment with sodium hydroxide or sodium methoxide, respectively. In some cases, products



(3) resulting from O-acylation of the Michael enolates are also obtained. A study was made of the effect of enone structure on the ratio of C- to O-acylation in order to delineate the scope of our approach to α,ω-alkanedioic acids.

Results

Reaction of 2-cyclohepten-1-one, 2-cyclohexen-1-one, or 2-cyclopenten-1-one with a variety of lithium dialkylcuprates[3a] followed by treatment of the resulting Michael enolates with methyl chloroformate gives enol carbonates of β′-alkyl cyclic β-keto esters (2) in moderate yields (see Table I). Optimum conditions for a particular application depend on the relative expense of the organometallic reagent vs. the α,β-unsaturated ketone. We chose to limit the amount of organocuprate to 1.1 equiv. However, some improvement in yield based on α,β-unsaturated ketone is obtained in the one case examined by the use of a larger excess (2.2 equiv) of organocuprate. Application of the conjugate addition–methoxycarbonylation sequence to a series of methyl-substituted 2-cyclohexen-1-ones gives enol carbonates (2) and/or enol carbonates (3) of polymethylcyclo-



hexanones. Yields of 2 as well as the relative yields of 2 vs. 3 are also given in Table I.

The enol carbonate structure assigned to the products 2 is consistent with their elemental analyses and proton magnetic resonance spectra. In addition, they all exhibit ultraviolet absorption at 234 ± 5 mμ (ε 3–6 × 10^3) due to an α,β-unsaturated ester chromophore.[3b] The enol carbonates 3 were characterized by elemental analyses and proton magnetic resonance spectra. A ^{1}H NMR resonance at δ 5.1–5.2 characteristic of the vinyl proton of an enol ester was observed.

Conversion of the enol carbonates (2) to the corresponding β-keto esters and subsequent retro-Dieckmann cleavage occurs in a single high-yield step upon treatment with sodium hydroxide in boiling ethanol or sodium methoxide in boiling methanol to give diacids or diesters,[4] respectively. The methoxide cleavage requires 1–6 days depending on keto ester structure, the more highly substituted keto es-

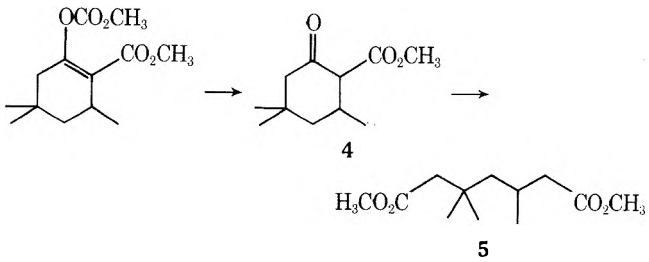


Table I
Michael Alkylation-Methoxycarbonylation of Cycloalkenones

Enone (1)	Cuprate[a]	Yield, %,[b] enol carbonate (2)	Mol %[c] enol carbonate (3)
2-Cyclopentenone (1a)	Me_2CuLi	46 (56)[d]	0
2-Cyclopentenone	n-Bu_2CuLi	71	0
2-Cyclopentenone	$Benzyl_2CuLi$	51[e]	0
2-Cyclohexenone (1b)	Me_2CuLi	58	0
2-Cyclohexenone	n-Bu_2CuLi	69	0
2-Cyclohexenone	$Benzyl_2CuLi$	43	0
2-Cycloheptenone (1c)	Me_2CuLi	47	0
5-Methyl-2-cyclohexenone (1d)	Me_2CuLi	54	0
5,5-Dimethyl-2-cyclohexenone (1e)	Me_2CuLi	20	68
3,5,5-Trimethyl-2-cyclohexenone (1f)	Me_2CuLi	0	100
4,4-Dimethyl-2-cyclohexenone (1g)	Me_2CuLi	51	9

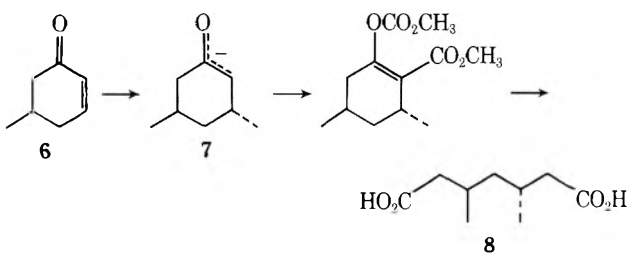
[a] 1.1 equiv. [b] Isolated by distillation. [c] Percent of enol carbonates (2 + 3) which is 3. [d] 2.2 equiv of Me_2CuLi used instead of 1.1 equiv. [e] Minimum yield (i.e., yield of diacid from retro-Dieckmann cleavage). See Experimental Section.

Table II

Diacid or diester	Yield, %	Cycloalkenone precursor
Dimethyl 3-methyladipate	99	Cyclopentenone (1a)
Dimethyl 3-methylpimelate	91	Cyclohexenone (1b)
Dimethyl 3-methylsuberate	89	Cycloheptenone (1c)
dl-3,5-Dimethylpimelic acid	85	5-Methylcyclohex-2-en-1-one (1d)
Dimethyl 3,3,5-trimethylpimelate	97	5,5-Dimethylcyclohex-2-en-1-one (1e)
Dimethyl 3,4,4-trimethylpimelate	90	4,4-Dimethylcyclohex-2-en-1-one (1g)
3-Benzyladipic acid	77	Cyclopentenone (1a)
Dimethyl 3-benzylpimelate	90	Cyclohexenone (1b)

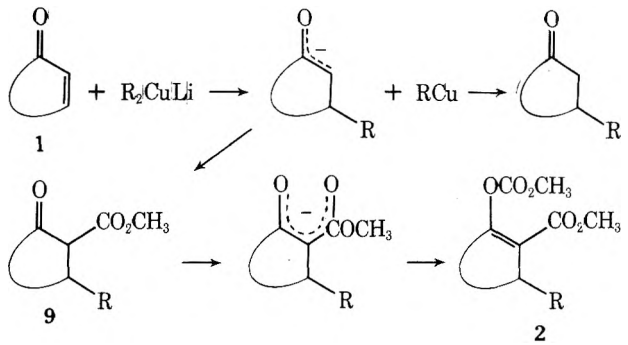
ters requiring longer reaction periods. Thus the enol carbonate of 2-carbomethoxy-3,5,5-trimethylcyclohexanone gives a 4:6 mixture of 2-carbomethoxy-3,5,5-trimethylcyclohexanone (4) and dimethyl-3,3,5-trimethylheptanedioic acid (5), respectively, after boiling for 1 day in the presence of excess sodium methoxide in methanol. After 6 days 4 is converted completely to 5. (See Table II.)

An important feature of the present approach to the synthesis of β-alkyl-α,ω-alkanedioic acids deserves comment. The method provides a *simple, highly stereoselective synthesis of polysubstituted alkanedioic acids*, since the conjugate addition of lithium diorganocuprates to substituted cycloalkenones is stereospecific.[5] For example, 5-methyl-2-cyclohexenone (6) reacts with lithium dimethylcuprate to give the Michael enolate (7) having a trans:cis ratio of 98:2.[6] We find that methoxycarbonylation of 7 followed by retro-Dieckmann cleavage gives *dl*-β,β′-dimethylpimelic acid (8).[7]



Discussion

The enol carbonates 2 presumably arise via C-acylation of the initial Michael enolate to give an intermediate β-keto ester, 9. Since this initial acylation product is an enolizable 1,3-dicarbonyl compound, a second equivalent of the original enolate might be expected to be consumed in the conversion of the 1,3-dicarbonyl compound to its enolate anion in the reaction mixture.[8] A maximum 50% theoretical yield of 2 based on 1 is anticipated in this event. The actual yields of 2 (see Table I) often exceed 50% and a larger excess of organocuprate increases the yield. These facts indicate that organocopper by-product and/or excess organocuprate compete with the original enolate in deprotonating the intermediate β-keto esters. Also butyl cuprate gives

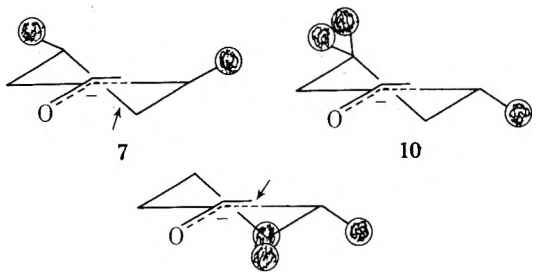


higher average yields (70%) than do methyl (49%) or benzyl (47%) cuprates. Thus butylcopper more effectively competes with the initial enolate in deprotonating the intermediate β-keto esters than do methyl- or benzylcopper.

The regioselectivity of acylation of the initial Michael enolates exhibits a dependence on the degree and position of substitution for the series of methyl-substituted 2-cyclohexen-1-ones examined. Generally O-acylation (3) increases relative to C-acylation (2) as the degree of substitution increases. For the series 2-cyclohexen-1-one, 5-methyl-2-cyclohexen-1-one, 5,5-dimethyl-2-cyclohexen-1-one, 3,5,5-trimethyl-2-cyclohexen-1-one the relative extent of O-acylation is 0, 0, 68, and 100%, respectively. The effect of disubstitution in the 5 position is more profound than of disubstitution in the 4 position in promoting O-acylation.

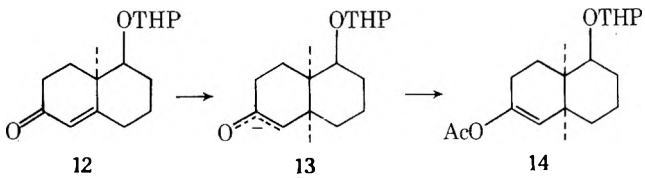
The sudden change from exclusive C-acylation of the enolate 7 (from Me_2CuLi + 5-methyl-2-cyclohexen-1-one) to predominant O-acylation of the enolate 10 (from Me_2CuLi + 5,5-dimethyl-2-cyclohexen-1-one) is readily explained in

terms of bimolecular nucleophilic substitution.[9] A transition state which involves axial attack of the methyl chloroformate on the enolate anion is expected.[3b] Axial attack on one face of **7** is not sterically hindered by a methyl group. In **10** both faces are shielded by methyl groups and acylation at the more accessible oxygen atom is favored. Predominant C-acylation (91%) of the enolate **11** (from Me_2CuLi + 4,4-dimethyl-2-cyclohexen-1-one) is expected for the conformer indicated (see figure) in which one face is sterically unencumbered. Other conformers (not pictured) favor O-acylation.

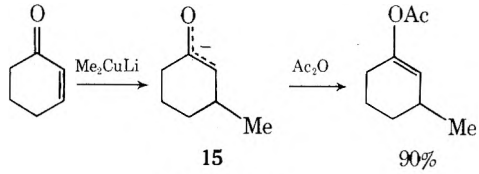


7 **10** **11**

It is both interesting and significant that acylation of the initial enolate occurs on carbon rather than oxygen in most cases examined. Others have noted that when enolate anions of ketones are treated with excess acid chloride, the acyl group is introduced predominantly at oxygen rather than at carbon.[6] Our contrary results may arise from the sensitivity of acylation regioselectivity to the identity of the enolate counterion.[10] That is, the presence of copper salts in the reaction mixture may influence the regioselectivity of the acylation of enolates produced by Michael alkylation of enones with organocuprates. However, comparison of an acylation with, for example, acetyl chloride and acylations with methyl chloroformate is beclouded by the greater reactivity and proclivity toward O-acylation of the former.[10] Thus O-acylation is observed upon conjugate addition of lithium dimethylcuprate to enone **12**, followed by rapid quenching of the reaction mixture with excess acetyl chloride to give **14** in 88% yield.[11] The regioselectivity of acylation of the Michael enolate **13** may be due to steric factors. However, the regiospecific O-acylation observed in reaction of the Michael enolate **15** with acetic anhydride[12] contrasts with the C-acylation of **15** with methyl chloroformate observed by us under otherwise identical reaction conditions.



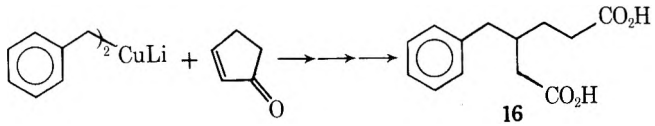
12 **13** **14**



15 90%

Conclusions

Michael alkylation–methoxycarbonylation–retro-Dieckmann cleavage is a simple and convenient new synthetic procedure for β-alkylalkanedioic acids starting from readily available cycloalkenones. Thus, for example, β-benzyladipic acid (**16**) is readily obtained (51%) in essentially one combined step (i.e., without isolation of pure intermediates) from lithium dibenzylcopper, cyclopentanone, and methyl chloroformate. Since Michael alkylation of substituted cycloalkenones is stereospecific, the procedure provides a highly stereoselective synthesis of polysubstituted alkanedioic acids. The applicability of the method is limited by the proclivity of highly substituted sterically congested enolates toward acylation at oxygen.



16

Experimental Section

General. Ethyl ether (Baker Analyzed anhydrous) was used without further drying. Methyllithium (1.7 *M* in ethyl ether), vinyllithium (1.8 *M* in tetrahydrofuran), and *n*-butyllithium (1.65 *M* in *n*-hexane) were from Lithium Corp. of America. Ventron Corp. 98% copper(I) iodide was used without further purification. All reactions involving organometallics were conducted under a blanket of dry nitrogen in flame-dried reaction vessels. NMR spectra were obtained on a Varian A-60A instrument on solutions in CCl_4. Ultraviolet spectra were measured with a Beckman Model DU spectrophotometer on solutions in anhydrous methanol. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., and by Par-Alexander Labs, South Daytona, Fla.

Michael Methylation–Methoxycarbonylation. A solution of methyllithium in ether (88 mmol) was added to a mechanically stirred suspension of CuI (8.4 g, 44 mmol) in ether (400 ml) cooled to 0° with an ice–water bath. After stirring for 0.5 hr, 2-cycloalkenone (40 mmol) was added over 3 min. After stirring for an additional 1 hr, methyl chloroformate (11 ml) was added in one portion. The resulting mixture was stirred for 1 hr and then allowed to warm to room temperature and stand for 10 hr. Cold aqueous 5% HCl (300 ml) was added. The aqueous layer was separated and washed with ether (3 × 150 ml). The combined ether extracts were washed with saturated aqueous NaCl (150 ml) and dried (Na_2SO_4). Solvent was removed by rotary evaporation, and the residue was distilled under reduced pressure. The distillations in cases A, B, D, F, and G were performed with a short-path distillation head (Kontes). In cases C and E, a vacuum-jacketed, 130-mm Vigreux column was included to improve fractionation.

A. Cyclohexenone (1b). Besides 3-methylcyclohexanone (1.2 g, 27%), the enol carbonate of 2-carbomethoxy-3-methylcyclohexanone, bp 98–102° (0.6 mm), was obtained (58%): NMR δ 1.07 (3 H, d, J = 7 Hz, C-3 methyl), 1.4–2.0 (4 H, C-4 and C-5), 2.0–2.4 (2 H, C-6), 2.6–3.0 (1 H, C-3), 3.70 (3 H, s, ester methyl), 3.80 (3 H, s, ester methyl); uv λ_{max} 238 mμ (ε 3600).

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.83; H, 7.00.

B. 5-Methyl-2-cyclohexenone (1d). The title enone, prepared by the method of Blanchard and Goering,[13] gave the enol carbonate of 2-carbomethoxy-*trans*-3,5-dimethylcyclohexanone: bp 97–99° (0.3 mm) (54%); NMR δ 0.9–1.2 (6 H, m, methyls), 1.3–1.6 (2 H, m, C-4), 1.7–2.4 (3 H, C-5 and C-6), 2.6–3.1 (1 H, C-3), 3.65 (3 H, s, ester methyl), 3.75 (3 H, s, ester methyl); uv λ_{max} 230 mμ (ε 4550).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.25; H, 7.42.

C. 5,5-Dimethyl-2-cyclohexenone (1e). The title enone, prepared by the method of Hiegel and Burk,[14] gave 1-methoxycarbonyloxy-3,5,5-trimethylcyclohexene: bp 118–124° (10 mm) (42%); NMR δ 0.9–1.1 (9 H, m, methyls), 1.1–1.6 (2 H, m, C-4), 1.8–1.9 (1 H, C-6), 1.9–2.1 (1 H, C-6), 2.1–2.6 (1 H, C-3), 3.70 (3 H, s, ester methyl), 5.1–5.3 (1 H, C-2, vinyl).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.66; H, 9.17.

Also the enol carbonate of 2-carbomethoxy-3,5,5-trimethylcyclohexanone, methyl 2-methoxycarbonyloxy-4,4,6-trimethylcyclohexenecarboxylate, was obtained: bp 100–106° (0.5–0.6 mm) (20%); NMR δ 0.9–1.2 (9 H, m, methyls), 1.2–1.8 (2 H, C-4), 1.8–2.0 (1 H, C-6), 2.1–2.3 (1 H, C-6), 2.4–2.8 (1 H, C-3), 3.69 (3 H, s, ester methyl), 3.77 (3 H, s, ester methyl), uv λ_{max} 229 mμ (ε 3100).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.71; H, 7.96.

Finally, 3,3,5-trimethylcyclohexanone (9%) was isolated from the distillation forerun (bp 80–118, 10 mm) by preparative gas–liquid chromatography on a 5 ft × 0.25 in. column filled with 20% FFAP on 60/80 Chromosorb P at 110°: NMR δ 0.9–1.1 (9 H, m, methyls), 1.2–1.6 (2 H, C-4), 1.7–2.5 (5 H, C-2, C-5, and C-6).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.98; H, 11.49.

D. 3,5,5-Trimethyl-2-cyclohexenone (Isophorone, 1f). The title enone gave 3,3,5,5-tetramethyl-1-methoxycarbonyloxycyclohexene-1, the enol carbonate of 3,3,5,5-tetramethylcyclohexanone: bp 52–62° (0.6–0.8 mm) (93%); NMR δ 1.03 (6 H, s, methyls), 1.07 (6 H, s, methyls), 1.33 (2 H, s, C-4), 1.91 (2 H, d, J = 1.2 Hz, C-6), 3.72 (3 H, s, ester methyl) 5.17 (1 H, t, J = 1.2 Hz, C-2 vinyl).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.00; H, 9.34.

E. 4,4-Dimethyl-2-cyclohexenone (1g). The title enone, prepared by the method of Eliel and Lurach,[15] gave the enol carbonate of 2-carbomethoxy-3,4,4-trimethylcyclohexanone, methyl 2-methoxycarbonyloxy-5,5,6-trimethylcyclohexenecarboxylate: bp 100–102° (0.25 mm) (51%); NMR δ 0.95 (3 H, s, methyl), 0.97 (3 H, d, J = 7 Hz, C-3 methyl), 0.99 (1 H, s, methyl), 1.1–2.0 (2 H, m, C-5), 2.0–2.6 (3 H, m, C-3 and C-6), 3.67 (3 H, s, ester methyl), 3.77 (3 H, s, ester methyl).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.11; H, 8.18.

Also 1-methoxycarbonyloxy-3,4,4-trimethylcyclohexene was obtained from the distillation forerun by preparative gas–liquid phase chromatography on a 5 ft × 0.25 in. column filled with 20% FFAP on 60/80 Chromosorb P at 180° (5%): NMR δ 0.8–1.0 [9 H, d (apparent), methyls], 1.1–1.7 (2 H, C-5), 1.8–2.3 (3 H, C-3 and C-6), 3.73 (3 H, s, ester methyl), 5.05–5.20 (1 H, m, C-2 vinyl).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.68; H, 9.33.

F. 2-Cyclopentenone (1a). The title enone gave the enol carbonate of 2-carbomethoxy-3-methylcyclopentanone, bp 125–135° (10–15 mm) (46%). The use of 2.2 equiv of Me_2CuLi instead of the usual 1.1 equiv gave an improved yield (56%): NMR δ 1.19 (3 H, d, J = 6 Hz, methyl), 1.3–3.3 (5 H, C-3, C-4, and C-5), 3.67 (3 H, s, ester methyl), 3.82 (3 H, s, ester methyl); uv λ_{max} 238 mμ (ε 5850).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.96; H, 6.60.

G. 2-Cycloheptenone (1c). The title enone gave the enol carbonate of 2-carbomethoxy-3-methylcycloheptanone: bp 98–101° (0.3 mm) (47%); NMR δ 1.14 (3 H, d, J = 7 Hz, methyl), 1.5–2.1 (6 H, C-4, C-5, and C-6), 2.2–2.6 (2 H, C-7), 2.6–3.1 (1 H, C-3), 3.66 (3 H, s, ester methyl), 3.78 (3 H, s, ester methyl); uv λ_{max} 229 mμ (ε 3000).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.32; H, 7.33.

Michael Butylation–Methoxycarbonylation. A solution of n-butyllithium in n-hexane (88 mmol) was added to a mechanically stirred suspension of CuI (8.4 g, 44 mmol) in ether (400 ml) cooled to −30°. After stirring for 30 min, cycloalkenone (40 mmol) was added over 3 min. The temperature of the reaction mixture was allowed to increase slowly to −10° over an additional 1 hr with continued stirring. Then methyl chloroformate (11 ml) was added in one portion. The resulting mixture was stirred for 1 hr at 0° and then allowed to warm to room temperature and stand for 10 hr. The rest of the procedure is the same as described above for methylation.

A. Cyclopentenone (1a). The title enone gave the enol carbonate of 3-butyl-2-carbomethoxycyclopentanone: bp 110–115° (0.7 mm) (71%); NMR δ 0.92 (3 H, t, J = 5 Hz, methyl), 1.1–3.2 (11 H), 3.68 (3 H, s, ester methyl), 3.82 (3 H, s, ester methyl); uv λ_{max} 234 mμ (ε 6100).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.80; H, 7.94.

B. Cyclohexenone (1b). The title enone gave the enol carbonate of 3-butyl-2-carbomethoxycyclohexanone: bp 118–122° (0.8 mm) (69%); NMR δ 0.90 (3 H, t, J = 5 Hz, methyl), 1.1–2.4 (12 H), 2.4–2.9 (1 H, C-3), 3.67 (3 H, s, ester methyl), 3.78 (3 H, s, ester methyl); uv λ_{max} 229 mμ (ε 3890).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.08; H, 8.20.

Michael Benzylation–Methoxycarbonylation. A solution of benzyllithium in ether (88 mmol) was prepared from tribenzyltin(IV) chloride[16] (12.8 g, 30 mmol) and methyllithium (120 mmol) according to the procedure of Seyferth et al.[17] This solution was drawn off from the white precipitate of LiCl with a hypodermic syringe and added to a suspension of CuI (8.4 g, 44 mmol) at −25 to −20° with mechanical stirring. After 1 hr, cycloalkenone (40 mmol) was added dropwise over 5 min. The mixture was stirred at −25 to −10° for 1.5 hr. Then methyl chloroformate (11 ml) was added in one portion to the dark green solution. The resulting mixture was slowly warmed to room temperature and stirred for 10 hr. Then cold aqueous 5% HCl (300 ml) was added. The aqueous layer was separated and washed with ether (3 × 150 ml). The combined ether extracts were washed with saturated aqueous NaCl (150 ml) and dried (Na_2SO_4). Solvent was removed by rotary evaporation. Further purification is detailed for each example studied (see below).

A. Cyclopentenone (1a). The crude product was purified by removal of volatile impurities by distillation under reduced pressure (up to 83°, 0.3 mm). The residue weighed 7.66 g (66% assuming pure enol carbonate of 3-benzyl-2-carbomethoxycyclopentanone).

B. Cyclohexenone (1b). The enol carbonate of 3-benzyl-2-carbomethoxycyclohexanone was obtained from the crude reaction product as follows. Some enol carbonate crystallized from the crude oily product mixture. The crystalline product was isolated by filtration on a Buchner funnel, and volatile impurities were removed from the filtrate by distillation under reduced pressure (up to 90°, 0.25 mm). The remaining oily product was taken up in a minimum of methanol and the solution was placed in the refrigerator for several days. Crystals of enol carbonate which separated were collected on a Buchner funnel and all crystalline product was recrystallized from methanol to give product: mp 109–110° (43%); NMR δ 1.3–2.1 (4 H, C-4 and C-5), 2.2–2.5 (2 H, C-6), 2.82 [2 H, dd (apparent), J = 9, 14 Hz, benzylic CH_2], 2.9–3.3 (1 H, C-3), 3.70 (3 H, s, ester methyl), 3.87 (3 H, s, ester methyl); uv λ_{max} 229 mμ (ε 4800).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.02; H, 6.75.

Michael Vinylation–Methoxycarbonylation of 2-Cyclopentenone (1a). A solution of vinyllithium in tetrahydrofuran (22 mmol) was added to a mechanically stirred suspension of CuI (2.1 g, 11 mmol) in ether (100 ml) at −50°. The resulting mixture was stirred for 1 hr at −55 to −35°. Then 2-cyclopentenone (10 mmol) was added and the resulting mixture was stirred at −40 to −35° for 10 min and then at 0° for 30 min. Then methyl chloroformate (2.8 ml) was added in one portion and the resulting mixture was stirred for 1 hr at 0° and then allowed to warm slowly to room temperature and stirred for 10 hr. An aqueous work-up analogous to those described above for methylation, etc., gave the enol carbonate of 2-carbomethoxy-3-vinylcyclopentanone: bp 98–100° (0.6 mm) (31%); NMR δ 3.67 (3 H, s, ester methyl), 3.84 (3 H, s, ester methyl), 4.8–5.3 (2 H, m, vinyl CH_2), 5.6–6.2 (1 H, m, vinyl CH).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.65; H, 6.23.

Dimethyl Alkanedioates via Retro-Dieckmann Cleavage with Sodium Methoxide.[4] Sodium (0.93 g, 41 mmol) was dissolved in anhydrous methanol (60 ml) and then the enol carbonate was added (15 mmol). The resulting mixture was boiled under reflux for 1–8 days, longer periods being required for more highly substituted enol carbonates. After cooling to 0° (ice–water bath), dry HCl was bubbled through the reaction mixture until it was acidic. Methanol was then removed by rotary evaporation and the residue was partitioned between water (20 ml) and ether (30 ml). The aqueous fraction was extracted with additional ether (30 ml), and the combined organic extracts were washed with saturated aqueous NaCl (30 ml) and dried (Na_2SO_4). Solvent was removed by rotary evaporation. In most cases the crude product which remained was almost pure diester, and an analytical sample was obtained by preparative gas–liquid phase chromatography on a 5 ft × 0.25 in. column of 20% FFAP on Chromosorb P (60/80). In some cases the residual oil was fractionally distilled under reduced pressure.

Dimethyl 3-Methyladipate. The enol carbonate of 2-carbomethoxy-3-methylcyclopentanone was cleaved in 1 day by boiling methanolic sodium methoxide. The crude product was pure dimethyl 3-methyladipate (99%), which had an identical NMR spectrum and gas–liquid chromatographic retention time with those of authentic diester prepared by methylation of the diacid (Aldrich) with diazomethane.

Dimethyl 3-Methylpimelate. The enol carbonate of 2-carbomethoxy-3-methylcyclohexanone was cleaved in 1 day by boiling methanolic sodium methoxide. The crude product was pure diester (91%): NMR δ 0.94 (3 H, d, J = 7 Hz, methyl), 1.1–2.0 (5 H, C-3, C-4, and C-5), 2.0–2.4 (4 H, C-2 and C-6), 3.61 (6 H, s, ester methyls).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.27; H, 9.26.

Dimethyl 3-Methylsuberate. The enol carbonate of 2-carbomethoxy-3-methylcycloheptanone was cleaved in 1 day by boiling methanolic sodium methoxide. The crude product was pure diester (89%): NMR δ 0.93 (3 H, d, J = 6 Hz, methyl), 1.1–2.0 (7 H, C-3,

C-4, C-5, and C-6), 2.0–2.5 (4 H, C-2 and C-7), 3.62 (6 H, s, ester methyls).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.01; H, 9.37.

***dl*-3,5-Dimethylpimelic Acid.** The enol carbonate of 2-carbomethoxy-*trans*-3,5-dimethylcyclohexanone was cleaved in 8 days by boiling methanolic sodium methoxide to give crude diester, NMR δ 3.62 (6 H, s, ester methyls), which was saponified with boiling aqueous methanolic KOH to give diacid (85%), mp 138–140° (reported[7] mp 139.9–140.5°), after crystallization from ethyl acetate. The alternative isomeric meso diacid has a reported melting point of 99.3–99.6°.

Dimethyl 3,3,5-Trimethylpimelate. The enol carbonate of 2-carbomethoxy-3,5,5-trimethylcyclohexanone gave a 6:4 mixture of 2-carbomethoxy-3,5,5-trimethylcyclohexanone and dimethyl 3,3,5-trimethylpimelate, respectively, upon boiling in methanolic sodium methoxide for 1 day. These products were separated by preparative gas–liquid phase chromatography on a 5 ft × 0.25 in. column of SE-30 on Chromosorb P (60/80) at 180°. Dimethyl 3,3,5-trimethylpimelate: NMR δ 1.00 [9 H, broad s (apparent), methyls], 1.2–1.4 (2 H, C-4), 1.5–2.5 (5 H, C-2, C-5 and C-6), 3.60 (6 H, s, ester methyls).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.72; H, 9.43.

2-Carbomethoxy-3,5,5-trimethylcyclohexanone: NMR δ 1.00 [9 H, d (apparent), J = 7 Hz, methyls], 1.2–1.8 (2 H, broad d, J = 12 Hz, C-4), 2.12 [2 H, broad s (apparent), C-6], 2.2–2.8 (1 H, m, C-3), 2.84 (1 H, d, J = 12 Hz, C-2), 3.70 (3 H, s, ester methyl).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.68; H, 9.17.

The enol carbonate gave almost pure diester (97% crude) upon boiling in methanolic sodium methoxide for 7 days.

Dimethyl 3,4,4-Trimethylpimelate. The enol carbonate of 2-carbomethoxy-3,4,4-trimethylcyclohexanone gave the title diester upon boiling in methanolic sodium methoxide (90%): bp 84–86° (1.5 mm); NMR δ 0.95 (6 H, s, methyls), 0.97 (3 H, d, J = 6 Hz, methyl), 1.3–2.5 (7 H, C-2, C-3, C-4, and C-5), 3.61 (6 H, s, ester methyls).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.33; H, 9.62.

Alkanedioic Acids via Retro-Dieckmann Cleavage with Sodium Hydroxide. Sodium hydroxide (4.2 g, 105 mmol) was boiled under reflux with magnetic stirring in anhydrous ethanol (52 ml) until the hydroxide dissolved. Then the crude enol carbonate of 3-benzyl-2-carbomethoxycyclopentanone (see above) (7.66 g) was added to the solution at 30–50° together with 10 ml of additional ethanol. The resulting mixture was boiled under reflux for 6 hr. The reaction mixture was cooled to room temperature and then poured into an ice–water mixture (50 ml). The resulting mixture was washed with ether (2 × 50 ml) and then acidified with excess concentrated HCl (50 ml). The diacid was extracted into ether (2 × 50 ml). The ether solution was dried (Na_2SO_4). Solvent was removed by rotary evaporation to yield crude diacid (51% based on starting cyclopentenone). This was crystallized from chloroform–pentane (1:1 v/v, 40 ml). The product was collected on a Buchner funnel, washed with 1:1 chloroform–pentane (15 ml), and air dried to yield 3-benzyladipic acid (40% based on starting cyclopentenone) as a white powder: mp 108–109° (yields are overall from cyclopentanone); NMR ($CDCl_3$) δ 1.4–1.9 (2 H, C-4), 1.9–2.5 (5 H, C-2, C-3, and C-5), 2.5–2.9 (2 H, benzylic), 7.20 (5 H, s, aromatic), 11.5 (2 H, s, carboxyl).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.95; H, 6.85.

Similar treatment of the enol carbonate of 3-benzyl-2-carbomethoxycyclohexanone (see above) gave 3-benzylpimelic acid, mp 71–74°, which was methylated with ethereal diazomethane to give dimethyl 3-benzylpimelate (90%): NMR δ 0.9–1.9 (5 H, C-3, C-4, and C-5), 1.9–2.3 (4 H, C-2 and C-6), 2.3–2.6 (2 H, benzylic), 3.51 (6 H, s, ester methyls), 7.08 (5 H, s, aromatic).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.99; H, 8.03.

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Registry No.—**1a,** 930-30-3; **1b,** 930-68-7; **1c,** 1121-66-0; **1d,** 7214-50-8; **1e,** 4694-17-1; **1f,** 78-59-1; **1g,** 1073-13-8; **2a** (R = Me), 54575-96-1; **2a** (R = Bu), 54575-97-2; **2a** (R = CH_2Ph), 54575-98-3; **2a** (R = $CH{=}CH_2$), 54576-00-0; **2b** (R = Me), 54576-01-1; **2b** (R = Bu), 54576-02-2; **2b** (R = CH_2Ph), 54576-03-3; **2c** (R = Me), 54575-99-4; **2d** (R = Me), 54576-20-4; **2e** (R = Me), 54576-04-4; **2f** (R = Me), 54576-05-5; **2g** (R = Me), 54576-06-6; **3e,** 54576-07-7; **3f,** 54576-08-8; **3g,** 54576-09-9; **4,** 54576-10-2; **5,** 54576-11-3; **8,** 54576-21-5; **16,** 54576-12-4; dimethyl 3-methyladipate, 54576-13-5; dimethyl 3-methylpimelate, 54576-14-6; dimethyl 3-methylsuberate, 54576-15-7; dimethyl 3,4,4-trimethylpimelate, 54576-16-8; 3-benzylpimelic acid, 54576-17-9; dimethyl 3-benzylpimelate, 54576-18-0; Me_2CuLi, 15681-48-8; n-Bu_2CuLi, 24406-16-4; $benzyl_2CuLi$, 51467-05-1; methyl chloroformate, 79-22-1; sodium methoxide, 124-41-4; sodium hydroxide, 1310-73-2; 3,3,5-trimethylcyclohexanone, 873-94-9; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5.

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Synthesis of Oxometacyclophanes with the Dieckmann Condensation

Clarence W. Schimelpfenig

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

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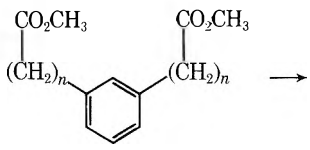
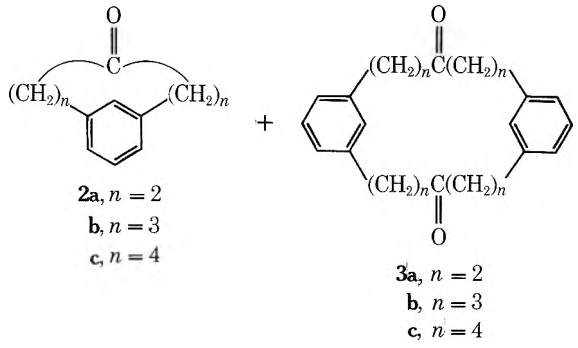
The Dieckmann condensation under conditions of high dilution has been used with methyl esters of *m*-benzenedialkanoic acids. The products, metacyclophanes with carbonyl groups at the centers of the meta bridges, are described. The particular meta-bridged compounds are **3** (n = 2, 3, 4) and a derivative of **2** (n = 4).

We have studied the preparation of oxometacyclophanes[1] with the Dieckmann condensation.[2] We originally wished to prepare phenalene[3] from 4-oxo[7]metacyclophane (**2b**); however, the ketone could not be prepared from ester **1b**. Therefore, we continued to investigate the



1a, $n = 2$
b, $n = 3$
c, $n = 4$



2a, $n = 2$
b, $n = 3$
c, $n = 4**

3a, $n = 2$
b, $n = 3$
c, $n = 4$

condensation to determine the limitations of the reaction and to study the properties of the ketone products.

Results and Discussion

The cyclization was conducted in the high-dilution manner used earlier[4,5] except for the following two changes. (1) Hydrolysis–decarboxylation of the intermediate keto esters in alcohol solution was changed to saponification followed by acidification and decarboxylation. Ketone product and recovered ester starting material boiled too close for facile separation. Starting material was isolated by extraction with bicarbonate, followed by acidification. (2) The ketones were isolated by vacuum distillation and sublimation of the neutral portion of the reaction mixture, instead of by recrystallization.

The Dieckmann cyclization did not lead to **2b**, the metacyclophane with a strategically placed functional group for phenalene synthesis. The isolable cyclic product was **3b**, 4,17-dioxo[7.7]metacyclophane. Homologous diesters were cyclized to **3a** as the only isolable cyclic product and to **3c** as major isolable cyclic product. A minor product from cyclization of **1c**, 5-oxo[9]metacyclophane (**2c**), was recognized but not isolated and purified.

Infrared spectra of the diketones were unusual. Each spectrum of the solid (mulled in mineral oil) contained one carbonyl stretching frequency band, while each carbon tetrachloride solution spectrum had two bands. In each solution spectrum, the higher frequency band was slightly less intense than the lower frequency band.

Nuclear magnetic resonance spectra of the diketones indicated two different environments for the aromatic hydrogens between the bridges in the smaller rings, **3a** and **3b**, but identical environments for the corresponding aromatic hydrogens in the largest ring **3c**.

Unsubstituted monoketones and diketones with structural formulas like **2** and **3** have been prepared earlier. 7-Oxo[13]metacyclophane [**2** (n = 6)] was prepared by pyrolysis of the cerium salt of *m*-benzenediheptanoic acid.[6] **3a** was prepared by the Thorpe–Ziegler cyclization of *m*-benzenedipropanenitrile, followed by hydrolysis.[7] Without high dilution the Dieckmann condensation of dimethyl *m*-benzenediacetate gave the intermediate salt of the keto ester, which was treated with methyl iodide to give the dimethyldicarbomethoxy derivative of **3** (n = 1), undoubtedly a mixture of isomers.[8]

Inspection of Dreiding models and Fisher–Taylor–Hirschfelder models reveals that refusal to form the eight-membered ring in **2a** and the ten-membered ring in **2b** and reluctance to form the 12-membered ring in **2c** should be expected. Interaction between nonbonded atoms severely reduces the frequency of collisions between carbanion moiety and ester moiety in the ring closure step to make monoketone. Interaction between these hydrogen atoms does not appreciably reduce the rates of reactions to make larger rings and linear polymers. Considering the coplanarity requirement of five ring atoms, three aromatic and two benzyl carbon atoms, the synthetic pattern is consistent with earlier investigations of the Dieckmann condensation. In the aliphatic series cyclononanone and cyclodecanone could not be prepared while cyclohendecanone and cyclododecanone were formed in extremely low yields.[5] In the paracyclophane series where six ring atoms, four aromatic and two benzyl carbon atoms, must remain coplanar, the smallest ring was the 17-membered ring in 7-oxo[13]paracyclophane.[4]

Experimental Section

***m*-Benzenedipropanoic Acid.**[9] One gram of 5% palladium on carbon was added to a solution of 150 ml of water, 65 ml of 20% aqueous NaOH, and 43.6 g (0.2 mol) of *m*-benzenediacrylic acid, which had been prepared from isophthalaldehyde and malonic acid in a Döbner synthesis:[7] mp 277–286° dec (lit.[10] mp 280° dec). The mixture was hydrogenated at room temperature in the Parr low-pressure apparatus. After catalyst had been removed by filtration, the filtrate was acidified with concentrated HCl. Then 50 ml of acetic acid was added and the suspension was digested at 80°. The mixture was cooled and filtered. After being dried, the product weighed 33.8 g (76%) and melted at 148–150.5° (lit.[11] mp 146–147°).

Dimethyl *m*-Benzenedipropanoate (1a). *m*-Benzenedipropanoic acid (1.6 mol) and 4.8 mol of thionyl chloride were refluxed until the mixture was homogeneous (1 hr). Excess thionyl chloride was removed by distillation at water aspirator vacuum. The molten acyl chloride was added slowly to 32 mol of methanol which was being stirred and chilled in an ice bath. The precipitate was removed by filtration, washed with cold methanol and with water, and dried in the vacuum desiccator. **1a** weighed 354 g (88%) and melted at 53.5–55° (lit.[12] mp 50–52°).

***m*-Benzenedipropanol.** In the customary manner,[4] 0.5 mol of **1a** was treated with lithium aluminum hydride to give 85.4 g (88%) of the glycol, bp 158° (0.5 mm) [lit.[6] bp 165–168° (0.2 mm)].

***m*-Bis(3-bromopropyl)benzene.** A mixture of 83.5 g (0.43 mol) of *m*-benzenedipropanol, 180 g of sodium bromide, and 155 ml of water was refluxed for 2 hr, while 128 ml of concentrated H_2SO_4 was added dropwise. After refluxing for 2 more hr, the mixture was cooled and extracted with ether. The ether solution was washed with aqueous $NaHCO_3$, water, aqueous $Na_2S_2O_3$, and water. The solution was dried and distilled, giving 115 g (83%) of the dibromide, bp 130–133° (0.3 mm) [lit.[6] bp 165–168° (0.2 mm)].

Higher boiling material, bp 190–250° (0.3 mm), and the undistillable residue showed strong absorption near 1110 cm^{-1} but only absorption due to C-H in the 3-μ region. This indicated some hydrolysis of the dibromide and ether formation during extraction.

***m*-Benzenedibutanoic Acid.** In the customary manner,[4] 32 g (0.1 mol) of *m*-bis(3-bromopropyl)benzene was treated with potassium cyanide to give *m*-benzenedibutanenitrile, bp 160–164° (0.2 mm). This nitrile was hydrolyzed to give 23.6 g (94%) of the acid, mp 131–135°. The analytical sample, recrystallized once from acetic acid and once from ethanol, melted at 135–136.2°[13]: NMR (CD_3SOCD_3) δ 11.8 (s, broad, 2, $-CO_2H$), 6.9–7.2 (m, 4, ArH), 2.56 (t, 4, J = 7 Hz, $ArCH_2-$) (contribution of CD_3SOCD_2H was subtracted out), 2.15 (m, 4, $-CH_2CO_2H$), 1.75 (m, 4, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.24; H, 7.24.

Dimethyl *m*-Benzenedibutanoate (1b). In the customary manner,[4] 23 g (0.092 mol) of *m*-benzenedibutanoic acid was esterified to give 21.4 g (77%) of **1b:** bp 143–146° (0.2 mm); NMR ($CDCl_3$) δ 7.03 (m, 3, ArH), 7.00 (s, 1, ArH), 3.65 (s, 6, $-CO_2CH_3$), 2.62 (t, 4, J = 6 Hz, $ArCH_2-$), 2.22 (t, 4, J = 6 Hz, $-CH_2CO_2-$), 2.00 (m, 4, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.15; H, 7.88.

Dimethyl *m*-Benzenedipentanoate (1c). Using the malonic ester synthesis, 80 g (0.25 mol) of *m*-bis(3-bromopropyl)benzene was starting material for preparation of *m*-benzenedipentanoic acid. After decarboxylation of the tetracarboxylic acid, the crude diacid was used to prepare **1c** by the method outlined above for **1b.** The product, **1c,** 48.8 g (64% after two steps from the dibromide), boiled at 164–165° (0.3 mm): NMR ($CDCl_3$) δ 7.03 (m, 3, ArH), 7.00 (s, 1, ArH), 3.65 (s, 6, $-CO_2CH_3$), 2.60 (t, 4, J = 6 Hz, $ArCH_2-$), 2.33 (t, 4, J = 6 Hz, $-CH_2CO_2-$), 1.65 (m, 8, $-CH_2CH_2-CH_2-$).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.42; H, 8.59.

A small quantity of **1c** was saponified. The mixture was acidified. The solid was recrystallized from benzene to give *m*-benzenedipentanoic acid: mp 85.9–87.2°; NMR ($CDCl_3$) δ 11.5 (s, 2, COOH), 7.12–6.88 (m, 3, ArH), 7.02 (s, 1, ArH), 2.60 (t, 4, J = 6 Hz, $ArCH_2-$), 2.37 (t, 4, J = 6 Hz, $-CH_2CO-$), 1.65 (m, 8, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.32; H, 7.71.

4,14-Dioxotricyclo[15.3.1.1^{7,11}]docosa-1(21),7,9,11(22),17,19-hexaene (3a) (3,14-Dioxo[5.5]metacyclophane). In the manner reported earlier[4] and with the two exceptions noted in the Results and Discussion section, 12.5 g (0.05 mol) of **1a** was treated with potassium *tert*-butoxide in xylene to give, after sublimation [180–200° (0.5 mm)] of the neutral residue and recrystallization of the sublimate from absolute ethanol, 0.90 g (11.3%) of **3a:** mp 117–118° (lit.[7] mp 116–117.5°); ir (5% in CCl_4) 1716 and 1708 cm^{-1} (carbonyl) and (mineral oil mull) 1701 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.22–6.86 (m, 6, ArH), 7.00 (s, 1, ArH), 6.78 (s, 1, ArH), 3.0–2.4 (m, 16, $ArCH_2CH_2CO-$).

Starting acid could not be recovered from the acidic fraction of the isolated products. Infrared spectra of these materials indicated presence of ketone and carboxylic acid groups, leading to the conclusion that the acidic fraction was composed of noncyclic condensation products.

5,17-Dioxotricyclo[19.3.1.1^{9,13}]hexacosa-1(25),9,11,13(26),-21,23-hexaene (3b) (4,17-Dioxo[7.7]metacyclophane). In the manner outlined above, 13.9 g (0.05 mol) of **1b** was treated with potassium *tert*-butoxide in xylene. Isolated were 5.00 g of *m*-benzenedibutanoic acid (40% of starting material recovered as acid) and 1.98 g of crude **3b.** This product was sublimed at 230° (0.3 mm) and the sublimate was triturated with 20 ml of boiling ethanol to give 1.38 g (14.6%) of **3b,** colorless plates: mp 164–166.3°; ir (1% in CCl_4) 1717 and 1710 cm^{-1} (carbonyl) and (mineral oil mull) 1706 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.07 (m, 6, ArH), 7.00 (s, 1, ArH), 6.83 (s, 1, ArH), 2.60 (t, 8, J = 6 Hz, $ArCH_2-$), 2.08 (t, 8, J = 6 Hz, $-CH_2CO-$), 1.93 (m, 8, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{26}H_{32}O_2$: C, 82.93; H, 8.57; mol wt, 376.52. Found: C, 82.87; H, 8.47; mol wt (Rast), 350.

6-Oxobicyclo[9.3.1]pentadeca-1(15),11,13-triene (2c) Semicarbazone (5-Oxo[9]metacyclophane Semicarbazone) and 6,20-Dioxotricyclo[23.3.1.1^{11,15}]triaconta-1(19),11,13,15(30),-25,27-hexaene (3c) (5,20-Dioxo[9.9]metacyclophane). In the manner outlined above, 15.3 g (0.05 mol) of **1c** was treated with potassium *tert*-butoxide in xylene to give 5.5 g of *m*-benzenedipentanoic acid (40% of starting material recovered as acid), a very small amount of **2c,** and 0.51 g of **3c.**

2c was in a fraction (0.15 g) that distilled at 160° (0.7 mm). The carbonyl absorption frequency (1710 cm^{-1}, neat) distinguished **2c** from the precursor ester with absorption at 1735 cm^{-1}. The distillation fraction slowly turned pink while standing for several days in a vial. It had a musky odor characteristic of macrocyclic ketones. Attempts to purify **2c** were unsuccessful, although a small portion was used to prepare a semicarbazone: mp 198–199.5°; NMR ($CDCl_3$) δ 7.93 (s, 1, $=NNHCO-$), 7.3–6.9 (m, 4, ArH), 5.52 (s, broad, 2, $CONH_2$), 2.75 (m, 4, $ArCH_2-$), 2.0–1.2 (m, 12).

Anal. Calcd for $C_{16}H_{23}N_3O$: C, 70.30; H, 8.47; mol wt, 273.38. Found: C, 70.50; H, 8.52; mol wt (Rast), 304.

3c was isolated by subliming at 180–220° (0.3 mm) the residue after distilling **2c,** above. The sublimate was recrystallized from ethanol to give 0.51 g (4.7%) of **3c,** colorless plates: mp 71–73.6°; ir (5% in CCl_4) 1719 and 1707 cm^{-1} (carbonyl) and (mineral oil mull) 1703 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.01 (m, 6, ArH), 6.97 (s, 2, ArH), 2.57 (t, 8, J = 6 Hz, $ArCH_2-$), 2.30 (t, 8, J = 6 Hz, $-CH_2CO-$), 1.53 (m, 16, $-CH_2CH_2CH_2-$).

Anal. Calcd for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32; mol wt, 432.62. Found: C, 83.20; H, 9.30; mol wt (Rast), 455.

Registry No.—**1a,** 6221-61-0; **1b,** 54698-69-0; **1c,** 54698-70-3; **2c,** 54698-71-4; **2c** semicarbazone, 54698-72-5; **3a,** 54698-73-6; **3b,** 54698-74-7; **3c,** 54738-98-6; *m*-benzenedipropanoic acid, 6082-86-6; *m*-benzenediacrylic acid, 37710-81-9; *m*-benzenedipropanol, 41009-85-2; *m*-bis(3-bromopropyl)benzene, 41009-86-3; *m*-benzenedibutanoic acid, 54698-75-8; *m*-benzenedibutanenitrite, 54698-76-9; *m*-benzenedipentanoic acid, 54698-77-0.

References and Notes

(1) The metacyclophane nomenclature is that proposed by R. W. Griffin, Jr., *Chem. Rev.*, **63,** 45 (1963), and B. H. Smith, "Bridged Aromatic Compounds", Academic Press, New York, N.Y., 1964. Systematic names are also given in the Experimental Section.

(2) For a review of the Dieckmann condensation, see J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15,** 1 (1967).

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(7) K. Ziegler and A. Lüttringhaus, *Justus Liebigs Ann. Chem.*, **511,** 1 (1934).

(8) A. F. Titley, *J. Chem. Soc.*, 2571 (1928). The catalyst for this condensation was a combination of sodium, originally present, and sodium methoxide, formed during the reaction. Acyloins are possible coproducts in this reaction.

(9) It is a pleasure to acknowledge the help of Dr. Kurt L. Loening, Chemical Abstracts Service, in naming many of the compounds in the systematic manner.

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(13) W. Reppe, *Justus Liebigs Ann. Chem.*, **596,** 158 (1955). Reppe suspected this acid to be a component in a mixture, but he never isolated and characterized the compound.

Synthesis of Dimethylsilylbis(benzoxazoles)

John H. Cornell*[1] and David Remy

U.S. Army Natick Laboratories, Natick, Massachusetts 01760

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Dimethylsilylbis(benzoxazoles) and related substances were required as model compounds in a study of the thermal stability of organosilicon structural units. Nitration of *p,p'*-dimethylsilyldiphenol with acetyl nitrate gave moderate yields of 4,4'-dimethylsilylbis(2-nitrophenol), which in contrast to the starting material does not undergo desilylation by acid or bromine and is resistant to cleavage by diazonium salts. Catalytic hydrogenation gave 4,4'-dimethylsilylbis(2-aminophenol) in excellent yield. The corresponding tetraacetyl derivative underwent thermal ring closure with elimination of acetic acid to give 5,5'-dimethylsilylbis(2-methylbenzoxazole) in high yield. Analogous reactions afforded 5,5'-dimethylsilylbis(2-phenylbenzoxazole). These bis(benzoxazoles), although relatively low melting (below 150°), are very stable to heat; thus 5,5'-dimethylsilylbis(2-methylbenzoxazole) was heated to 515° for 30 min in a sealed tube without decomposition.

Dimethylsilylbis(benzoxazoles) and their precursors were required as model compounds and as potential starting materials for the preparation of thermally stable organosilicon polymers. In the carbon series polymers containing the isopropylidenebis(benzoxazole) moiety in the main chain have exhibited a high degree of thermal stability as well as desirable mechanical properties.[2-4] Substitution of the dimethylsilyl group for the isopropylidene group offered the possibility of further enhancement of mechanical properties, with no decrease in thermal stability.

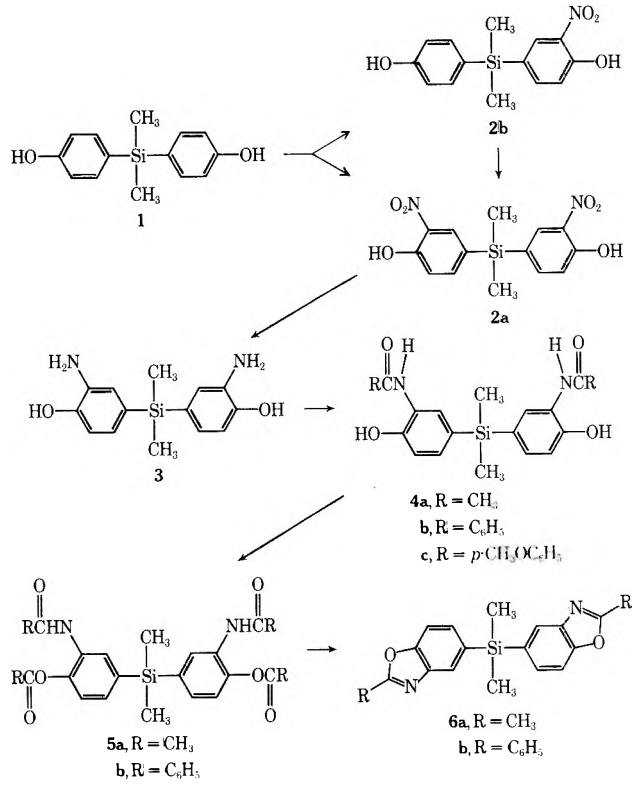
The effects of organosilicon substitution on benzoxazoles have not yet been studied. However, Kovacs[5] reported that the solubility in organic solvents of benzimidazole derivatives containing the triphenylsilyl group was greater than the solely organic analogs, with no decrease of thermal stability or melting point. The preparation of representative substituted dimethylsilylbis(benzoxazoles) and some of their thermal properties are described in the present report.

Discussion

Preparation of Compounds 2a–6. The reactions involved in the synthesis of the dimethylsilylbis(benzoxazoles) are shown in Scheme I. The starting material, *p,p'*-dimethylsilyldiphenol (1), was prepared by known methods.[6] Unlike the carbon analog, *p,p'*-isopropylidenediphenol,[7] direct nitration of 1 with nitric acid in glacial acetic acid resulted in cleavage; the main product was a mixture of o- and *p*-nitrophenol. However, the desired nitration could be carried out in moderate yields with nitric acid in the presence of acetic anhydride. Under the reaction conditions employed it has been shown that this reagent consists largely of acetyl nitrate.[8] It seems probable that acetyl nitrate generated in situ is responsible for the successful nitration in this case. Since the starting *p,p'*-dimethylsilyldiphenol decomposes slowly at room temperature, even under anhydrous conditions, it is important for optimum yields to use a freshly prepared sample of 1; even small amounts of decomposition products yield intractable tars during the nitration.

Catalytic hydrogenation of **2a** gave 4,4'-dimethylsilylbis(2-aminophenol) (**3**) in good yield. Although this intermediate is quite stable in crystalline form, its isolation and purification by crystallization from aqueous sulfurous acid according to the procedure given in the Experimental Section is recommended. Alternatively the hydrogenation can be conducted in acetic anhydride as solvent. Under the latter conditions the product is 4,4'-dimethylsilylbis(2-acetaminophenol) (**4**), a stable intermediate for 5,5'-dimethylsilylbis(2-methylbenzoxazole) (**6a**).

Scheme I



Heating of **3** under reflux with excess acetic anhydride gave 4,4'-dimethylsilylbis(2-acetaminophenol) diacetate (**5a**), which upon distillation at reduced pressure lost the elements of acetic acid to give 5,5'-dimethylsilylbis(2-methylbenzoxazole) (**6a**). 4,4'-Dimethylsilylbis(2-benzamidophenol) dibenzoate (**5b**) was obtained by treatment of **3** in pyridine with the stoichiometric quantity of benzoyl chloride.

When **5b** was heated in programmed increments between 200 and 275° in a thermobalance, 5,5'-dimethylsilylbis(2-phenylbenzoxazole) (**6b**) was formed almost quantitatively with the elimination of 2 mol of benzoic acid. This reaction was also carried out in good yield on a preparative scale under similar conditions.

Structure and Properties of Compounds 2a–6b. Unlike its precursor **1**, 4,4'-dimethylsilylbis(2-nitrophenol) (**2a**) is very stable. It resisted acidic hydrolysis under progressively more vigorous conditions until cleavage was finally obtained with concentrated hydrochloric acid in a sealed tube after 50 hr at 150°. Under these conditions *o*-nitrophenol was obtained cleanly and in good yield. At-

tempted brominolysis of **2a** in a sealed tube at 115° failed, and the resulting material consisted largely of unchanged starting material.

Benzenediazonium chloride solutions cleaved *p,p'*-isopropylidenediphenol and its homologs quantitatively under mild conditions to give *p*-hydroxyazobenzene and acetone or homologous ketones.[9]

An analogous cleavage takes place with *p,p'*-dimethylsilyldiphenol, but its dinitro derivative **2a** is recovered unchanged under similar conditions.

The postulated structure of **2a** is supported by its NMR spectrum, the aromatic portion of which is consistent with an ABX system (symmetrical 1,2,4 substitution in both rings). One half of the AB quartet (J_{ab} = 8.1 Hz) is split into a doublet of doublets (J_{ax} = 1.5 Hz) by the meta proton.

Further evidence for the presence of a nitro group in each ring of **2a** is adduced by titration of both phenolic groups (equivalence point pH 9.7) with sodium hydroxide in methanol–water. In contrast, only one of the phenolic groups of 4,4'-dimethylsilyl(2-nitrophenol)phenol (**2b**) was titrated under these conditions.

4,4'-Dimethylsilylbis(2-aminophenol) (**3**) is quite stable in crystalline form, but in solution it darkens rapidly on exposure to air or light. It is most easily recrystallized from aqueous sulfurous acid by vacuum stripping of the sulfur dioxide; under these conditions a stable, crystalline product is obtained with minimum decomposition.

If the hydrogenation of **2a** is conducted in acetic anhydride, 4,4'-dimethylsilylbis(2-acetaminophenol) (**4a**), a stable derivative, is obtained. The amino groups of **3** could be acetylated with acetic anhydride in a buffered aqueous solution to give **4a.** Acetylation of **3** under more drastic conditions results in esterification of the hydroxyl groups also to give 4,4'-dimethylsilylbis(2-acetamino)phenol diacetate (**5a**). This is a crystalline substance which is stable to 250°, at which temperature ring closure to the corresponding bis(benzoxazole) takes place.

5,5'-Dimethylsilylbis(2-methylbenzoxazole) (**6a**) and 5,5'-dimethylsilylbis(2-phenylbenzoxazole) (**6b**) are crystalline solids which possess a remarkable degree of thermal stability. They can be recovered unchanged after heating to 515° in a sealed tube for 30 min, or at 320° for 3 hr. The ir spectra showed bands which are characteristic of the benzoxazole moiety[10] and the other spectral data support the assigned structures.

Experimental Section

Elemental microanalyses were performed by Midwest Microlabs, Ltd., Indianapolis, Ind.

Infrared spectra were obtained with a Perkin-Elmer Model 521 spectrophotometer, uv spectra with a Perkin-Elmer Model 202 visible–ultraviolet spectrophotometer, NMR data with Varian A-60 and HA-100 spectrometers, and mass spectra with a C. E. C. Model 21-110 spectrometer.

Thermogravimetric analyses were performed with a custom-made instrument comprising a Cahn RG electrobalance with a R. I. Data-Trak temperature programmer.

Preparation of 4,4'-Dimethylsilylbis(2-nitrophenol) (2a). Dimethylsilyldiphenol (14.07 g, 0.0575 mol), freshly prepared,[6] was briefly exposed to reduced pressure at room temperature to remove volatiles, and dissolved in 100 ml of acetic anhydride. The solution was cooled by stirring in a Dry Ice–acetone bath for about 45 min.

During this time the nitrating solution was prepared by adding concentrated nitric acid (10.8 g, 0.160 mol) slowly with stirring and cooling to 75 ml of acetic anhydride. During the addition the temperature was maintained between 35 and 40°. The nitrating solution was cooled to just above the appearance of crystals, and was added dropwise to the stirred cooled solution of dimethylsilyldiphenol. The addition required about 90 min, at the end of which the bath was removed and the stirring continued for 15 min. The reaction mixture was poured onto 800 ml of cracked ice and 600 ml of water and stirred, and the hydrolysis was completed at room temperature.

The mixture was extracted with four 200-ml portions of dichloromethane and the combined extracts were washed twice with 300-ml portions of water and dried over anhydrous magnesium sulfate. The filtrate was concentrated to give an orange-brown oil, which was freed from tars by passing it through a column (5.7 × 46 cm) packed with silica gel (Grace 950, 60–200 mesh) with benzene as solvent.

The product, together with a trace of *o*-nitrophenol, emerged in the first fraction (ca. 700 ml) and crystallized upon concentration of the eluate and addition of *n*-hexane. The crude product (11.9 g, 61.8%) was obtained as bright yellow crystals, mp 88–95°.

The foregoing product is of adequate purity for the reduction step; however, pure 4,4'-dimethylsilylbis(2-nitrophenol) was obtained by recrystallization of the crude product from *n*-hexane. The product crystallized very slowly as long, yellow needles: mp 101.1–101.5°; uv max (CH_3OH) 225 mμ (ε 15,700), (aqueous NaOH) 249 mμ (ε 39,700); ir (KBr) 3250, 3030, 2950, 1610, 1520, 1310, 1245, 1155, 895, and 670 cm^{-1}; NMR (CCl_4) δ 10.7 (s, 2 H), 8.25 (d, 2 H, J_{ac} = 1.5 Hz), 7.55 (m, 4 H, J_{bc} = 8.1 Hz), and 0.66 ppm (s, 6 H); mass spectrum *m/e* 334 (M), 319, 303, 289, 273, 258, 227, 212, 196, 150, 135, 85, 73, and 55.

Anal. Calcd for $C_{14}H_{14}O_6N_2Si$: C, 50.28; H, 4.22; N, 8.38. Found: C, 50.50; H, 4.20; N, 8.75.

Cleavage of 4,4'-Dimethylsilylbis(2-nitrophenol) (2). A small sample (0.10 g, 0.3 mmol) of **2** was heated with 3 ml of concentrated (36 *N*) hydrochloric acid in a sealed tube for 50 hr at 150°. A yellow aqueous layer and a gummy residue were formed. The gummy residue proved to be dimethylsilicone polymer; the aqueous phase was separated and extracted with dichloromethane. Chromatography (TLC) of the dried ($MgSO_4$) extracts indicated presence of only one component, a nitro compound having the same R_f as *o*-nitrophenol. Evaporation of the extracts gave yellow crystals of *o*-nitrophenol, 0.06 g (84%), mp 42.5–43.5°; no melting point depression with authentic *o*-nitrophenol (Eastman No. 191), mp 44.5–45°, was noted and the two samples had identical infrared spectra.

4,4'-Dimethylsilylbis(2-nitrophenol) (0.32 g, 0.96 mmol) failed to react with a slight excess of benzenediazonium chloride at 0° in excess 10% sodium hydroxide. However, in a control experiment under similar conditions dimethylsilyldiphenol was rapidly cleaved by benzenediazonium chloride to give *p*-hydroxyazobenzene and dimethylsilicone polymer.

Treatment of **2** with refluxing 20% sodium hydroxide for 64 hr, or with an excess of bromine in carbon tetrachloride at room temperature, failed to cleave it. The starting material was quantitatively recovered.

4,4'-Dimethylsilyl(2-nitrophenol)phenol (2b). Nitric acid, (70%, 3.61 g, 0.04 mol) was dissolved dropwise with stirring in 25 ml of acetic anhydride, maintaining the temperature between 25 and 35°. The nitrating solution was added dropwise with stirring to 4.69 g (0.0194 mol) of dimethylsilyldiphenol dissolved in 200 ml of dry ether. During the addition, which required 0.5 hr, the reaction mixture was maintained at about −40° by stirring in a Dry Ice–dichloromethane bath. The solution was allowed to warm to room temperature and stood overnight (16 hr). It turned from light yellow (2 hr) to amber at the end of this time.

The solution was poured on water and stirred for 1.5 hr, and the ethereal layer was thoroughly washed with water and dried over anhydrous magnesium sulfate. The crude product was obtained as an amber oil by evaporation on a rotary evaporator. It was chromatographed on a silica gel column with dichloromethane as developing solvent. The small forerun consisted of 4,4'-dimethylsilylbis(2-nitrophenol) (**2a**), but was soon followed by a larger fraction containing 4,4'-dimethylsilyl(2-nitrophenol)phenol (**2b**). This fraction (2.1 g, 36%) partly solidified on standing, and TLC showed it to be almost completely **2b**. This product was purified by recrystallization from *n*-hexane: mp 84–85.5°; uv max (CH_3OH) 232 mμ (ε 19,400), (aqueous NaOH) 252 mμ (ε 35,900); ir ($CHCl_3$) 3270, 2995, 1625, 1575, 1525, 1480, 1400, 1310, 1240, 1190, 1160, 1110, 1080, 813, and 786 cm^{-1}; NMR (CCl_4) δ 10.6 (s, 2 H), 8.1 (d, 2 H), 7.1 (m, 6 H), and 0.4 ppm (s, 6 H); mol wt (vapor pressure osmometry, $CHCl_3$) calcd, 289; found, 281. Titration: calcd, 10.0 ml; required 9.9 ml of 0.01 *M* NaOH to titrate 19.93 mg of **2a** as monobasic acid, single inflection at pH 9.5 in aqueous methanol.

Anal. Calcd for $C_{14}H_{15}O_4NSi$: C, 58.11; H, 5.23; N, 4.84. Found: C, 58.26; H, 5.47; N, 4.95.

Conversion of 4,4′-Dimethylsilyl(2-nitrophenol)phenol (2b) to 2a. 4,4′-Dimethylsilyl(2-nitrophenol)phenol (0.25 g, 0.86 mmol) was dissolved in 100 ml of acetic anhydride. A nitrating solution was prepared by dropwise addition of 0.5 g of 70% nitric acid to 20 ml of acetic anhydride, such that the temperature remained between 20 and 25°. The nitrating solution was added dropwise to the solution of the phenol at −5 to −10° with stirring. The reaction mixture was allowed to warm to 0° and held at that temperature for 1 hr, and then for 1 hr at 20°. At this time TLC indicated complete conversion of the starting material. The reaction mixture was poured into cold water and stirred for 1 hr. After cooling, yellow crystals separated which were collected by filtration (0.20 g, 70%), mp 93–100.5°. After recrystallization from *n*-hexane, this product had the same melting point as 4,4′-dimethylsilylbis(2-nitrophenol), produced no depression in a mixture melting point with an authentic sample, and exhibited identical ir spectra with the latter.

4,4′-Dimethylsilylbis(2-nitrophenol) Diacetate (2c). 4,4′-Dimethylsilylbis(2-nitrophenol) (1.51 g, 4.53 mmol) was refluxed for 4 hr with 50 ml of acetic anhydride. The solution turned from a bright to light yellow, and was poured on boiling water at the termination of refluxing. The cooled hydrolyzate was extracted with dichloromethane, which was then evaporated to dryness. The residue was recrystallized from 250 ml of boiling petroleum ether to give 0.79 g (63.8%) of product as fine yellowish-white needles: mp 119.5–120.0°; ir (KBr) 3080, 2960, 1775, 1600, 1530, 1350, 1190, 1085, 920, and 825 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}N_2O_8Si$: C, 51.67; H, 4.04; N, 6.70. Found: C, 51.40; H, 4.12; N, 6.75.

4,4′-Dimethylsilylbis(2-aminophenol) (3). 4,4′-Dimethylsilylbis(2-nitrophenol) (**2a**, 4.0 g, 0.012 mol) was dissolved in 250 ml of dry ethyl ether. Approximately 100 mg of 10% palladium on charcoal was suspended in 10 ml of absolute ether and added to the ethereal solution, which was then shaken at an initial hydrogen pressure of 50 psig in a Parr hydrogenator. Shaking was continued with replenishment of hydrogen when necessary until the calculated pressure drop (100 psi) was obtained after about 3 hr.

The hydrogenation mixture was treated with 100 ml of a saturated solution of sulfurous acid which dissolved precipitated **3** and allowed removal of the catalyst by filtration. The combined ethereal and aqueous filtrates were evaporated on a rotary evaporator at room temperature. When approximately one-half of the aqueous phase remained, yellowish-white crystals of the product began to appear. The solution was chilled and the first crop collected by filtration (1.2 g). A second crop (1.1 g), mp 148–150°, was obtained by decolorization of the filtrate with charcoal, further concentration, and adjustment to pH 6 with dilute ammonium hydroxide. The combined yield of **3** was 2.3 g (70%). The first crop was of sufficient purity for analysis: mp 150–151°; ir (KBr) 3360, 3290, 1500, 1270, 805, and 775 cm^{-1}; NMR (DMSO-d_6) δ 6.6 (m, 6 H), 0.3 (s, 6 H).

Anal. Calcd for $C_{14}H_{18}N_2O_2Si$: C, 61.05; H, 6.95; N, 10.17. Found: C, 61.40; H, 6.60; N, 10.15.

4,4′-Dimethylsilylbis(2-acetamidophenol) (4a). Method A. 4,4′-Dimethylsilylbis(2-aminophenol) (1.3 g, 4.74 mmol) was dissolved in dilute hydrochloric acid and the brownish solution was decolorized by stirring with activated charcoal at ca. 50°. The filtered solution was shaken with 1.0 g (10 mmol) of acetic anhydride, to which was immediately added an excess of saturated sodium acetate solution with further shaking. After stirring for several minutes in an ice bath, crystallization took place. The precipitate was collected by filtration, washed several times with water, and recrystallized from acetone–water. The product was obtained as fine white needles, mp 209.5–211.0°, 0.7 g (30%). An analytical sample was recrystallized from methanol: mp 212.5–213.0°; ir (Nujol) 3410, 1655, 1530, 1400, 1100, 1090, and 700 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}N_2O_4Si$: C, 60.31; H, 6.19; N, 7.82. Found: C, 60.24; H, 5.99; N, 7.49.

Method B. 4,4′-Dimethylsilylbis(2-nitrophenol) (**2a**) was catalytically hydrogenated in a Parr apparatus under the same conditions as were used to prepare **3**, with the exception that the solvent was acetic anhydride. After uptake of the theoretical quantity of hydrogen, the catalyst was removed by filtration and the excess acetic anhydride was removed by rotary evaporation. The residue was recrystallized from aqueous acetone to give 4,4′-dimethylsilylbis(2-acetamidophenol), mp 209–212°, in 73% yield. A small sample, recrystallized from methanol, had an ir spectrum identical with that of **4a** prepared by method A and exhibited no depression of mixture melting point.

4,4′-Dimethylsilylbis(2-acetamidophenol) Diacetate (5a). 4,4′-Dimethylsilylbis(2-aminophenol) (1.0 g, 3.66 mmol) was refluxed for 6 hr with 50 ml of acetic anhydride. The reaction mixture was evaporated to dryness and the residue was boiled with water. The resulting slurry was extracted with dichloromethane; the extracts were washed thoroughly with water and dried over Drierite. The residue obtained by evaporation of the filtered extracts was recrystallized from carbon tetrachloride to give **5a**, 1.38 g (85.3%), as colorless needles: mp 149.5–151°; ir (KBr) 1780, 1710, 1365, 1250, 1180, 1100, and 780 cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_2O_6Si$: C, 59.71; H, 5.92; N, 6.34. Found: C, 59.77; H, 5.91; N, 6.19.

4,4′-Dimethylsilylbis(2-benzamidophenol) (4b). 4,4′-Dimethylsilylbis(2-aminophenol) (**3**, 0.4 g, 1.46 mmol) was slurried in a mixture consisting of 10 ml of dimethylacetamide and an equal amount of carbon tetrachloride. Benzoyl chloride (0.41 g, 2.92 mmol) dissolved in 15 ml of carbon tetrachloride was added while the mixture was stirred in ice. The solution was further stirred in the cold, after addition of sufficient carbon tetrachloride to dissolve the solids. After about 1 hr, 50 ml of ethanol was added and the reaction mixture warmed to room temperature. The volatiles were evaporated and the remaining orange-brown oil was stirred with petroleum ether and water until it crystallized. The brownish crude product was recrystallized from acetone–water with decolorizing charcoal. Fine yellowish crystals of **4b** (0.703 g, 57%) were obtained: mp 205–206°; ir (Nujol) 3420, 3400, 1640, 1540, 1530, 1400, and 700 cm^{-1}.

Anal. Calcd for $C_{28}H_{26}N_2O_4Si$: C, 69.75; H, 5.40; N, 5.81. Found: C, 69.43; H, 5.64; N, 5.69.

4,4′-Dimethylsilylbis[2-(p-anisamido)phenol] (4c). This compound was prepared by the foregoing method starting with *p*-anisoyl chloride (Eastman 2668). It was obtained in 63% yield as a yellowish solid by recrystallization from ethanol–water: mp 245–246°; ir (Nujol) 3410, 2950, 2840, 1640, 1605, 1535, 1505, 1495, and 1255 cm^{-1}; NMR (DMSO-d_6) δ 7.4 (m, 14 H), 3.75 (s, 6 H), and 0.35 ppm (s, 6 H).

Anal. Calcd for $C_{30}H_{30}N_2O_6Si$: C, 66.40; H, 5.57; N, 5.16. Found: C, 66.10; H, 5.71; N, 5.00.

4,4′-Dimethylsilylbis(2-benzamidophenol) Dibenzoate (5b). 4,4′-Dimethylsilylbis(2-aminophenol) (**4**, 0.4 g, 1.46 mmol) was dissolved in 10 ml of dimethylacetamide and cooled in an ice–salt bath. Benzoyl chloride (0.41 g, 2.92 mmol) in 10 ml of carbon tetrachloride was added with stirring. Additional carbon tetrachloride was added to dissolve the slurry that formed. After 1 hr the solution was removed from the bath and 10 ml of ethanol was added. It was then evaporated to an orange-brown oil which crystallized on stirring with water and petroleum ether. The product was recrystallized from acetone–water to give yellowish needles: 0.4 g (57%); mp 216–217°; ir (KBr) 3200–3500 (broad), 2950, 1730, 1645, 1515, 1480, 1390, 1240, 1035, 800, and 700 cm^{-1}; NMR [$(CD_3)_2CO$] δ 10.27 (s, 2 H), 8.1 (m, 6 H), 7.6 (d, 10 H), and 0.7 (s, 6 H).

Anal. Calcd for $C_{42}H_{34}N_2O_6Si$: C, 73.05; H, 4.96; N, 4.06. Found: C, 73.01; H, 5.06; N, 3.96.

Thermal Analysis of 5b. 4,4′-Dimethylsilyl(2-benzamidophenol) dibenzoate (**5b**, 101 mg, 0.146 mmol) was charged to the pan of a thermobalance and heated by increments under a nitrogen flow until a significant weight loss began (between 200 and 250°). The temperature was maintained at 250° for 25 min, and was then increased to 275° for an additional 25 min. At the end of this time the rate of loss had become slow and heating was terminated. The total weight loss was 40 mg; elimination of two molecules of benzoic acid to form **6b** corresponds to 35.6 mg. The amber glassy residue which remained in the pan was recrystallized from ethanol–water. It proved to be identical with **6b** by mixture melting point and ir spectra. Examination of the sublimate deposited in the thermobalance suggested that it consisted of benzoic acid mixed with a small amount of **6b**. The benzoic acid was separated from the sublimate by recrystallization and its identity established by comparison with an authentic sample.

5,5′-Dimethylsilylbis(2-methylbenzoxazole) (6a). 4,4′-Dimethylsilylbis(2-acetamidophenol) diacetate (**5a**, 0.34 g, 0.77 mmol) was refluxed for 1 hr in a small distilling flask (oil bath at 230°) and was then distilled at 10 mm. The distillate solidified and was recrystallized from acetone–hexane to give **6a** (0.2 g, 80%) as a fine white powder: mp 111.5–113.5°; ir (KBr) 3050, 2960, 1610, 1570, 1410, 1275, 1240, 1180, 1070, 930, 920, 820, 785, 665, and 400 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}N_2O_2Si$: C, 67.05; H, 5.63; N, 8.69. Found: C, 67.05; H, 5.84; N, 8.43.

Thermal Stability of 6a. Two portions of the distillate (**6a**) were sealed in Pyrex tubes at 0.1 mm. One tube was heated at 320° for 3 hr and the other at 515° for 0.5 hr. A slight discoloration was

noted in the sample heated to the higher temperature. The contents were otherwise identical in melting point and ir spectra with the original **6a**.

5,5'-Dimethylsilylbis(2-phenylbenzoxazole) (6b). 4,4'-Dimethylsilylbis(2-benzamidophenol) dibenzoate (**5b**, 1.6 g, 2.32 mmol) was placed in a 100-ml three-neck round-bottom flask provided with a metal bath, cold finger, connections for nitrogen flow, and an outlet cold trap. The reaction mixture was heated under identical conditions as previously described for the thermal analysis of **5b**. The residue was dissolved in chloroform and extracted three times with 5% sodium bicarbonate solution and finally twice with water. The chloroform layer was separated, dried (Drierite), filtered, and evaporated to dryness. The product was recrystallized twice from absolute ethanol and from carbon tetrachloride–hexane (1:1). **6b** (8.86 g, 83%) was obtained as white needles: mp 148–148.5°; ir (KBr) 3040, 2960, 1610, 1550, 1485, 1445, 1325, 1280, 1265, 1230, 1065, 1050, 1020, 920, 810, 800, 775, 705, 690, and 420 cm^{-1}; NMR (CCl_4) δ 8.4 (m, 4 H), 8.2 (s, 2 H), 7.6 (m, 10 H), 0.9 ppm (s, 6 H); mass spectrum *m/e* 446 (M^+), 431, 254, 222, 215.

Anal. Calcd for $C_{28}H_{22}N_2O_2Si$: C, 75.31; H, 4.97; N, 6.27. Found: C, 75.40; H, 4.76; N, 6.19.

Thermal Analysis of 6b. A 5-mg sample of **6b** was sealed in a Pyrex capillary tube and run on a differential scanning calorimeter using an empty sealed Pyrex capillary as reference. The instrument was operated under nitrogen at a heating rate of 50°/min to a maximum temperature of 550°. With the exception of the expected melting endotherm at 149° the DSC scan exhibited no additional features.

Registry No.—1, 2915-36-8; **2a**, 54677-68-8; **2b**, 54677-69-9; **2c**, 54677-70-2; **3**, 54677-71-3; **4a**, 54677-72-4; **4b**, 54677-73-5; **4c**, 54677-74-6; **5a**, 54677-75-7; **5b**, 54677-76-8; **6a**, 54677-77-9; **6b**, 53543-27-4; acetic anhydride, 108-24-7; benzoyl chloride, 98-88-4; *p*-anisoyl chloride, 100-07-2.

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Thermodynamic Stabilities of Carbanionic σ Complexes. II. Simple Ketones and Their Cyclic Analogs

Robert M. Murphy, Claus A. Wulff, and Michael J. Strauss*

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

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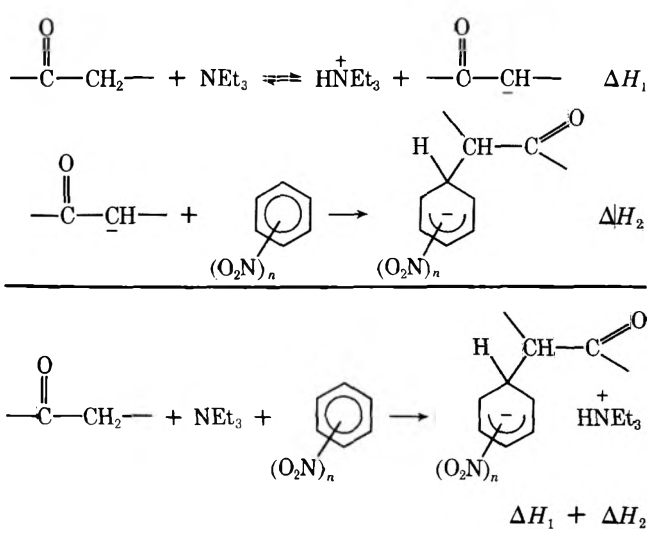
We recently reported initial calorimetric studies of the relative enthalpic stabilities of σ complexes formed from a series of polynitroaromatics with acetone and cyclopentanone.[1] These results tended to substantiate earlier predictions of structural features in the complex responsible for stabilization with *sym*-trinitrobenzene (TNB), 1,3-dinitronaphthalene (DNN), and 1,3,6,8-tetranitronaphthalene (TNN) as the aromatic precursors.[1,2] The initial data we had obtained showed an unusual enthalpic stability for the complex of TNB and cyclopentanone relative to TNB and acetone, and we felt that additional data would be helpful in confirming this observation. In addition we wished to extend the series to other simple ketones. We report here a completed study for the simple three- and five-carbon symmetrical ketones and for cyclopentanone and cyclohexanone.

The heats of formation of the complexes studied are summarized in Table I and represent the sum of ΔH_1 and ΔH_2 in the following general scheme.



As we noted earlier,[1] it is not easy to compare relative stabilities of different carbanionic σ complexes because complex formation is characterized by a thermodynamically unfavorable equilibrium, followed by an essentially irreversible reaction to yield the complex. Since both ΔH_1 and ΔH_2 may vary as the ketone is varied, relative comparisons of the sum $\Delta H_1 + \Delta H_2$ may be meaningless. This problem can be overcome by comparing a series of complexes in which ΔH_1 is always the same, i.e., the complexes of acetone with DNN, TNB, and TNN, and comparing the trend of stabilities observed in such a case (due to changes in ΔH_2) with those of another series, i.e., diethyl ketone.

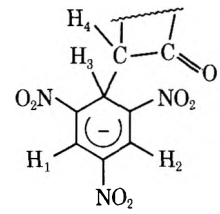
The data in Table I show several interesting trends. The increase in stability on going from DNN to TNB to TNN is

Table I
Enthalpies of Complexation ($\Delta H_1 + \Delta H_2$) of DNN, TNB, and TNN σ Complexes in DMSO[a]

	Acetone[b]	Diethyl ketone[c]	Cyclopentanone[d]	Cyclohexanone[e]
DNN	−2.3	−2.6	−6.2	−1.4
TNB	−5.1	−4.5	−27.2	−9.4
TNN	−24.2	−17.1	−28.2	−18.8

[a] In kilocalories per mole. [b] Registry no. are, respectively, 53032-16-9, 54643-41-3, 53032-19-2. [c] Registry no. are, respectively, 54643-37-7, 54643-43-5, 54643-49-1. [d] Registry no. are, respectively, 53092-10-7, 54643-45-7, 53032-23-8. [e] Registry no. are, respectively, 54643-39-9, 54643-47-9, 54643-51-5.

Table II
^{1}H NMR Data for Ketone Complexes with TNB[a]



Ketone	ν_1	ν_2	ν_3	$\Delta_{1,2}$	$J_{3,4}$
Acetone	−501.0	−501.0	−306.0	0	3.0
Diethyl ketone	−507.0	−507.0	−318.6	0	5.5
Cyclohexanone	−500.0	−495.9	−319.2	4.1	5.0
Cyclopentanone	−501.7	−497.1	−300.4	5.4	1.0

[a] In ν, downfield from internal Me_4Si in DMSO at 60 MHz.

quite similar for formation of both the acetone and diethyl ketone complexes and is in general accord with what has been predicted from earlier thermodynamic[1] and equilibrium constant[3] measurements. The trend of increasing stability for the complexes of cyclohexanone with DNN, TNB, and TNN is similar to that of the acyclic ketones, except for the complex with TNB, which is slightly more stable than might have been expected.

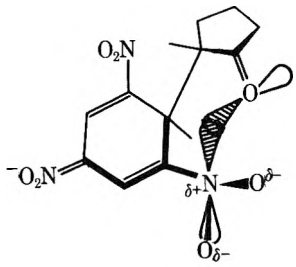
The most intriguing aspect of the data shown in Table I is the much greater stability of the cyclopentanone complexes with all three aromatics relative to the other ketone complexes. This is especially evident in the cyclopentanone complex with TNB, which is much more stable in the cyclopentanone series than would be expected.

We have proposed that a stabilizing dipole attraction may result from interaction of the cyclopentanone carbonyl and an adjacent nitro group which results in the added enthalpic stability of the cyclopentanone–TNB complex. Evidence supporting this possibility can be obtained by examining ^{1}H NMR absorptions of all the complexes with TNB.[4] These are summarized in Table II.

The differences in chemical shift of H_1 and H_2 are due to asymmetry at the carbon exocyclic to the ring. It has been argued that for these particular complexes, since $\Delta_{1,2}$ is zero for the diethyl ketone complex, the value of this difference measures a large unequal weighting of rotamer populations.[4] The complex of acetone has been included for comparative purposes, since in this instance ν_1 must equal

ν_2. It should be noted from the data summarized in Table II that $\Delta_{1,2}$ is the largest for cyclopentanone and appreciable for cyclohexanone. This would be expected if a strong stabilizing dipole attractive force exists between functionalities on the ketonic and anionic rings of the complex so that rotation about the CH^3–CH^4 bond is hindered. This conclusion is exactly the opposite of that offered earlier to explain the large values for $\Delta_{1,2}$ in the cyclic ketone complexes where restricted rotation was attributed to a repulsive interaction.[4] At the time this explanation was advanced no thermodynamic data were available, however.

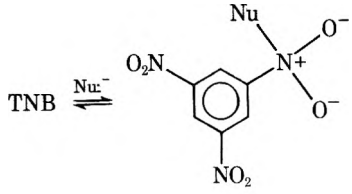
We propose that the conformation of the cyclopentanone–TNB complex 1 in which steric repulsions of the



1

rings are minimized may be additionally favored because of the stabilizing overlap of a filled nonbonding orbital on carbonyl oxygen with the positively polarized end of the carbon–nitrogen bond of a partially formed ortho nitronate function. Conformations leading to such an interaction are readily attained in Drieding models of the complex. With acyclic ketones the much greater rotational freedom may not favor such an interaction, since other low-energy conformations may be available which minimize nonbonded interactions.[5]

Interaction of nucleophiles with nitrogen of an aromatic nitro group is not unusual. Substantial evidence has been obtained for such an interaction with nitrogen nucleophiles and adducts like 2 have been characterized from the reaction of TNB with certain nitrogen bases.[6,7] Since most of



2

the charge on the trinitrocyclohexadienate ring of 1 resides on the para NO_2 group, the ortho NO_2 groups probably contain nitrogen with a considerable positive polarization. Certainly there is sufficient polarization for a dipole interaction such as we propose here.

Experimental Section

Materials. Diethyl ketone (Eastman) and cyclohexanone (Mallinkrodt) were each distilled twice and the fractions boiling at 102 and 156°, respectively, were collected and stored in the dark over molecular sieves until use. The preparation and purification of all other materials has been reported previously.[1]

Calorimetry. The apparatus and techniques for this study were identical with those employed earlier.[1] Two types of experiments were conducted and are presented as "Dilution Series" (Table III) and "Reaction Series" (Tables IV and V).[8] The terms "dilution" and "reaction" indicate the absence or presence, respectively, of samples of the aromatic in the DMSO-filled ampoules that were reacted with mixtures of DMSO, triethylamine, and ketone. Values obtained for the "Dilution Series" become the vaporization correction, q', that appears in Tables IV and V. In each experiment the reaction mixture comprised 90 ml of DMSO, 5 ml of triethylamine, and 5 ml of the appropriate ketone. The values of ΔH listed in Tables IV and V may be obtained from the data by $\Delta H = (q - q')/n$, where n is the number of moles of aromatic that have reacted.

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Supplementary Materials Available. Thermodynamic data in Tables III, IV, and V 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 $2.50 for microfiche, referring to code number JOC-75-1499.

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Correlations of Electron Impact Fragmentations of Pyrimidyl Alkyl Ketones with Photochemical Reactivity

Edward C. Alexander* and Roy J. Jackson

Department of Chemistry, University of California at San Diego, La Jolla, California 92037

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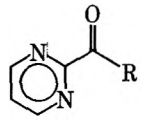
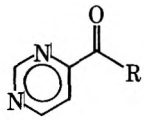
A number of studies designed to correlate the electron-impact fragmentation of organic molecules with their photochemical reactivity have been carried out over the past several years.[1] These studies have dealt primarily with molecules containing a carbonyl functionality and have focused on ketones. In general the studies have shown the behavior of ketones upon electron impact to be similar to that exhibited by them upon photochemical excitation. Thus, simple aromatic and aliphatic ketones having a propensity to undergo type I and type II cleavage reactions when exposed to ultraviolet light have been shown to undergo analogous α cleavage and McLafferty rearrangement reactions in the mass spectrometer. We recently reported[2] on the photochemistry of the propyl 2-, 4-, and 5-pyrimidyl ketones **1**, **2**, and **3**. Ketones **1**, **2**, and **3** were found to exhibit enhanced photochemical reactivity toward intramolecular hydrogen abstraction with respect to butyrophenone, and to the related butyrylpyridines. Moreover, in the case of the propyl 4-pyrimidyl ketone (**2**), intramolecular hydrogen abstraction in polar solvents occurred by way of a ring nitrogen atom and led to cyclopropanol formation. In light of these results we considered it informative to examine the mass spectra of the propyl 2-, 4-, and 5-pyrimidyl ketones **1**, **2**, and **3**, and a number of the homologous methyl, ethyl, and butyl pyrimidyl ketones. It was of interest to us to determine whether any analogy existed between the photochemical reactions of the ketones and their unimolecular framentations induced by electron impact.

Table I
Mass Spectra of Alkyl Pyrimidyl Ketones at 70 eV

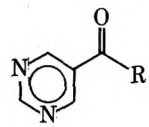
	Ketone										
m/e	1	2	3	4	5	6	7	8	9	10	11
164						27	25	6			
150	35	16	11								
136				62	27						
135	32	17				79	44				
122	12	16	39			100	24	100	53	25	58
108	14	21		23	70	53	45				
107	29	19	100	37	27	32	16	50	13		100
94	15	13			14	42	22		46	20	
85						18	17				
81	36	14		42	23	40	13		14		
80	100	100		100	100	97	100		100	45	
79	58	28	29	93	51	12	25		25	18	49
71	23	25									
57				66	99	40	38				
53	50	26	13	72	51				24	38	29
52	18	39	17	29	99		73			42	31
43	86	78	13						46	100	47



1, R = propyl
4, R = ethyl
6, R = butyl
9, R = methyl



2, R = propyl
5, R = ethyl
7, R = butyl
10, R = methyl



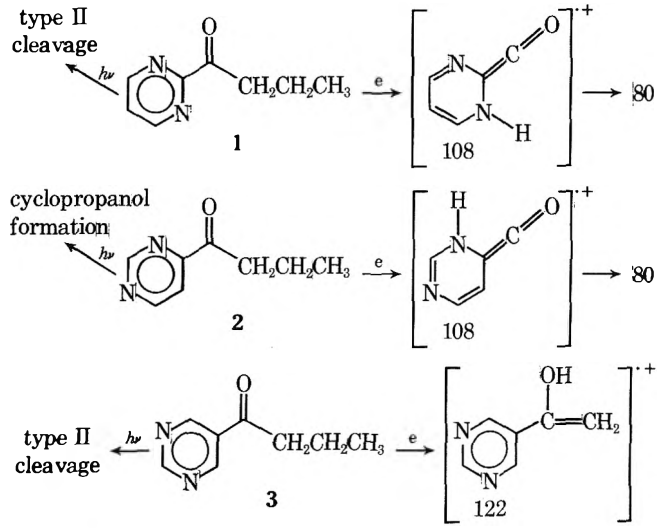
3, R = propyl
8, R = butyl
11, R = methyl

Results

The mass spectra of the propyl 2-, 4-, and 5-pyrimidyl ketones **1**, **2**, and **3**, and the 2- and 4-ethyl, 2-, 4-, and 5-butyl, and 2-, 4-, and 5-methyl pyrimidyl ketones **4**–**11** were measured at 70 eV. The principal ions (>10%) (Table I) from the fragmentation of the alkyl pyrimidyl ketones **1**–**11** were found to be very similar to those observed in the mass spectra[3] of the related alkyl pyridyl ketones. For the most part the principal fragments in the pyrimidyl series differed from those of the corresponding pyridyl solely by the additional ring nitrogen substitution.

Discussion

In the case of the propyl pyrimidyl ketones **1**–**3**, the mass spectral behavior of the 5 isomer (**3**) is found to be analogous to that reported[3] for butyrophenone and the related propyl 3- and 4-pyridyl ketones. Ketone **3** undergoes two principal modes of fragmentation, α cleavage (150 → 107) and McLafferty rearrangement (150 → 122). In comparison to the 5-propyl ketone **3** the 2- and 4-propyl ketones **1** and **2** show mass spectral behavior similar to that reported[3] for 2-propyl pyridyl ketone, their major mode of framentation being a McLafferty-type rearrangement via a ring nitrogen atom (150 → 108). The respective photochemical behaviors[2] of the propyl 4- and 5-ketones **2** and **3** parallel their principal modes of mass spectral fragmentation. In ketone **2** photochemical cyclopropanol formation requires intramolecular hydrogen abstraction by a ring nitrogen atom, and in ketone **3** the type II cleavage reaction occurs by way of the excited carbonyl. In marked contrast to the propyl pyrimidyl ketones **2** and **3**, propyl 2-pyrimidyl ketone (**1**) shows much less similarity in its principal mode of photochemical vs. mass spectral decomposition. The McLafferty-type rearrangement of ketone **1** involves a ring nitrogen atom, while its type II cleavage reaction involves the excited carbonyl.



In the homologous 2- and 4-ethyl pyrimidyl ketones **4** and **5**, where the nature of the carbonyl side chain allows for hydrogen abstraction by a ring nitrogen atom only, the anomalous behavior of the 2 isomer is maintained. The 2-ethyl pyrimidyl ketone (**4**) shows no detectable photochemical reaction;[4a] yet it undergoes a McLafferty-type rearrangement to nitrogen (136 → 108). This is in contrast to the 4-ethyl pyrimidyl ketone (**5**), which undergoes intramolecular hydrogen abstraction both photochemically[4a] and in the mass spectrometer via a ring nitrogen atom.

When the length of the carbonyl side chain is increased to four carbons, McLafferty rearrangement to oxygen can compete with the McLafferty-type rearrangement to nitrogen.[3] Such a competitive rearrangement process is observed in the mass spectra of the butyl 2- and 4-pyrimidyl ketones (**6** and **7**) (164 → 122, vs. 164 → 108). A similar process however, is not observed photochemically for ketones **6** and **7**. Upon electronic excitation both butyl ketones **6** and **7** undergo hydrogen abstraction by way of the carbonyl oxygen exclusively.[4a,b]

The mass spectra of the methyl 2-, 4-, and 5-pyrimidyl ketones **9**, **10**, and **11** show that loss of ketene (122 → 80) is an important mode of fragmentation in the 2 and 4 isomers **9** and **10** but not in the 5 isomer **11**, where α cleavage (122 → 107) predominates. This suggests that the loss of ketene involves a McLafferty-type rearrangement via a ring nitrogen atom and that the rearrangement can occur by way of a five-membered transition state. Since neither loss of ketene nor type I cleavage is observed photochemically in ketones **9** and **10**,[4a] there appears to be little analogy existing between the mass spectral and photochemical behavior of the methyl pyrimidyl ketones **9**–**11**.

From the above discussion it is clear that the best correlation of photochemical and mass spectral decomposition of alkyl pyrimidyl ketones exists in the 5-alkyl systems. While the 4-alkyl pyrimidyl ketones show good correlation when the alkyl substituent is ethyl and propyl, they show poorer correlation when it is methyl or butyl. This is in contrast to the 2-alkyl pyrimidyl ketones, which show virtually no correlation at all. The good correlation observed in the 5-alkyl pyrimidyl ketones in comparison to the isomeric 2- and 4-alkyl ketones can best be explained in terms of stereochemical and stereoelectronic factors. In the 5-alkyl ketone systems the geometrical features of the ketones ensure little to no involvement of a ring nitrogen atom in both photochemical and electron impact induced reactions. This leads to behavior in these ketones which is similar to that reported[3,5] for butyrophenone, valerophenone, and the 3- and 4-butyryl and valeryl pyridines. In the case of the 2- and 4-alkyl pyrimidyl ketones the close proximity of a ring nitrogen atom to the reaction center necessitates its involvement. The degree of involvement, however, will depend to a great extent on the relative electron densities of the nitrogen atoms in the excited ketones. When the nature of the electron densities of these atoms in the electronically excited state differ substantially from their relative charge densities in the corresponding ionized state, the photochemical and mass spectral behavior of the ketones will show poor correlation. This appears to be the case for the 4-butyl pyrimidyl ketone **7**, where exclusive type II reaction occurs photochemically and competitive nitrogen and oxygen hydrogen atom abstraction occurs in the mass spectrometer. This is also apparently true of the 2-propyl and 2-butyl pyrimidyl ketones **1** and **6** and of the 2-butyryl and 2-valeryl pyridines,[3,5] where exclusive type II cleavage occurs photochemically and a McLafferty-type rearrangement via a ring nitrogen atom predominates upon electron impact.

Experimental Section

The recorded mass spectra were obtained with an LKB 9000 mass spectrometer at a nominal ionizing voltage of 70 eV.

The alkyl pyrimidyl ketones were prepared as previously described[2] and were purified by gas chromatography.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and The Research Corporation for support of this work.

Registry No.—**1**, 53342-24-8; **2**, 53342-25-9; **3**, 53342-26-0; **4**, 54643-09-3; **5**, 54643-10-6; **6**, 54643-11-7; **7**, 54643-12-8; **8**, 54643-13-9; **9**, 53342-27-1; **10**, 39870-05-8; **11**, 10325-70-9.

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A Method for Cleaving 2,4-Dinitrophenylhydrazones to Ketones

John E. Mc Murry* and Michael Silvestri

Thimann Laboratories, University of California, Santa Cruz, California 95064

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2,4-Dinitrophenylhydrazone (2,4-DNP) derivatives of ketones and aldehydes are important, both because of their use in purifying and characterizing the parent compounds, and because of their occasional use in synthesis.[1] Regeneration of the parent carbonyl compound from a 2,4-DNP can present severe problems, however. The major difficulty is that 2,4-DNP's are stable to acid hydrolysis. A variety of methods have been devised to overcome this problem.

The most common method of cleaving a 2,4-DNP is to effect an exchange reaction with another carbonyl compound such as pyruvic acid[2,3] or levulinic acid.[4] Yields are often unacceptable in these reactions, however. A second method is to ozonize the C=N double bond at low temperatures.[1,5] The reaction works moderately well, but is clearly incompatible with the presence of unsaturation within the molecule. A third general method is to activate the 2,4-DNP toward hydrolysis. This is usually done by reducing the nitro groups to amines with either stannous ion,[6,7] lithium aluminum hydride,[8] or chromous ion.[9] The resulting 2,4-diaminophenylhydrazone then hydrolyzes. Yields are generally acceptable if there are no other reactive functional groups present, but acidic conditions are necessary.

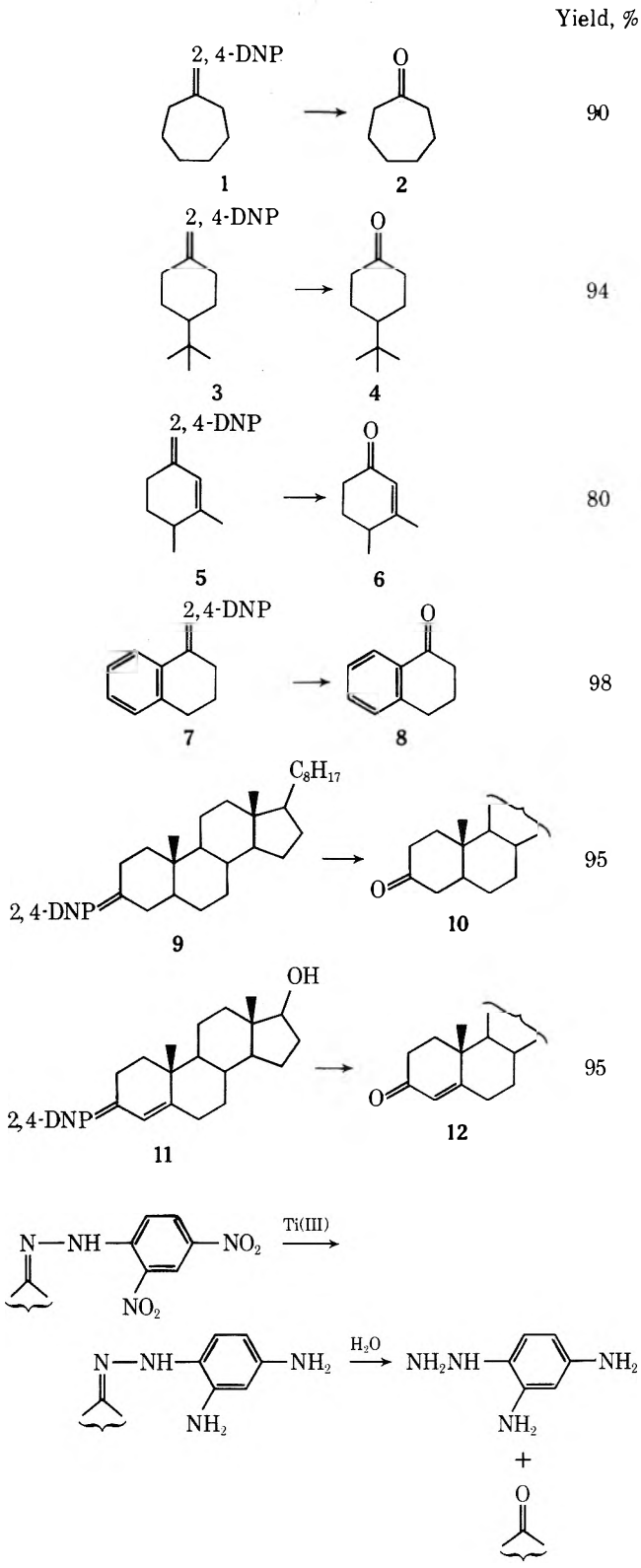
We have had several occasions in our own laboratory to regenerate the parent carbonyl compounds from their 2,4-DNP's, and we have found aqueous titanous ion to be an excellent and convenient new reagent for effecting this transformation.[10] Some of our results are given in Chart I.

We believe that this method has several advantages over presently known ones. The reaction works for a variety of cases, both saturated and unsaturated, and has given high yields of carbonyl products in all examples tested. Further, titanous ion is inexpensive and commercially available as a stable 20% aqueous solution.[11] It thus does not have to be prepared freshly before use as does chromous ion. Most important, however, is the fact that the reaction can be carried out under neutral conditions whereas other methods require acidic conditions.

Mechanistically, there are two obvious possibilities for the course of the cleavage reaction. The simplest possibility is to assume that titanous ion acts by reducing the nitro groups to amino groups in a manner similar to that of stannous or chromous ion, and that the resulting 2,4-diaminophenylhydrazone then undergoes hydrolysis.

It is well known that titanous ion can rapidly reduce nitroarenes to aminoarenes,[12] and thus we cannot completely rule out this mechanism. We nevertheless feel that it is unlikely because, as we have demonstrated, the cleavage reaction works equally well under buffered conditions, and we consider it surprising that a 2,4-diaminophenylhydrazone would hydrolyze so readily at neutral pH.

Chart I
Reaction of 2,4-Dinitrophenylhydrazones with Titanous Ion



A second possibility, and one which we favor, is that titanous ion acts by first reducing the nitro groups, and then by cleaving the hydrazone N–N bond to generate an imine. The imine should then hydrolyze readily to a carbonyl compound.

Titanous ion is well known for its ability to cleave the N–O bond of oximes[13] and nitro compounds,[14] and the S–O bond of sulfoxides.[15] We consider the cleavage of the N–N hydrazone bond to be exactly analogous. Good evidence for this hypothesis comes from the fact that when we examined the basic reaction products from the titanous ion cleavage of 2,3-dimethylcyclohexenone 2,4-DNP, we isolated 1,2,4-triaminobenzene rather than 2,4-diaminohydrazine. Clearly, titanous ion is capable of cleaving a N–N bond, and we feel that this supports our hypothesis.

In summary, we have developed a mild, new method for the regeneration of carbonyl compounds from their 2,4-dinitrophenylhydrazones. The process proceeds in high yield, and has considerable advantage over other known procedures.

Experimental Section

General Reaction Procedure for the Reductive Cleavage of 2,4-Dinitrophenylhydrazones. Cholestanone (10). Cholestanone 2,4-DNP (0.34 g, 0.60 mmol) was dissolved in 30 ml of dry dimethoxyethane, and a 20% aqueous solution (1.6 *M*) of titanium trichloride (5.60 ml, 9.0 mmol) was added. The reaction mixture was refluxed for 30 min under a nitrogen atmosphere, then cooled, diluted with water, and extracted with ether. The combined ether extracts were washed with water and with saturated brine, then dried ($MgSO_4$), filtered, and concentrated at the rotary evaporator. The solid residue was recrystallized from 2-propanol to give 220 mg (95%) of pure cholestanone, mp 128–130°. The product was identified by melting point and by comparison of its infrared and NMR spectra with those of an authentic sample.

In a similar manner, the following compounds were prepared.

Testosterone (12) was prepared by reduction of its 2,4-DNP (0.26 g, 0.56 mmol) with a 20% aqueous $TiCl_3$ solution (5.3 ml, 8.4 mmol): yield 0.15 g (95%); mp 154–155; identified by melting point and by comparison of infrared and NMR spectra with those of an authentic sample.

α-Tetralone (8) was prepared by reduction of its 2,4-DNP (0.53 g, 1.62 mmol) with 20% aqueous $TiCl_3$ (15 ml, 24.2 mmol): yield 0.23 g (98%); purified by chromatography on silica gel; identified by comparison of infrared and NMR spectra with those of an authentic sample.

Cycloheptanone (2) was prepared by reduction of its 2,4-DNP (0.61 g, 2.1 mmol) with 20% aqueous $TiCl_3$ (19.6 ml, 31.3 mmol): yield 210 mg (90%); purified by chromatography on silica gel; identified by comparison of infrared and NMR spectra with those of an authentic sample.

3,4-Dimethylcyclohexenone (6) was prepared from its 2,4-DNP (0.50 g, 1.65 mmol) by reduction with 20% aqueous $TiCl_3$ (15.5 ml, 24.7 mmol): yield 164 mg (80%); purified by chromatography on silica gel and identified by comparison of infrared and NMR spectra with those of an authentic sample.

4-*tert*-Butylcyclohexanone (4) was prepared from its 2,4-DNP (0.40 g, 1.2 mmol) by reduction with 20% aqueous $TiCl_3$ (11.25 ml, 18 mmol): yield 175 mg (94%); purified by chromatography on silica gel and identified by comparison of infrared and NMR spectra with those of an authentic sample.

The above reactions could also be carried out at a buffered pH by adding ammonium acetate to the reaction until the desired pH was obtained.

Acknowledgment. This work was supported by a research grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1**, 3349-73-3; **2**, 502-42-1; **3**, 54532-12-6; **4**, 98-53-3; **5**, 54532-13-7; **6**, 10463-42-0; **7**, 853-95-2; **8**, 529-34-0; **9**, 47825-04-7; **10**, 15600-08-5; **11**, 2347-93-5; **12**, 58-22-0.

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Concerning the Stereochemistry of Cyclohexenone Alkylations

Kundanbhai M. Patel and William Reusch*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

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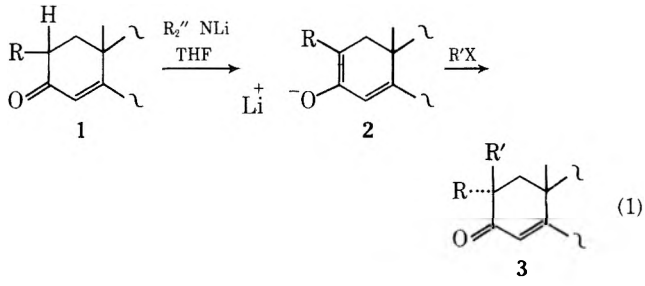
Recently we reported[1] that substituted cyclohexenone systems can be selectively alkylated at the α' position via the kinetically favored cross-conjugated dienolate base (eq 1). In the case of cholest-4-en-3-one (**1**, R = H) the product



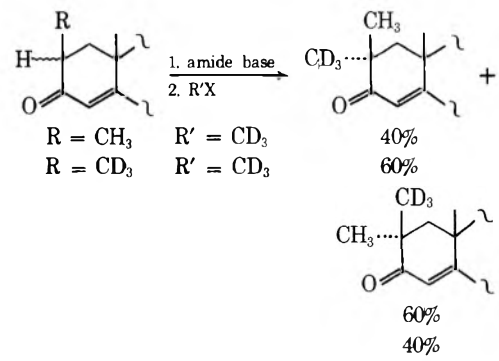
1 **2** **3** (1)

of methylation (R′X = CH_3I) was regarded as the previously unknown 2β-methyl epimer (**3**, R′ = CH_3, R = H) because it appeared to be homogeneous (TLC analysis on silical gel and alumina), melted sharply at 110–111°, and was different from the known α epimer[2] (mp 122–124°) into which it was transformed by the action of base.

A subsequent study of the 100-MHz ^1H NMR spectrum of this substance suggested that it might be a mixture of epimers, and this has now been confirmed by high-pressure liquid chromatography on a 15-cm column packed with Zorbex (a small diameter porous silica provided by Du Pont). The roughly 60:40 α:β composition of this epimeric mixture has been further indicated by careful europium shift measurements conducted by Dr. D. N. Kirk and R. D. Burnett of Westfield College, University of London. In the latter work the C-2 methyl doublets, which normally overlapped at ca. δ 1.05 ppm, were caused to shift to a lower field than the C-19 methyl signals for the α and β epimers. Although the methyl doublets still overlapped, they were easily discernible and well separated from the other methyl signals.

At this point, two possible explanations for the inhomogeneous nature of the methylation product were considered. (1) The alkylation reaction itself may have been essentially nonstereoselective. (2) A stereoselective alkylation step may have been followed by a partial epimerization of the kinetically favored β-methyl product. A combination of these factors may also be operating. Since the same mixture of product epimers was obtained from several experiments in which the time and temperature of the alkylation step varied, we were inclined to favor the first rationale. However, it seemed appropriate to settle the question by effecting the alkylation of a similar substrate, chosen so that product epimerization could not take place.

The possibility of effecting a second alkylation reaction at C-2 was demonstrated by methylation of 2α-methylcholest-4-en-3-one (**1**, R = CH_3) under the conditions noted in eq 1. Formation of 2,2-dimethylcholest-4-en-3-one (3, R = R′ = CH_3)[3] in 97% yield follows the previously stated general rule[1,4] that α'-proton abstraction is kinetically favored in α,β-unsaturated ketones. By effecting this sequential dimethylation with CH_3I followed by CD_3I, and in a second case with CD_3I followed by CH_3I, we have been able to ascertain the stereoselectivity of the second alkylation step (eq 2).



(2)

The very poor stereoselectivity observed for these alkylation reactions is similar to that reported for the methylation of 2-cyanocholest-4-en-3-one,[5] and is presumably due in part to a flattening of the six-membered ring caused by the double bond. Since other factors may influence the stereochemistry of β-keto nitrile alkylation reactions,[6] this similarity may not be very significant. While this manuscript was being prepared, Girard and Conia reported[7] that cyclopropanation of the trimethylsiloxy derivative of the 2-enolate base derived from testosterone proceeded with essentially no stereoselectivity.

Experimental Section

All reactions involving strong bases were conducted under dry nitrogen or argon, using solvents purified by distillation from suitable drying agents. Melting points were obtained with a Hoover-Thomas apparatus or on a Reichert hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on Varian A-60, T-60, and HA-100 spectrometers with deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

General Procedure for α'-Methylation. To a cold solution of 1.30 mmol of isopropylcyclohexylamine in 0.5 ml of dry tetrahydrofuran (THF) was added 1.25 mmol of *n*-butyllithium in hexane. After this mixture was stirred at 0° for 15 min, 1.0 mmol of the α,β-unsaturated ketone in 5 ml of THF was slowly added and the resulting solution was maintained at 0° for 90 min. Following rapid addition of 4.00 mmol of methyl iodide, the reaction mixture was allowed to warm to room temperature and held there for 3 hr before being mixed with water and extracted with ether. The combined ether extracts were washed (twice each) with water and brine, dried, and distilled under reduced pressure.

Results of Specific Methylations. A. Cholest-4-en-3-one. The yield of crude 2-methylcholest-4-en-3-one was 98%. Recrystal-

lization from methanol afforded 95% colorless crystals, mp 110–111°, $[\alpha]_D$ 33.76° (2.14 g/100 ml $CHCl_3$).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.36; H, 11.63. Found: C, 84.28; H, 11.69.

This mixture of 2α- and 2β-methylcholest-4-en-3-one (150 mg) was treated with 50 mg of potassium hydroxide in 25 ml of methanol for 3 hr at 25°. The usual work-up gave 2α-methylcholest-4-en-3-one (**3**, R = CH_3; R = H) in 98% yield, mp 122–124° (lit.[2] mp 122–124), $[\alpha]_D$ 89° (lit.[2] 94°).

B. 2-Methylcholest-4-en-3-one. The yield of crude 2,2-dimethylcholest-4-en-3-one (**3**, R = R′ = CH_3) was 97%. Recrystallization from methanol afforded 93% of pure material, mp 94–95° (lit.[3] mp 94–95°), molecular ion (70 eV) *m/e* 412.

C. 2-Methyl-d_3-cholest-4-en-3-one. A mixture of diastereoisomers (**3**, R = CH_3; R′ = CD_3 and R = CD_3; R′ = CH_3) was obtained in 90% yield: mp 86–87°; ir (KBr) 2220 cm^{-1} (C–D stretch); molecular ion (70 eV) *m/e* 415.

Results of Specific Methylation with CD_3I. A. Cholest-4-en-3-one. The yield of crude 2-methyl-d_3-cholest-4-en-3-one was 75%, mp 98–100°, ir (KBr) 2220 cm^{-1}.

B. 2-Methylcholest-4-en-3-one. A mixture of diastereoisomers (**3**, R = CD_3; R′ = CH_3 and R = CH_3; R′ = CD_3) was obtained in 40% yield after preparative TLC on a 2-mm silica gel plate eluent 9:1 cyclohexane–ethyl acetate): mp 80–82°; ir (KBr) 2220 cm^{-1}; molecular ion (70 eV) *m/e* 415.

Analysis of the diastereoisomeric mixtures of deuterium-labeled 2,2-dimethylcholest-4-en-3-ones was effected by observing the relative intensities of the resonance signals at δ 1.06 and 1.12 ppm in the 100-MHz spectra of these mixtures.

Acknowledgments. We thank the National Institutes of Health for their support of this work (Grant 2 R01 AM 10849-08), Mrs. Lorraine Guile for her assistance in obtaining mass spectra, and Dr. D. N. Kirk of Westfield College, London, for his interest in and helpful comments regarding this work.

Registry No.—**1** (R = H), 601-57-0; **3** (R = H; R′ = CH_3), 54446-37-6; **3** (R = CH_3; R′ = H), 54446-38-7; **3** (R = R′ = CH_3), 17305-84-9; **3** (R = H; R′ = CD_3), 54446-39-8; **3** (R = CD_3; R′ = H), 54446-40-1; **3** (R = CH_3; R′ = CD_3), 54515-22-9; **3** (R = CD_3; R′ = CH_3), 54515-23-0; CH_3I, 74-88-4; CD_3I, 865-50-9.

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Conversion of Amino Acids to β-Lactam Derivatives via Cyclopropanone

Harry H. Wasserman* and Edward Glazer[1]

Department of Chemistry, Yale University, New Haven, Connecticut 06520

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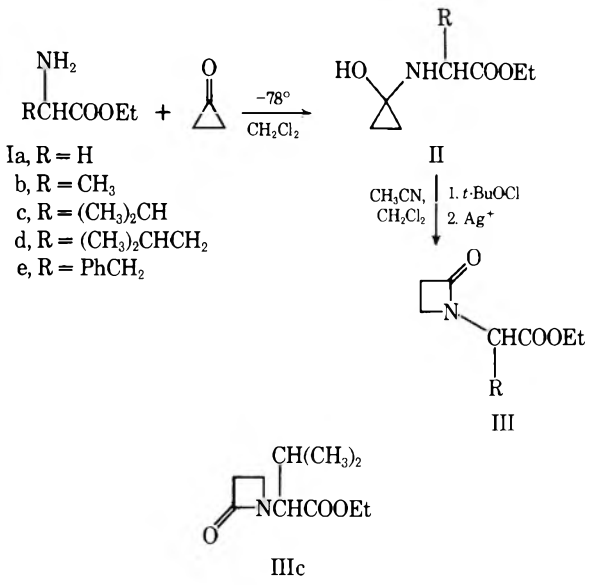
During studies on ring-enlargement reactions of cyclopropanones[2,3] we have recently reported a convenient synthesis of *N*-alkyl β-lactams via the silver ion catalyzed rearrangement of the corresponding *N*-chloro cyclopropylcarbinolamines.[2] We now report the extension of this procedure to the preparation of novel derivatives of amino acids. In particular, the method may be used as a simple route to β-lactams related to the penicillins, such as IIIc.

Scheme I

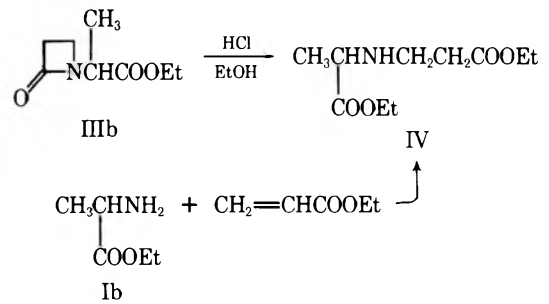


As outlined in Scheme I, the method involves addition of an equimolar amount of the amino acid ester to a purified solution of cyclopropanone[4] (or a suitable cyclopropanone precursor such as 1-acetoxycyclopropanol)[5] in methylene chloride at −78°. The resulting carbinolamine (II) in methylene chloride–acetonitrile (1:1) is then treated with 1 equiv of *tert*-butyl hypochlorite at ca. −10°, followed by addition of a threefold excess of silver nitrate. The reaction mixture is worked up in a manner identical with that reported for the simple alkyl primary amines.[2,6]

The β-lactams were characterized by NMR, ir, and mass spectra, as well as by the hydrolytic procedure described below. The NMR spectra show characteristic multiplets for the β-lactam ring protons[7] near δ 3.2 (2 H) and 2.9 (2 H), while the ir spectra exhibit the expected lactam carbonyl peaks at 1745 cm^{-1}.[8] Table I lists β-lactams derived from the ethyl esters of glycine, alanine, phenylalanine, valine, and leucine.

Chemical confirmation of the presence of the β-lactam ring in these systems was obtained by ethanolysis of IIIb with dry hydrogen chloride gas in absolute ethanol. The structure of the acyclic amino diester IV was established by its synthesis from ethyl acrylate and the ethyl ester of alanine as shown in Scheme II.

Scheme II



Experimental Section

Preparation of Cyclopropanone Solutions. Solutions of cyclopropanone in methylene chloride were prepared by the reaction at −78° of ketene with diazomethane, according to established procedures.[4b] Best results were obtained by using doubly distilled ketene and rigorously dried solvent.

1-Acetoxycyclopropanol. To a solution of cyclopropanone (50 mmol) in methylene chloride at −78° was added glacial acetic acid (2.3 g). Removal of solvent on the rotary evaporator at 0° gave 1-

Table I

Ester	Registry no.	Yield of β-lactam III, %	Registry no.
a. $NH_2CH_2CO_2Et$	56-40-6	33[a]	54643-14-0
b. NH_2CHCO_2Et $CH(CH_3)_2$	56-41-7	47	34094-43-4
c. NH_2CHCO_2Et $CH_2CH(CH_3)_2$	72-18-4	65	54643-15-1
d. NH_2CHCO_2Et CH_2Ph	61-90-5	65	54643-16-2
e. NH_2CHCO_2Et	63-91-2	70	54643-17-3

[a] Yield based on the carbinolamine intermediate (IIa).

acetoxycyclopropanol (50–70%), showing properties identical with those previously reported for this compound.[4b] The alcohol could be stored for several weeks at 0° without serious decomposition.

Conversion of Amino Acid Esters to β-Lactams. In a typical experiment, 35 mmol of the appropriate amino acid ethyl ester was added at once to the cyclopropanone solution and the resulting mixture was stirred for 45 min at −78° and 30 min at 0°. The solution was then treated with 0.5 g of sodium bicarbonate, followed by the addition of 3.8 g (35 mmol) of *tert*-butyl hypochlorite at −15 to −10° in the dark. The resulting mixture was stirred for an additional 40 min followed by dilution with 200 ml of dry acetonitrile and then treatment with 17.0 g of silver nitrate. Immediately after the addition of silver ion a copious white precipitate was observed, and the solution was allowed to warm to room temperature. After stirring for an additional 1.5 hr the solution was filtered, and the solvent was removed in vacuo at 35°. The residue was treated with 200 ml of 15% ammonium hydroxide and extracted with ether (3 × 100 ml). The extracts were dried over magnesium sulfate, and the solvent was removed under reduced pressure to afford the desired β-lactam as a yellow liquid. The method of purification, along with physical and spectroscopic data, is given below for each β-lactam.

1-(α-Carbethoxy)ethylazetidin-2-one (IIIb). The β-lactam (3.6 g, 47%) was purified by preparative VPC (12 ft × 0.75 in. 9% SE-30 column at 140°): ir (film) 3.38–3.50 (split), 5.75, 6.90, 7.15, 8.25, 8.40, 9.40, 10.85 μ; NMR ($CDCl_3$) δ 1.30 (6 H, m) 2.96 (2 H, t, J = 4 Hz), 3.40 (2 H, m), 4.20 (2 H, q, J = 7 Hz), 4.50 (1 H, q, J = 7 Hz); mass spectrum m/e (rel intensity) 171 (M^+, 5.5), 40 (29), 44 (26), 56 (96), 70 (14), 98 (100).

Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.30; H, 7.72; N, 8.26.

1-(α-Carbethoxy-β-phenyl)ethylazetidin-2-one (IIIe). The product (70%) was subjected to preparative thick layer chromatography on silica gel (15% CH_2Cl_2–85% ether): ir (film) 3.22–3.45 (split), 5.75, 7.25 (split), 7.95, 8.20, 8.40, 9.75, 13.40, 14.40 μ; NMR ($CDCl_3$) δ 1.28 (3 H, t, J = 7 Hz), 2.90 (2 H, m), 3.00–3.60 (4 H, m), 4.20 (2 H, q, J = 7 Hz), 4.66 (1, H, d of d, J = 6 and 8 Hz), 7.48 (5 H, m); mass spectrum m/e (rel intensity) 247 (M^+, 14), 91 (86), 114 (95), 132 (100), 156 (46), 174 (74), 176 (96).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.28; H, 6.94; N, 5.85.

1-(α-Carbethoxy)isoamylazetidin-2-one (IIId). The crude product (65%) was purified by VPC (12 ft × 0.75 in. 9% SE-30 column at 145°): ir (film) 3.28–3.50 (split), 5.75, 6.80, 7.20 (split), 7.40, 7.92, 8.15, 8.43, 9.73, 10.80 μ; NMR ($CDCl_3$) δ 1.00 (6 H, m), 1.32 (3 H, t, J = 7.5 Hz), 1.72 (3 H, m), 3.04 (2 H, t, J = 4 Hz), 3.30 (1 H, m), 3.52 (1 H, m), 4.25 (2 H, q, J = 7.5 Hz), 4.56 (1 H, t, J = 7.5 Hz); mass spectrum m/e rel intensity 213 (M^+, 1), 58 (51), 98 (35), 140 (100).

Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.81; H, 8.75; N, 6.51.

1-(α-Carbethoxy)isobutylazetidin-2-one (IIIc). The crude addition product (65%) was purified by VPC (12 ft × 0.75 in. 9% SE-30 column at 140°): ir (film) 3.34–3.50 (split), 5.75, 6.65, 7.17 (split), 7.35, 8.00, 8.30, 8.45, 9.75 μ; NMR ($CDCl_3$) δ 1.04 (6 H, d, J = 6 Hz), 1.32 (t, 3 H, J = 7.5 Hz), 2.28 (br septet, 1 H, J = 6 Hz), 3.10 (2 H, t, J = 4 Hz), 3.52 (1 H, m), 3.72 (1 H, m), 4.36 (3 H, m); mass spectrum m/e (rel intensity) 199 (M^+, 5.6), 41 (11), 84 (79), 114 (13), 126 (100).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.30; H, 8.63; N, 7.21.

1-Carbethoxymethylazetidin-2-one (IIIa). 1-Acetoxycyclopropanol (2.32 g, 15 mmol) in 15 ml of methylene chloride was added dropwise to a solution of ethyl glycinate (3.09 g, 30 mmol) in 100 ml of methylene chloride at −5° under nitrogen. The mixture was stirred for 1 hr and allowed to warm to 0°, followed by addition with vigorous stirring of 50 ml of cold saturated aqueous sodium bicarbonate. The phases were separated, and the organic layer was dried over magnesium sulfate. Removal of the solvent below 20° on the rotary evaporator gave 1.43 g (60%) of the carbinolamine as a clear oil: ir (film) 2.95, 3.45, 5.75, 7.25, 8.30, 9.85, 10.2 μ; NMR ($CDCl_3$) δ 0.78 (4 H, m), 1.22 (3 H, t, J = 7.5 Hz), 3.40 and 3.46 (4 H, two singlets), 4.20 (2 H, q, J = 7.5 Hz). To a solution of the carbinolamine (1.39 g, 8.8 mmol) in 100 ml of acetonitrile–methylene chloride (1:1) at −15° was added 0.5 g of solid sodium bicarbonate, followed by *tert*-butyl hypochlorite (1.05 g, 9.7 mmol) in the dark under nitrogen. The mixture was stirred for 1.5 hr and 5.0 g of silver nitrate was added at once. After stirring for 1.5 hr, the reaction mixture was worked up in the usual way to give the product (33%), purified by VPC (5 ft × 0.75 in. 9% SE-30 column at 130°): ir (film) 3.45, 5.74, 7.10, 8.20, 9.60, 10.7 μ; NMR ($CDCl_3$) δ 1.24 (3 H, t, J = 7 Hz), 3.00 (2 H, t, J = 4 Hz), 3.40 (2 H, t, J = 4 Hz), 3.92 (2 H, s), 4.18 (2 H, q, J = 7 Hz); mass spectrum m/e (rel intensity) 157 (M^+, 2), 42 (100), 56 (12), 69 (25), 84 (77), 129 (22).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.29; H, 7.13; N, 8.93.

Ethanolysis of the β-Lactam Derived from Ethyl Alanate. A solution containing 500 mg (2.92 mmol) of the β-lactam in 15 ml of absolute ethanol was treated with dry hydrogen chloride gas for 30 min and the resulting mixture was heated at 72° for 6 hr. The solvent was removed under reduced pressure, the residue was taken up in 40 ml of chloroform, and ammonia gas was bubbled through the solution for 15 min. The white precipitate was filtered and the solvent was removed in vacuo to give 470 mg (74%) of a light yellow liquid, purified by VPC (5 ft × 0.25 in. 20% SE-30 column at 145°): ir (film) 3.00, 3.37 (5.80, 6.95, 7.30, 8.45–8.76 (split), 9.80 μ; NMR ($CDCl_3$) δ 1.22 (9 H, m), 1.82 (1 H, s), 2.38 (2 H, t, J = 6 Hz), 2.70 (2 H, m), 3.24 (1 H, q, J = 7.5 Hz), 4.02 (4 H, m); mass spectrum m/e (rel intensity) 217 (M^+, 1), 42 (11), 44 (17), 55 (12), 56 (83), 98 (44), 130 (30), 144 (100).

Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.50; H, 8.86; N, 6.45.

Chemical confirmation of this structure was provided by its synthesis from ethyl acrylate and ethyl alanate. A solution containing 2.0 g (20 mmol) of ethyl acrylate and 2.92 g (25 mmol) of ethyl alanate in 25 ml of absolute ethanol was stirred at room temperature for 18 hr and for an additional 4 hr at 35–40°. The solvent was removed on the rotary evaporator and excess starting material was removed by evacuation at 20° (2 mm) to give a liquid (3.8 g, 88%). The product was purified by VPC and was shown to be identical (by ir, NMR, and GLC retention time) with the product obtained upon ethanolysis of the β-lactam.

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Registry No.—IV, 54643-18-4; 1-acetoxycyclopropanol, 16223-79-3.

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Decomposition of *tert*-Butyloxycarbonylamino Acids during Activation[1]

Miklos Bodanszky,* Yakir S. Klausner, and Agnes Bodanszky

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

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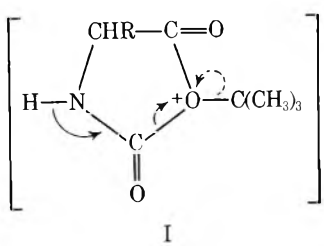
The formation of ninhydrin-positive impurities on reaction of *tert*-butyloxycarbonyl (Boc) amino acids with dicyclohexylcarbodiimide (DCC) was reported earlier.[2,3] The presence of ninhydrin-positive materials, presumably free amines, in solutions that contain a large excess of an acylating agent such as *O*-acylisourea derivatives[4] was intriguing. The free amines should be acylated under such conditions. An examination of the reaction mixture composed of equimolecular amounts of Boc-alanine and DCC in dichloromethane revealed that the ninhydrin-positive materials are not present as such in the mixture, but form on exposure to moist air or on contact with the chromatographic medium, thin layers of silica gel or paper. This observation not only resolves the apparent conflict of the simultaneous presence of amines and acylating agents, but also supports our earlier assumption that *N*-carboxyanhydrides (NCA's) are intermediates in the decomposition.

While the amount of the by-products allows their detection by the sensitive ninhydrin reaction, it turned out to be insufficient for a demonstration of the assumed intermediate NCA through ir spectra. Attempts to reveal the presence of an NCA through reaction with valyl polymer[5] or valine *tert*-butyl ester also failed.

Ninhydrin-positive spots were revealed on paper chromatograms[6] when reaction mixtures containing DCC and Boc derivatives of any of the 20 amino acids that occur in proteins was applied. The same pattern of spots could be observed: the most intense spot was that of the amino acid itself, a weak spot was found to correspond to the dipeptide consisting of two residues of the same amino acid, a spot at the origin suggested a polymer (or an aminoacyl derivative of cellulose), while a fast-moving species was identified as the *tert*-butyl ester of the amino acid. The outcome of the reaction was independent of the solvent. The same pattern, albeit in different intensities, was observed when toluene, dichloromethane, chloroform, acetonitrile, ethyl acetate, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide, or hexamethylphosphoramide was used. The method of activation also could be varied. When, instead of DCC, ethyl chloroformate,[7] Woodward's reagent,[8] or EEDQ,[9] all in the presence of equimolar amounts of triethylamine, were applied, the decomposition products remained the same. None of these methods of activation affected benzyloxycarbonylamino acids. On the other hand, when a solution of Boc-alanine in ethyl acetate was treated with phosphorus pentoxide, evaporation of the decanted solution left the crystalline NCA of alanine, that after sublimation was identified by its characteristic ir spectrum and by its readiness to form, on exposure to water, polyalanine.

The formation of amino acid *tert*-butyl esters can be rationalized by the attack of the oxygen of the *tert*-butyloxy group on the carbonyl of the activated carboxyl group (I). The resulting oxonium intermediate could produce both an NCA that yields the free amino acid, the dipeptide, and also an isocyanate, the *N*-carbonylamino acid *tert*-butyl ester that in turn is hydrolyzed—on the chromatographic paper—to the amino acid *tert*-butyl ester.



I

Experimental Section

Reaction of Boc-Ala with DCC. To a solution of Boc-Ala (95 mg) in CH_2Cl_2 (2 ml), DCC (103 mg) was added at room temperature. From time to time, spots were applied to filter paper (Whatman No. 1) and stained with a 0.3% solution of ninhydrin in acetone. A purple spot developed after about 10 min. The same reaction was carried out also on a porcelain spot plate in a desiccator over P_2O_5. Ninhydrin (3 drops of above-mentioned solution) was added, and the mixture stored at room temperature. No purple color was observed until about 24 hr later, when the mixture was exposed to moist air. Then a positive reaction could soon be observed.

The formation of ninhydrin-positive by-products on filter paper was also found in a series of tests in which solvents other than dichloromethane (cf. introduction) were used.

Reactions of Boc-Ala with Activating Reagents. Boc-L-Ala (19 mg) in tetrahydrofuran (1 ml) was treated with triethylamine (TEA, 0.015 ml) and ethyl chloroformate (0.010 ml). A spot on filter paper gave a positive reaction with ninhydrin. A control mixture with benzyloxycarbonyl-L-alanine (Z-L-Ala) instead of Boc-L-Ala gave no reaction with ninhydrin.

Boc-L-Ala (19 mg) in CH_2Cl_2 (1 ml) was allowed to react with TEA (0.015 ml) and EEDQ[9] (25 mg). A positive ninhydrin reaction was observed on filter paper, but none in the control experiment with Z-Ala.

Similarly, Boc-L-Ala (19 mg) in CH_3CN (1 ml), when treated in the presence of TEA (0.015 ml) with Woodward's reagent K[8] (25 mg), gave a purple spot with ninhydrin on filter paper. The parallel experiment with Z-Ala produced no ninhydrin-positive material.

In all three experiments with Boc-L-Ala, a similar pattern was observed on descending paper chromatograms in the solvent system 1-butanol–acetic acid–water (4:1:5, upper phase).[6] The principal ninhydrin-positive spot corresponds to alanine; a somewhat faster moving component was identified as alanylalanine. A fast-moving spot was also observed (cf. below). In the experiment with ethyl chloroformate as activating reagent, an additional ninhydrin-positive spot was found at the origin.

Identification of the By-products with the Amino Acid Analyzer. A mixture of Boc-L-Ala (76 mg) in CH_2Cl_2 (3 ml) was neutralized with TEA (0.060 ml) and allowed to react with DCC (90 mg). After standing overnight at room temperature, the crystals were removed by filtration and H_2O (1 ml) was added to the filtrate. The CH_2Cl_2 layer was evaporated, and the residual aqueous solution was diluted to 3 ml with a pH 2.2 buffer. A portion (1 ml) of this solution was applied to the long column of a Beckman-Spinco 120C amino acid analyzer.[10] The largest peak corresponded to alanine; a significant peak eluted at 149 min was identified as alanylalanine by comparison, via elution times, with an authentic sample. For confirmation, a second sample (1 ml) was applied, together with authentic L-Ala-L-Ala. A third sample (1 ml) was applied to the short column of the amino acid analyzer. A peak emerged at 62 min; an authentic sample of L-alanine *tert*-butyl ester appeared exactly at that elution time. The presence of alanine *tert*-butyl ester was confirmed also on TLC (cellulose powder, 1-butanol–acetic acid–water, 4:1:1).

***N*-Carboxyanhydride from Boc-Ala.** To a solution of Boc-Ala (0.40 g) in EtOAc (20 ml), P_2O_5 (2.2 g) was added in small portions. The solution was spotted on filter paper and stained with ninhydrin: a strong positive reaction was observed. After 1 hr at room temperature, the mixture was filtered on a dry sinter-glass filter and the filtrate was evaporated to a crystalline residue (0.20 g) which in the ir lacked the urethane carbonyl band of the starting material, and showed two new carbonyl bands at 1780 and 1864 cm^{-1}. A sample was crystallized from ethyl acetate–petroleum ether (bp 50–70°), mp 92° (lit.[11] mp 92°). The NMR spectrum ($CDCl_3$) confirmed the absence of the *tert*-butyl group: only the signals of the CH_3, α-CH, and NH protons were present. The product sublimed as a single compound at 50° (0.1 mm). When treated with H_2O, evolution of gas could be observed, followed by the separation of insoluble polyalanine.

Registry No.—Boc-L-Ala, 15761-38-3; DCC, 538-75-0; EEDQ, 16357-59-8; Woodward's reagent K, 4156-16-5; ethyl chloroformate, 541-41-3.

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Use of (2,3-Dihydro-2-oxo-1*H*-1,4-benzodiazepin-3-yl)-phosphonic Acid Esters as Novel "Wittig Reagents"

John H. Sellstedt

Research Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087

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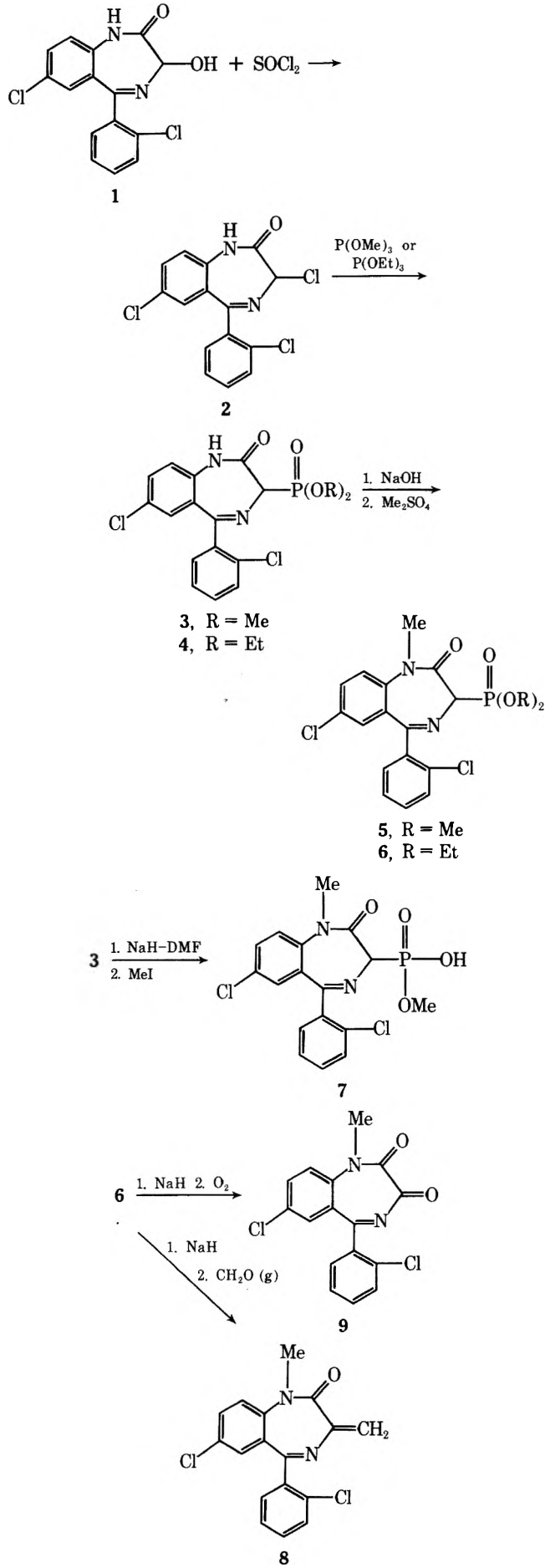
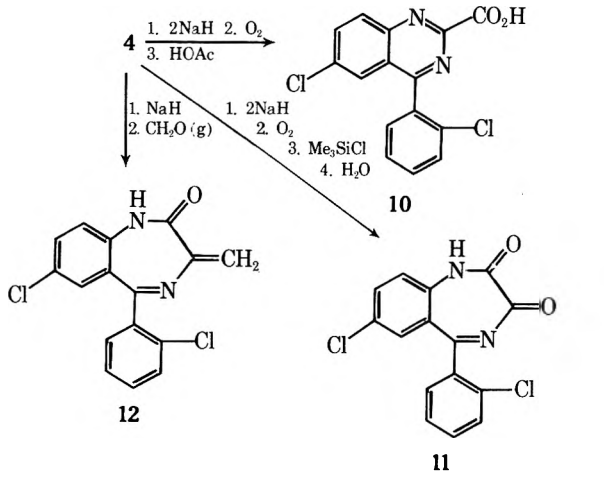
Because of our interest in the 1,4-benzodiazepine field, we sought a convenient method for the preparation of various useful lorazepam (**1**)[1] derivatives having functional substituents at the 3 position. One of our first thoughts was to prepare the 3-ketone and 3-methylene derivatives of **1** and use these groups as reactive intermediates. Only one paper[2] has described the preparation of any 1*H*-1,4-benzodiazepine-2,3-diones, and these preparations required the use of ruthenium tetroxide, which on any large preparative scale would be prohibitively expensive (5 g/$195.00). The preparation of 3-methylene-2*H*-1,4-benzodiazepin-2(3*H*)-ones has not been described. Instead of using this oxidation approach for the 3-keto type compounds, we decided to try making a "Wittig–Horner" type reagent from the benzodiazepine itself and using this reagent for the preparation of our desired intermediates. We found that **1** was easily converted to its corresponding 3-chloro derivative (**2**) with $SOCl_2$.[3] Condensation of **2** with $P(OMe)_3$ and $P(OEt)_3$ gave respectively **3** and **4**, by an Arbuzov–Perkow reaction.[4–6] Both **3** and **4** were methylated on the amide nitrogen by sodium hydroxide and dimethyl sulfate, giving respectively **5** and **6**. The acidic 3 carbon adjacent to the phosphorus was not methylated, at least on **3**, as evidenced by the P–H_3 coupling of **3** which is still present in the product **5**. Presumably this was also true in methylation of **4** to **6**, because **6** behaved like a Wittig reagent and the exchangeable NH of **4** disappeared. During one attempt to methylate the nitrogen of **3** with sodium hydride and methyl iodide in DMF, only **7** was isolated. Apparently the sodium iodide formed from the methylation on nitrogen caused an anionic demethylation of one of the phosphate OMe groups.[7]

The phosphonate carbanion of **6** was prepared in 1,2-dimethoxyethane with sodium hydride,[8] and reaction with gaseous formaldehyde readily gave **8**. Surprisingly, in spite of the apparent stability of phosphonate carbanions to oxygen,[4] reaction of the sodium salt of **6** with oxygen readily gave **9**.



In order to prepare the carbanion of **4** it was necessary to use 2 mol of sodium hydride, and in the subsequent oxygenation and acid work-up only **10** was formed, by a known rearrangement.[2] In subsequent oxygenations, the intermediate salt of **11** was neutralized with Me_3SiCl and the resulting silylated amide was hydrolyzed under neutral conditions. Analogous to the reactions of **6**, the carbanion of **4** gave **11** on oxygenation and **12** when condensed with gaseous formaldehyde.



Experimental Section

Melting points were taken in capillary tubes in an oil bath and are uncorrected. Solvents were removed in vacuo on a Büchi Rotavapor R. Anhydrous sodium sulfate was used for all solution drying. Spectra were obtained under the supervision of Mr. Bruce Hofmann. Ir spectra were determined in KBr pellets using a Perkin-Elmer Model 21 spectrophotometer. NMR spectra were determined with a Varian Model A-60 or a Jeolco Model C-60HL NMR spectrometer using TMS in DMSO-d_6. Analyses were carried out on a Perkin-Elmer Model 240 elemental analyzer.

[7-Chloro-5-(*o*-chlorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepin-3-yl]phosphonic Acid Dimethyl Ester (3). 7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one (**1**, 32.1 g, 0.1 mol) and 150 ml of $SOCl_2$ were refluxed on a steam bath for 1.25 hr using a $CaCl_2$ tube. The solution was concentrated using a vacuum pump and a rotary evaporator. The residue was scrubbed twice with toluene and 125 ml of $P(OMe)_3$ was added. The mixture was heated on a steam bath for 2 hr, refluxed for 1.5 hr, and warmed on the steam bath overnight under N_2. The mixture was filtered and the cake was washed well with toluene, giving 42.5 g of crude **3** (mp 242° dec), which on crystallization (MeCN) gave 30 g (73%) of **3**: mp 248° dec; ir 5.94 μ (C=O); NMR (DMSO-d_6) δ 3.78 (d, 3, J = 11 Hz, CH_3), 3.82 (d, 3, J = 11 Hz, CH_3), 4.50 (d, 1, J = 11 Hz, 3-CH), 7.01 (d, 1, J = 1.5 Hz, 6-CH), 7.2–7.85 (m, 6, aromatic), 11.05 (d, 1, J = 5 Hz, exchangeable NH).

Anal. Calcd for $C_{17}H_{15}Cl_2N_2O_4P$: C, 49.42; H, 3.66; N, 6.78; Cl, 17.16. Found: C, 49.45; H, 3.76; N, 6.85; Cl, 17.17.

[7-Chloro-5-(*o*-chlorophenyl)-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepin-3-yl]phosphonic Acid Diethyl Ester (4). A solution of **1** (6.42 g, 0.02 mol) in 50 ml of $SOCl_2$ was refluxed for 1 hr on a steam bath using a $CaCl_2$ tube. The solution was concentrated using a vacuum pump and a rotary evaporator. The residue was scrubbed twice with toluene, 45 ml of $P(OEt)_3$ was added, and the mixture was heated on the steam bath overnight under N_2. The resulting solution was concentrated and the residue was crystallized (MeCN), giving 6.5 g (74%) of **4**: mp 172–174°; ir 5.92 μ (C=O); NMR (DMSO-d_6) δ 1.25 (t, 6, J = 7.5 Hz, CH_3), 3.92–4.64 (m, 4, CH_2), 4.42 (d, 1, J = 12 Hz, 3-CH), 7.02 (d, 1, J = 2 Hz, 6-CH), 7.24–7.85 (m, 6, aromatic), 11.02 (d, 1, J = 5 Hz, exchangeable NH).

Anal. Calcd for $C_{19}H_{19}Cl_2N_2O_4P$: C, 51.71; H, 4.34; N, 6.45; Cl, 16.07. Found: C, 52.06; H, 4.35; N, 6.81; Cl, 15.96.

[7-Chloro-5-(*o*-chlorophenyl)-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]phosphonic Acid Dimethyl Ester (5). Addition of 10 ml of 1 *N* NaOH to a mixture of 4.14 g (0.01 mol) of **3** in 50 ml of THF caused the solid to dissolve, giving a red solution. Addition of 0.944 ml (0.01 mol) of Me_2SO_4 was carried out over 1 min, and the solution was stirred for 3 hr at room temperature. The solution was concentrated, H_2O was added, and the solution was extracted twice with CH_2Cl_2. The organic layer was washed successively with H_2O and brine, dried, and concentrated. The product (3.89 g) was crystallized (toluene and EtOAc–hexane), giving 2.6 g (61%) of **5**: mp 185–187°; ir 6.00 μ (C=O); NMR (DMSO-d_6) δ 3.4 (s, 3, NCH_3), 3.75 (d, 3, J = 11 Hz, OCH_3), 3.85 (d, 3, J = 11 Hz, OCH_3), 4.49 (d, 1, J = 11.25 Hz, 3-CH), 7.02 (s, 1, 6-CH), 7.45–7.8 (m, 6, aromatic).

Anal. Calcd for $C_{18}H_{17}Cl_2N_2O_4P$: C, 50.60; H, 4.01; N, 6.56; Cl, 16.60. Found: C, 50.61; H, 3.89; N, 6.48; Cl, 16.76.

[7-Chloro-5-(*o*-chlorophenyl)-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]phosphonic Acid Diethyl Ester (6). The title compound (**6**) was prepared using the same method as for preparation of **5**, but starting with 4.41 g (0.01 mol) of **4**. The crude product (3.4 g) was crystallized (EtOAc–hexane), giving 2.5 g (55%) of **6**: mp 163–166°; ir 5.94 μ (C=O); NMR (DMSO-d_6) δ 1.29 (t, 6, J = 7.5 Hz, CH_2CH_3), 3.42 (s, 3, NCH_3), 3.9–4.59 (m, 5, CH_2CH_3 and 3-CH), 7.04 (s, 1, 6-CH), 7.41–7.84 (m, 6, aromatic).

Anal. Calcd for $C_{20}H_{21}Cl_2N_2O_4P$: C, 52.76; H, 4.65; N, 6.16; Cl, 15.58. Found: C, 52.80; H, 4.82; N, 6.31; Cl, 15.73.

[7-Chloro-5-(*o*-chlorophenyl)-2,3-dihydro-1-methyl-2-oxo-1*H*-1,4-benzodiazepin-3-yl]phosphonic Acid Methyl Ester (7). To 0.421 g (0.01 mol) of hexane-washed 57% NaH was added 20 ml of DMF, followed dropwise by 4.13 g (0.01 mol) of **3** in 40 ml of warm DMF. After the evolution of H_2 ceased, 1.4 ml (0.022 mol) of MeI was added slowly and the solution was stirred overnight at room temperature. The solution was concentrated to dryness, H_2O was added, and the solution was washed with Et_2O. The aqueous layer was acidified to pH 1.5, extracted three times with CH_2Cl_2, washed with brine, dried, and concentrated to dryness. Crystallization (MeCN) gave 1.49 g (36%) of **7**: mp 171° dec; ir 5.97 μ (C=O); NMR (DMSO-d_6) δ 3.39 (s, 3, NCH_3), 3.74 (d, 3, J = 10.5 Hz, OCH_3), 4.18 (d, 1, J = 11 Hz, 3-CH), 7.06 (s, 1, 6-CH), 7.44–7.96 (m, 6, aromatic), 8.89–9.39 (broad s, 1, POH).

Anal. Calcd for $C_{17}H_{15}Cl_2N_2O_4P$: C, 49.42; H, 3.66; N, 6.78; Cl, 17.15. Found: C, 49.08; H, 3.77; N, 6.79; Cl, 17.21.

7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-1-methyl-3-methylene-2*H*-1,4-benzodiazepin-2-one (8). A solution of 18.2 g (0.04 mol) of **6** in 100 ml of dry $(MeOCH_2)_2$ was added to a mixture of 1.70 g (0.04 mol) of hexane-washed 57% NaH in 40 ml of dry $(MeOCH_2)_2$ and the mixture was stirred at 20–30° until 970 ml (0.04 mol) of H_2 was evolved. Gaseous CH_2O, evolved from the pyrolysis (190°) of two separate batches of paraformaldehyde (1.44 g, 0.048 mol each), was passed into the solution in a stream of N_2, the first at 20° and the second at 35°. The solution was stirred for 1 hr at 25–35°, refluxed for 0.25 hr, concentrated to dryness, and, after the addition of H_2O–EtOAc, extracted with EtOAc. The organic layer was washed successively with H_2O and brine, dried, and concentrated, giving 12.8 g (mp 147–150°) of crude **8**. Crystallization (MeCN) gave 6.87 g (52%) of **8**: mp 163–165°; ir 6.02 μ (C=O); NMR (DMSO-d_6) δ 3.44 (s, 3, NCH_3), 5.05 (s, 1, C=CH**H**), 5.16 (s, 1, C=C**H**H), 7.0 (s, 1, 6-CH), 7.44–7.95 (m, 6, aromatic).

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O$: C, 61.64; H, 3.65; N, 8.46; Cl, 21.41. Found: C, 61.80; H, 3.69; N, 8.48; Cl, 21.37.

7-Chloro-5-(o-chlorophenyl)-1-methyl-1*H*-1,4-benzodiazepine-2,3-dione (9). A warm solution of 13.66 g (0.03 mol) of **6** in 75 ml of warm, dry $(MeOCH_2)_2$ was added to a mixture of 1.27 g (0.03 mol) of hexane-washed 57% NaH in 30 ml of $(MeOCH_2)_2$ and the mixture was stirred at ca. 30° until H_2 ceased to be evolved (ca. 1 hr). The solution was cooled to 10–15° and O_2 was passed in through a sintered tube for ca. 1 hr. The mixture was filtered through Celite and the filtrate was poured into 1.5 l. of H_2O and extracted with ether. The solid which crystallized from the mixture was collected. Crystallization (EtOAc) gave 2.08 g (21%) of **9**: mp 204–206°; ir 5.82, 5.96 μ (C=O); NMR (DMSO-d_6) δ 3.61 (s, 3, CH_3), 7.35 (s, 1, 6-CH), 7.62–8.08 (m, 6, aromatic).

Anal. Calcd for $C_{16}H_{10}Cl_2N_2O_2$: C, 57.68; H, 3.03; N, 8.41; Cl, 21.28. Found: C, 57.56; H, 2.90; N, 8.22; Cl, 21.32.

The ether extract was washed successively with H_2O and brine, dried, and concentrated, giving an additional 1.8 g (18%) of **9**, mp 204–207°.

6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid (10). A solution of 13.24 g (0.03 mol) of **4** in 75 ml of DMF was added to a mixture of 2.53 g (0.06 mol) of hexane-washed 57% NaH in 30 ml of DMF and the mixture was stirred for 2 hr at 5–10°. Dry O_2 was passed into the resulting solution through a sintered tube for 0.5 hr while the temperature was raised to 25°. The solution was poured into 2 l. of water and filtered, and 25 ml of HOAc was added. The residue was extracted with EtOAc, washed successively

with H_2O and brine, and dried. Concentration and crystallization (MeCN) gave 3.2 g (33%) of **10**: mp 218–219° dec; ir 5.83 μ (C=O); NMR (DMSO-d_6) δ 7.5–7.85 (m, 5, aromatic), 8.18–8.35 (m, 3, aromatic plus exchangeable CO_2H).

Anal. Calcd for $C_{15}H_8Cl_2N_2O_2$: C, 56.45; H, 2.52; N, 8.78; Cl, 22.22. Found: C, 56.55; H, 2.77; N, 8.89; Cl, 22.41.

7-Chloro-5-(*o*-chlorophenyl)-1*H*-1,4-benzodiazepine-2,3-dione (11). A solution of 13.24 g (0.03 mol) of **4** in 60 ml of DMF was added to a mixture of 2.54 g (0.06 mol) of hexane-washed 57% NaH in 30 ml of DMF and the mixture was stirred for 1 hr at 20°. Dry O_2 was passed into the solution through a sintered tube at 20–30° for 1.5 hr, 3.8 ml (0.03 mol) of Me_3SiCl was added, and the solution was stirred for 0.25 hr. The mixture was concentrated to dryness at 40° and water and EtOAc were added. The residue was extracted twice with EtOAc. The organic layer was washed successively with H_2O and brine and dried, giving 5.73 g (mp 250° dec) of crude **11** after concentration. Crystallization (MeCN) gave 4.1 g (43%) of **11**: mp 258° dec; ir 5.77, 6.00 μ (C=O); NMR (DMSO-d_6) δ 7.18 (d, 1, J = 2 Hz, 6-CH), 7.32–7.91 (m, 7, aromatic and exchangeable NH).

Anal. Calcd for $C_{15}H_8Cl_2N_2O_2$: C, 56.45; H, 2.52; N, 8.78; Cl, 22.22. Found: C, 56.55; H, 2.62; N, 9.15; Cl, 22.53.

7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-methylene-2*H*-1,4-benzodiazepin-2-one (12). A solution of 4.41 g (0.01 mol) of **4** in 75 ml of dry $(MeOCH_2)_2$ was added to a mixture of 0.85 g (0.02 mol) of hexane-washed 57% NaH in 10 ml of dry $(MeOCH_2)_2$ and the mixture was stirred at 30–40° until H_2 ceased to be evolved. Gaseous CH_2O from the pyrolysis (190°) of 1 g (0.033 mol) of paraformaldehyde was passed into the solution at 35–42° in a stream of N_2. The solution was stirred for 1 hr at room temperature, refluxed for 0.5 hr, concentrated to dryness, and, after the addition of H_2O–EtOAc, extracted three times with EtOAc. The organic layer was washed successively with H_2O and brine, dried, and concentrated, giving 3 g of crude **12**. The solid was chromatographed on 100 g of silica gel, starting with $CHCl_3$. The desired product was removed with 10% v/v Et_2O in $CHCl_3$ and was crystallized (MeCN), giving 2.0 g (63%) of **12**: mp 200–202° dec; NMR (DMSO-d_6) δ 5.18 (s, 1, C=CHH), 5.39 (s, 1, C=CHH), 6.96 (d, 1, J = 1.5 Hz, 6-CH), 7.25–7.91 (m, 6, aromatic), 11.12 (s, 1, NH).

Anal. Calcd for $C_{16}H_{10}Cl_2N_2O$: C, 60.59; H, 3.18; N, 8.81; Cl, 22.35. Found: C, 60.65; H, 3.46; N, 9.20; Cl, 22.43.

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Registry No.—**1**, 846-49-1; **3**, 54643-73-1; **4**, 54677-79-1; **5**, 54643-74-2; **6**, 54643-75-3; **7**, 54643-76-4; **8**, 54643-77-5; **9**, 54643-78-6; **10**, 54643-79-7; **11**, 54643-80-0; **12**, 54643-81-1.

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Preparation of Oxathiapentadecanes[1]

J. S. Bradshaw,* B. L. Haymore, R. M. Izatt, and J. J. Christensen

Departments of Chemistry and Chemical Engineering, and Contribution No. 56 from the Center for Thermochemical Studies, Brigham Young University, Provo, Utah 84602

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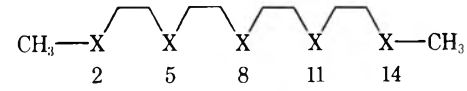
Our interest in the synthesis and complexation of cations by cyclic polyether sulfides[2-5] has led us to prepare a series of oxathiapentadecanes. These compounds are of interest because they are polydentate chelates with unique and unusual coordination properties. Such a series of related compounds may help determine how and where coordination to various cations takes place. Indeed, coordination with silver(I) and mercury(II) by these compounds appears to show definite structural features. These properties will be reported elsewhere.[5] This report deals only with the synthesis and properties of the oxathiapentadecanes.

Table I
Yield and Physical Properties of the Oxathiapentadecanes



Compd	Position of Heteroatoms 2	5	8	11	14	Yield, %	Bp, °C (0.1 mm) (mp, °C)
1	O	O	S	O	O	67	120–121 (0.1)
2	S	O	O	O	S	75	133–134 (0.1)
3	O	S	O	S	O	70	137–138 (0.1)
4	O	S	S	S	O	75	(56)
5	S	S	O	S	S	78	(36–37)[a]
6	S	S	S	S	S	89	(87–88)[b]

[a] Lit.[12] mp 37°. [b] Lit.[12] mp 88°.

The dimethyl ethers of the polyethylene glycols (often called glymes) have been prepared using the Williamson synthesis from the polyethylene glycols and alkyl halides or sulfates.[6-8] Chakhovskoy and coworkers have prepared certain glymes using alkyl tosylates which gave better yields than the halides.[9] The oxathiapentadecanes (see Table I) were prepared in a similar manner from the reaction of a mercaptan or sodium sulfide and an alkyl halide in basic media. These reactions are easier to perform than a Williamson synthesis using an alkoxide and an alkyl halide, since they require less severe conditions.[10,11] In addition, better yields are obtained. We tried to use compounds other than sulfur vesicants (blister-producing mustards) for these syntheses. Only one such compound was used (2-chloroethyl methyl sulfide in the preparation of **5**). In our synthesis of compound **1**, 1-(2-chloroethoxy)-2-methoxyethane was treated with sodium sulfide while compound **4** was prepared from bis(2-mercaptoethyl) sulfide and 2-bromoethyl methyl ether. The other compounds were prepared in a similar manner.

$$CH_3OCH_2CH_2OCH_2CH_2Cl + Na_2S \longrightarrow \mathbf{1}$$

$$HSCH_2CH_2SCH_2CH_2SH + 2BrCH_2CH_2OCH_3 \longrightarrow \mathbf{4}$$

Compounds **5** and **6** as well as other similar compounds have been prepared from the corresponding β-chloro sulfides (mustard compounds).[12-14] Meade and Moggridge[12] prepared **5** and **6** from the reaction of methyl mercaptan with 2,2′-(2-chloroethylthia)diethyl ether (**7**, X = O) and the corresponding sulfide (**7**, X = S), respectively. Williams and Woodward prepared similar compounds from **7** (X = S) using aromatic oxides and sulfides.[13] The bis(*n*-propoxyethylmercaptoethyl) ether (the di-*n*-propyl ether similar to **3**) was prepared[14] by treating the corresponding glycol with *n*-propyl alcohol in acid media.

$$X(CH_2CH_2SCH_2CH_2Cl)_2 + CH_3SH \xrightarrow{\text{base}} \mathbf{5}\ (X = O)\ \text{or}\ \mathbf{6}\ (X = S)$$

The nuclear magnetic resonance (NMR) spectra for the oxathiapentadecanes are similar to those observed for the

macrocyclic polyether sulfides.[2] The hydrogen atoms located on the ethylene groups between oxygen atoms were observed as singlets at δ 3.56 ± 0.04 while those between sulfur atoms were at δ 2.77 ± 0.00. The hydrogen atoms on methylene groups α to oxygen and β to sulfur were observed as triplets at δ 3.62 ± 0.04. The hydrogen atoms on methylene groups α to sulfur and β to oxygen were observed as triplets at δ 2.70 ± 0.02. The methyl hydrogen atoms adjacent to sulfur and oxygen were observed at δ 2.14 ± 0.01 and 3.32 ± 0.01, respectively. The physical properties of the thiatetraglymes also were similar to those of the macrocyclic polyether sulfides in that the melting point increased as the number of sulfur atoms was increased.[3,4]

Experimental Section

All infrared (ir) spectra were obtained on a Perkin-Elmer 457 spectrophotometer. A Varian A-60A spectrometer was used to record the proton nuclear magnetic resonance (NMR) spectra. Elemental analyses and molecular weight determinations were performed by M-H-W Laboratories, Garden City, Mich. Melting points were determined on a Thomas-Hoover capillary type melting point apparatus and are uncorrected.

Preparation of 2,5,11,14-Tetraoxa-8-thiapentadecane (1). A mixture of 46.2 g (0.33 mol) of 1-(2-chloroethoxy)-2-methoxyethane (Eastman) and 350 ml of reagent ethanol were placed in a flask fitted with a stirrer, reflux condenser, and addition funnel. After the mixture was brought to reflux, an aqueous solution of 40.0 g of sodium sulfide nonahydrate, 0.5 g of sodium hydroxide, and 75 ml of water was slowly added over a 60-min period. The reaction mixture was then cooled and filtered and the ethanol was removed under vacuum. The aqueous residue was extracted three times with 150-ml portions of ether. The ether was removed and the crude product was distilled to give 26.6 g (67%) of product: bp 120–121° (0.1 mm); NMR δ 3.64 (t, 4, OCH_2CH_2S), 3.54 (s, 8, OCH_2CH_2O), 3.33 (s, 6, OCH_3), 2.72 (t, 4, SCH_2CH_2O).

Anal. Calcd for $C_{10}H_{22}O_4S$: C, 50.39; H, 9.30; S, 13.45; mol wt, 238.4. Found: C, 50.60; H, 9.05; S, 13.22; mol wt, 239.

Preparation of 5,8,11-Trioxa-2,14-dithiapentadecane (2). A mixture of 25 g of sodium hydroxide in 500 ml of reagent ethanol was cooled to −15°. Methanethiol (26.0 g, 0.54 mol, Eastman) at −15° was added to the above solution. A solid formed which dissolved when the mixture was allowed to warm to room temperature. The solution was then refluxed while 62.4 g (0.27 mol) of tetraethylene glycol dichloride[2] was slowly added. The resulting mixture was cooled and treated as in the previous example to yield 51.6 g (75%) of product: bp 133–134° (0.1 mm); NMR δ 3.68 (t, 4, OCH_2CH_2S), 3.62 (s, 8, OCH_2CH_2O) 2.68 (t, 4, SCH_2CH_2O), 2.13 (s, 6, SCH_3).

Anal. Calcd for $C_{10}H_{22}O_3S_2$: C, 47.21; H, 8.72; S, 25.21; mol wt, 254.4. Found: C, 47.20; H, 8.81; S, 25.16; mol wt, 253.

Preparation of 2,8,14-Trioxa-5,11-dithiapentadecane (3). A mixture of 12.4 g (0.09 mol) of bis(2-mercaptoethyl) ether (Aldrich) and 12 g of potassium hydroxide in 500 ml of reagent ethanol was heated to reflux. To this solution was slowly added 25.0 g (0.18 mol) of 2-bromoethyl methyl ether (Eastman) in 50 ml of reagent ethanol. The resulting mixture was refluxed for 30 min, allowed to cool, and treated as for compound 1 to give 16.1 g (70%) of product, bp 137–138° (0.1 nm); NMR δ 3.65 (t, 4, OCH_2CH_2S), 3.56 (t, 4, OCH_2CH_2S), 3.32 (s, 6, OCH_3) 2.72 (t, 8, SCH_2CH_2O).

Anal. Calcd for $C_{10}H_{22}O_3S_2$: C, 47.21; H, 8.72; S, 25.21; mol wt, 254.4. Found: C, 47.14; H, 9.01; S, 25.06; mol wt, 254.

Preparation of 2,14-Dioxa-5,8,11-trithiapentadecane (4). A mixture of 13.9 g (0.09 mol) of bis(2-mercaptoethyl) sulfide (Pfaltz and Bauer), 25.0 g (0.18 mol) of 2-bromoethyl methyl ether (Eastman), and 12.0 g of potassium hydroxide in 500 ml of ethanol was treated as above for compound 3. The product was distilled to give 18.3 g (75.3%): bp 154–155° (0.1 mm); NMR δ 3.56 (t, 4, OCH_2CH_2S), 3.34 (s, 6, OCH_3), 2.77 (s, 8, SCH_2CH_2S), 2.68 (t, 4, SCH_2CH_2O).

Anal. Calcd for $C_{10}H_{22}O_2S_3$: C, 44.41; H, 8.20; S, 35.56; mol wt, 270.48. Found: C, 44.62, H, 8.34; S, 35.40; mol wt, 268.

Preparation of 8-Oxa-2,5,11,14-tetrathiapentadecane (5). A mixture of 8.5 g (0.06 mol) of bis(2-mercaptoethyl) ether (Aldrich), 13.5 g (0.12 mol) of 2-chloroethyl methyl sulfide (City Chemical) (vesicant, use caution) and 5.5 g of sodium hydroxide in 300 ml of ethanol was refluxed and the product was isolated as described for 3. The product (13.6 g, 78%) was a white solid which was recrystallized from benzene–hexane: mp 36–37°; NMR δ 3.66 (t, 4, OCH_2CH_2S), 2.77 (s, 8, SCH_2CH_2S), 2.72 (t, 4, SCH_2CH_2O), 2.13 (s, 6, SCH_3).

Anal. Calcd for $C_{10}H_{22}OS_4$: C, 41.92; H, 7.74; S, 44.76; mol wt, 286.54. Found: C, 41.99; H, 7.83; S, 45.01; mol wt, 284.

Preparation of 2,5,8,11,14-Pentathiapentadecane (6). This compound was prepared from 8.4 g (0.054 mol) of bis(2-mercaptoethyl) sulfide, 12.0 g (0.108 mol) of 2-chloroethyl methyl sulfide, 5.0 g of sodium metal and 300 ml of ethanol as above for compound 3. The product (14.5 g, 89%) was a white solid which was recrystallized from benzene–hexane: mp 87–88°; NMR δ 2.77 (s, 16, SCH_2CH_2S), 2.15 (s, 6, SCH_3).

Anal. Calcd for $C_{10}H_{22}S_5$: C, 39.69; H, 7.33; S, 52.98; mol wt, 302.61. Found: C, 39.49; H, 7.22; S, 53.69; mol wt, 301.

Registry No.—1, 54595-64-1; 2, 54595-65-2; 3, 54595-66-3; 4, 54595-67-4; 5, 54595-68-5; 6, 54595-69-6; 1-(2-chloroethoxy-2-methoxyethane, 52808-36-3; methanethiol, 74-93-1; tetraethylene glycol dichloride, 638-56-2; bis(2-mercaptoethyl) ether, 2150-02-9; 2-bromoethyl methyl ether, 6482-24-2; bis(2-mercaptoethyl) sulfide, 3570-55-6; 2-chloroethyl methyl sulfide, 542-81-4.

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Pyrolysis of Some Methyl- and Benzylindoles

John M. Patterson,* Charles F. Mayer, and Walter T. Smith, Jr.

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

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Under drastic pyrolytic conditions, alkylpyrroles exhibit competitive alkyl group migrations, alkyl group cleavage, and ring expansion reactions to pyridines. The benzo analogs, methylindoles, likewise have been reported to undergo the ring expansion and dealkylation reactions. Thus, 2-methylindole is converted into quinoline[2] (17% yield) and 3-methylindole is converted into indole[3] when their vapors are passed through a glowing tube. The observation that allyl groups undergo competitive [3,3] and [1,5] sigmatropic shifts on the pyrolysis of allylindoles[4] prompted this investigation of the migratory behavior of alkyl groups in alkylindoles.

Results and Discussion

The pyrolysis of *N*-, 2-, and 3-methylindole and of *N*- and 3-benzylindole resulted in the formation of products arising from alkyl group migrations in addition to those arising from cleavage (dealkylation) and from ring expansion reactions (see Tables I and II). As was observed in the pyrrole series[5] and in contrast to the Claisen migrations of crotylindole,[4] the N to C isomerizations of the alkylindoles were irreversible processes. On the other hand, the 2- and

Table I
Pyrolyzate Composition[a] of the Methylindoles as a Function of Temperature

Methylindole	Temp, °C	Methylindoles			Indole	Quinoline
		N-	2-	3-		
2-	550	0	99	1	0	0
3-	550	0	3	97	0	0
N-	600	93	1	0	3	3
2-	600	0	92	8	0	0
3-	600	0	10	89	1	0
N-	650	71	5	2	10	12
2-	650	0	75	23	0.5	1.5
3-	650	0	45	52	2	1
N-[b]	700	21 ± 2	15 ± 1	8 ± 1	26 ± 1	30 ± 1
N-[c,d]	700	16 ± 1	16 ± 2	7 ± 1	23 ± 1	19 ± 1
2-	700	0	58	26	10	6
3-	700	0	49	28	13	10
N-	750	6	7	4	41	43
2-	750	0	16	9	39	36
2-[c,e]	750	0	20 ± 2	7 ± 1	27 ± 4	18 ± 1
3-	750	0	20	11	35	34

[a] Area percent of component in pyrolyzate. [b] Averages and average deviations of area percents from triplicate pyrolyses. [c] Weight percent yields (weight of component per 100 g of substance pyrolyzed) and two-standard-deviation ranges were determined by GLC (triplicate analyses) using 2,3,6-trimethylnaphthalene as internal standard and correcting for detector response. [d] Weight recovery, 81%. [e] Weight recovery, 73%.

Table II
Pyrolyzate Composition[a,b] of the Benzylindoles as a Function of Temperature

Benzylindole	Temp, °C	Benzylindoles			Indole	Phenylquinolines			Quinoline	Bibenzyl	Others
		N-	2-	3-		2-	3-	4-			
N-[c]	500	92	1	2	2	1	0	0	0	2	0
N-[d]	550	47 ± 2	4	10 ± 1	18 ± 2	3 ± 1	1	0.5	5 ± 1	10	1
3-	550	0	15	73	9	0	0	0	0	2	0
N-[d]	600	2 ± 1	11 ± 1	12 ± 1	40 ± 1	4 ± 1	2	2	5 ± 2	12 ± 2	7 ± 1
3-	600	0	46	24	20	0	2	2	3	1	1
3-	650	0	10	7	55	0	5	5	11	0	5

[a] Pyrolyses of melted solid. [b] Compositions reported as area percent. [c] Pyrolyzed as a 20% solution in benzene. [d] Averages and average deviations of area percents from duplicate pyrolyses.

3-methylindoles interconverted under all the reaction conditions used. These interconversions are first observed at temperatures (550°) at which the N isomer is not isomerized. The 2 to 3 isomer ratio, which becomes ca. 2:1 at higher temperatures regardless of the isomer pyrolyzed (N, 2, or 3), suggests that the 2 and 3 isomers have equilibrated under the higher temperature conditions.

In the pyrolyses of *N*-methylindole, the yield of the 2-methyl isomer always exceeds that of the 3 isomer and at 600° the 2 isomer was the only alkyl migration product. Also, since at 650° the pyrolysis of *N*-methylindole produced a 2 to 3 isomer ratio of ca. 2.5:1 and under the same conditions only half of a sample of 3-methylindole was converted to 2 isomer, it is concluded that the 2 isomer is a primary pyrolysis product. By similar reasoning, the appearance of the 3 isomer in the *N*-methylindole pyrolysis is very likely the result of a secondary reaction of the initially formed 2 isomer.

The extent to which the primary reactions, isomerization, cleavage, or ring expansion, occur depends upon the position of methyl substitution in the indole. Over the temperature range 600–700° *N*-methylindole reacted approximately equally among the three paths while 2- and 3-methylindole reacted predominantly by alkyl group migration. The 3 isomer exhibited about twice the reactivity of the 2 isomer in the isomerization. At 750°, cleavage and ring expansion became the predominant processes followed by all isomers.

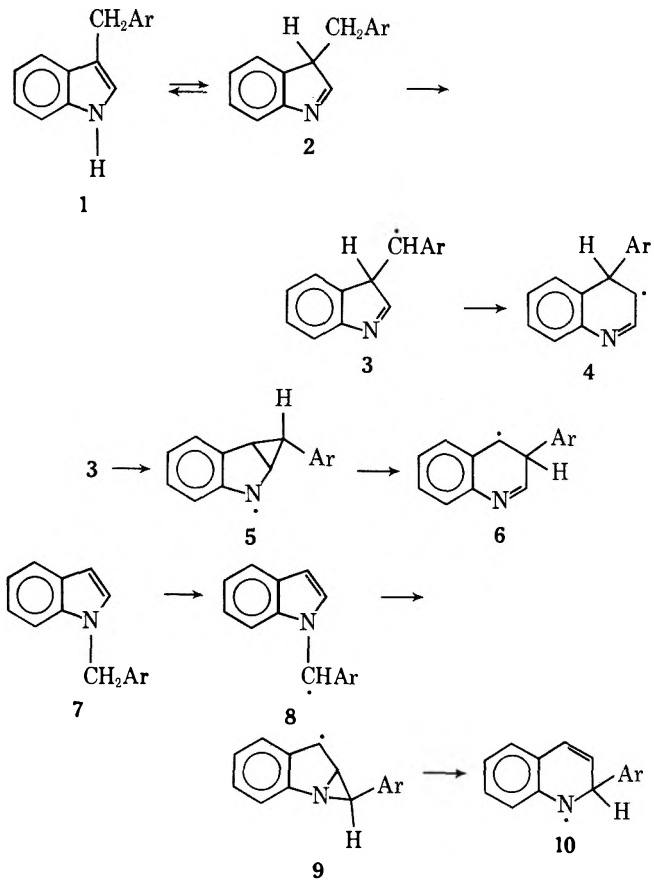
The benzylindoles were pyrolyzed to provide information about the effect of phenyl substitution on the alkyl migration path as well as other competitive reaction paths and about the position occupied by the alkyl substituent in the ring expansion product.

Generally, the benzylindoles were more reactive than the methylindoles in each of the reaction paths—isomerization, cleavage, and ring expansion. This is consistent with expected radical character or partially developed radical character associated with each of the transition states of these processes.

As was observed with the methylindoles, the C-substituted indole (3-benzyl) was more reactive in the migration reaction than the N-substituted indole. Somewhat unexpected, however, was the observation that the yield of 3 isomer was greater than that of the 2 isomer in the *N*-benzylindoles pyrolyses. This suggests that the 3 isomer is either a primary product from N isomer or that it is formed from 2 isomer at a rate faster than the N to 2 isomerization.

In the pyrolysis of *N*-benzylindole, the majority of the cleavage product arises from N isomer rather than from 3 isomer as secondary product. For example, at 550° a 20% yield of indole is obtained from N isomer while under the same conditions only a 9% yield is produced from 3 isomer.

Chart I



The relative amounts of cleavage and ring expansion appear to parallel the relative magnitudes of the ArC–C, ArC–H, and ArC–N bond energies. (The ring expansion reactions are presumed to be initiated by a C–H bond cleavage in the alkyl substituent.) Cleavage was found to be the more facile reaction of the two.

In the ring-expansion reaction, the major products arise from an insertion of the benzyl–methylene carbon between the atom to which it is attached and an adjacent ring carbon. 3-Benzylindole produced only 3- and 4-phenylquinoline but no 2-phenylquinoline. Similarly, only 2-phenylquinoline was produced from *N*-benzylindole at 500°, and at higher temperatures the 2-phenylquinoline remained as the major ring-expansion product. The appearance of 3- and 4-phenylquinoline at higher temperatures in the *N*-benzylindole pyrolyzate is probably due in part to secondary decomposition of the primary product, 3-benzylindole. Quinoline formation accompanied the isomeric phenylquoline formation, the yield of quinoline and the sum of yields of the phenylquinolines being approximately equivalent. It is postulated that the ring expansion reaction involves an initial C–H bond cleavage followed by isomerization to a quinolinyl radical which then loses either Ar· or H· with equal facility to form the quinoline or phenylquinoline, respectively. A possible scheme for the process is outlined in Chart I.

The conversion of **3** to **4** involves a 1,2-phenyl shift while conversions **3** to **6** and **8** to **10** involve either a vinyl-type shift or its equivalent. The equivalent process consists of a radical addition to a double bond followed by ring opening to the quinolinyl radical.

Experimental Section

Melting points are corrected. Infrared spectra were measured on a Beckman IR-8 spectrophotometer; ultraviolet spectra were measured on a Perkin-Elmer Model 202 spectrophotometer; and NMR spectra were measured on a Varian T-60 spectrometer in carbon tetrachloride or chloroform using Me_4Si as internal standard. Gas chromatographic analyses and separations were made on a Hewlett-Packard Model 5750 or an F & M Model 810 gas chromatograph.

The methylindoles were obtained from commercial sources. *N*-,[6,7] 2-,[8,9] and 3-benzylindole,[10] 2-,[11] 3-,[12] and 4-phenylquinoline[13,14] were synthesized by methods described in the literature.

Pyrolyses. The pyrolyses were carried out in the apparatus previously described[15] using a nitrogen flow of 100 ml/min. Berl saddles, filling a 12.5-cm length of the pyrolysis tube 1 cm from the top of the furnace, were used to volatilize the sample. The pyrolysis temperature quoted refers to the temperature in the empty region of the pyrolysis tube below the Berl saddles.

Samples were introduced into the reaction tube from a syringe (heated when melts were added) at a constant rate as neat liquids or molten solids (1 ml/40 min) or as 20% (w/v) benzene solutions (1 ml/15 min). Pyrolyzates obtained from the pyrolysis of benzene solutions contained biphenyl while those obtained from the pyrolysis of neat samples did not.

Analysis and Identification of Products. A. Methylindole Pyrolyses. Pyrolyzates were analyzed by GLC using a 12 ft × 0.125 in. Hewlett-Packard Hi-Pak Carbowax 20M column at 170 and 200° and a 12 ft × 0.125 in. 2% polyphenyl ether (six-ring) 90/100 Anakrom ABS column at 170°. The former column separated quinoline, *N*-methylindole, biphenyl, and indole but not 2- and 3-methylindole, while the latter column separated indole, biphenyl, and 2- and 3-methylindole but not *N*-methylindole and quinoline. The 2- and 3-methylindole ratio obtained from the polyphenyl ether column was used to calculate the yields of these indoles from the combined peak exhibited by the Carbowax column.

Pyrolyzate constituents were isolated by preparative GLC using a 15 ft × 0.375 in. 20% SE-30 50/60 Anakrom U column (isolation of quinoline, *N*-methylindole, and indole) and a 20 ft × 0.375 in. 20% polyphenyl ether (six-ring) 50/60 Anakrom U column (isolation of biphenyl, 2-, and 3-methylindole). Constituents were identified by comparisons of GLC retention times and ultraviolet spectra with those obtained from authentic samples.

B. Benzylindole Pyrolyses. The pyrolyzates were analyzed on an 8 ft × 0.375 in. 25% SE-30 column heated isothermally at 100° for 7 min and then programmed at 2°/min to 250° and on a 12 ft × 0.125 in. 2% polyphenyl ether (six-ring) column at 250°. The SE-30 column separated quinoline, indole, bibenzyl, 4-phenylquinoline, 3-benzylindole, and an additional peak consisting of 2-benzylindole, 2-, and 3-phenylquinoline. The polyphenyl ether column separated *N*-, 2-, and 3-benzylindole as well as the 2-, 3-, and 4-phenylquinolines.

Components of the pyrolyzate were isolated by preparative GLC using the SE-30 column. Identifications of all components, except the mixture of 2-benzylindole, 2-, and 3-phenylquinoline, are based on comparisons of GLC retention times and ultraviolet spectra with those of authentic compounds. Extraction of crude pyrolyzate with 1 *M* HCl removed only those components corresponding to quinoline, 2-, 3-, and 4-phenylquinoline and 2-benzylindole was isolated from the neutral fraction using a 15 ft × 0.375 in. 20% SE-30 column. The GLC retention time, infrared, and NMR spectra were identical with those obtained from an authentic sample.

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Registry No.—*N*-Methylindole, 603-76-9; 2-methylindole, 95-20-5; 3-methylindole, 83-34-1; *N*-benzylindole, 3377-71-7; 3-benzylindole, 16886-10-5.

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A Convenient Preparation of Optically Active 2-Halooctanes and Related Compounds[1]

Joseph San Filippo, Jr.,* and Louis J. Romano

School of Chemistry, Rutgers University, New Brunswick, New Jersey 08903

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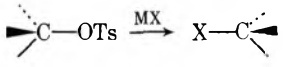
Optically active 2-haloalkanes have been of considerable utility in the elucidation of the mechanisms of many organic reactions and also serve as models for the theoretical study of optical activity.[2] The practical synthesis of these compounds is, therefore, a matter of some importance. We wish to report that 2-halooctanes can be conveniently prepared in good yields and in generally high optical purity by halide ion displacement on the tosylate formed from optically active 2-octanol.[3]



(1)

In a typical experiment, the tosylate (7.10 g, 25.0 mmol) of (+)-(*S*)-2-octanol, α^{20}_{589} +7.97°, optical purity 99.4%, was stirred vigorously with anhydrous potassium fluoride (7.25 g, 125 mmol) in 25.0 ml of triethylene glycol at 110° under a reduced pressure of 4.0 Torr. The volatile materials were allowed to distil from the reaction mixture and collected in a cold trap (−50°). Analysis of the crude distillate by GLC indicated a 52% yield of 2-fluorooctane (based on starting alcohol), accompanied by a 27% yield of octene(s). This crude distillate was treated with a slight excess of bromine in carbon disulfide, washed with aqueous sodium thiosulfate, dried ($MgSO_4$), and distilled to afford pure (−)-(*R*)-2-fluorooctane (1), α^{20}_{589} −9.99°.[4] The results of similar reactions employing lithium chloride, potassium bromide, and lithium iodide are listed in Table I.

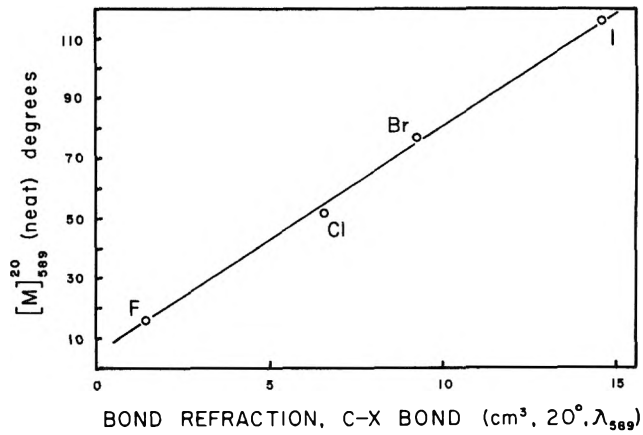


Figure 1. A plot of the molecular rotation, [M], vs. the common bond refraction, [R] (C–X bond), for 2-halooctanes.

The synthesis of (−)-(*R*)-2-fluorooctane (1) is particularly noteworthy. Its preparation provides the first completed series of configurationally related 2-haloalkanes. The resulting relationship can be used to estimate the optical purity of this compound based on the empirically observed linear correlation between the optical rotation and bond refraction developed by Davis and Jensen.[5] Figure 1 shows this relationship plotted for values of optically pure 2-chloro-, 2-bromo-, and 2-iodooctane of the same configuration. The extension of this line to include 2-fluorooctane leads to predicted molecular rotation for (−)-(*R*)-2-fluorooctane of $[M]^{20}_{589}$ −16.6°.[6] The agreement between this value and the observed molecular rotation of $[M]^{20}_{589}$ −16.4° suggests that displacement has proceeded with essentially complete *inversion* of configuration, to produce optically pure 1.

Of the existing procedures for the preparation of optically active 2-chloro- and 2-bromooctane, the reaction of an optically active alcohol with phosphorous trihalides and related reagents provides products of highest optical purity,[7] although overall yields are sometimes poor and conditions frequently critical. It is clear that the reaction of 2-octyl tosylate with halide ion as described above provides a significantly improved procedure for the synthesis of optically

Table I
Reaction of (+)-(*S*)-2-Octyl Tosylate with Potassium Fluoride, Lithium Chloride, Potassium Bromide, and Lithium Iodide (Eq 1)

MX (concn, *M*)	Solvent[a]	Temp, °C (Torr)	Reaction time, hr	2-Halooctane (%)[b]	α^{20}_{589}	Optical purity, %	C–X bond refraction,[c] cm^3, 20° (λ = 589)	Octene (s), %[b,d]
KF (5.0)	Triethylene glycol	110 (4.0)	3	2-Fluorooctane (52)	−9.99[e]	~100[f]	1.44	27
LiCl (5.0)	Triethylene glycol	110 (1.0)	2	2-Chlorooctane (80)	−30.72[e]	97.2[g]	6.74	16
KBr (1.2)	Triethylene glycol	65 (0.1)	2	2-Bromooctane (75)	−41.56[e]	95.4[g]	9.80	8.0
LiI (1.2)	Tetraethylene glycol	90 (0.1)	1.5	2-Iodooctane (83)	−19.32[e]	30.6[g,h]	14.08	8.0

[a] All solvents were vacuum distilled under nitrogen immediately prior to use. [b] These values represent GLC yields based on starting alcohol; isolated halocarbon yields were somewhat lower. [c] The specific value for 2-fluoro-, 2-chloro-, 2-bromo-, and 2-iodooctane are unavailable. This number represents the common bond refraction of a number of fluoro-, chloro-, bromo-, and iodo-substituted alkanes. A tabulation of these values is given in ref 5. [d] No attempt was made to distinguish possible octene isomers. [e] GLC analysis indicated minimum sample purity >99%. [f] See text for discussion of this value. [g] Calculated for optically pure (+)-(*S*)-2-halooctane: α^{20}_{589} +31.6° (Cl), α^{20}_{589} +43.6° (Br), α^{20}_{589} +63.2° (I), taken from ref 7, Table V, footnote c. [h] The considerable racemization observed in this instance is presumably a result of iodide exchange; see ref 12.

active 2-halooctanes (and by extension, other 2-haloalkanes) in generally high optical purity. It should be further noted that only 2-halooctanes were observed. Rearranged halocarbons were not detected. Taken together, these data are consistent with a mechanism for carbon–halogen bond formation which involves an SN2 displacement at carbon. Finally, and not unexpectedly, nucleophiles other than halide ions appear to behave similarly. Thus, for example, (+)-(*S*)-2-octyl tosylate reacts with lithium azide to yield (−)-(*R*)-2-azidooctane (93%, α^{20}_{589} −40.20°).[8]

Experimental Section[9]

(+)-(*S*)-2-Octyl tosylate was prepared from (+)-(*S*)-2-octanol (α^{20}_{589} +7.97°) by the procedure described by Streitwieser and coworkers.[10]

(−)-(*R*)-2-Fluorooctane (1). Into a dry two-neck 50-ml flask containing a Teflon-coated stirrer bar was placed 7.25 g (125 mmol) of anhydrous potassium fluoride. One neck was capped with a rubber septum, the other was connected to a cold trap, and the apparatus was flushed with nitrogen. Anhydrous triethylene glycol (25 ml) and 7.10 g (25 mmol) of the tosylate of (+)-(*S*)-2-octanol (α^{20}_{589} +7.97°, optical purity 99.4%) were added by syringe. The rubber septum was replaced with a glass stopper and the flask was heated to 110° with vigorous stirring under reduced pressure (4 Torr). The volatile materials were allowed to distil from the reaction mixture and collected in the cold trap (−50°) over a period of 3 hr. Analysis of the crude distillate by GLC indicated a 52% yield of 2-fluorooctane accompanied by a 27% yield of octene(s). The crude distillate was treated with a slight excess of bromine in carbon disulfide, washed with aqueous sodium thiosulfate, dried ($MgSO_4$), and distilled to afford 1.45 g (44%) of (−)-(*R*)-2-fluorooctane (1): α^{20}_{589} −9.99°, bp 55–57° (43 Torr) [lit.[11] bp 139° (760 Torr)]; ^{1}H NMR (CCl_4) δ 4.50 [1 H, d of multiplets, J(HCF) = 48 Hz], ~1.4 [10 H, br, complex multiplet, $(CH_2)_5$], 1.26 [3 H, d of d, J(CH_3–CHF) = 23 Hz, J(CH_3–CHF) = 7.0 Hz], 0.96 (3 H, t); ir (CCl_4) 870 cm^{-1} (vs, C–F).

(−)-(*R*)-2-Chlorooctane was prepared from 4.24 g (100 mmol) of anhydrous lithium chloride and 5.68 g (20.0 mmol) of the tosylate of (+)-(*S*)-2-octanol in 20 ml of triethylene glycol by a procedure analogous to that described for the synthesis of 1. After treatment with a slight excess of bromine (CS_2) and subsequently with aqueous sodium thiosulfate, the crude product mixture was dried ($MgSO_4$) and fractionated to yield 1.80 g (61%) of (−)-(*R*)-2-chlorooctane, bp 74–76° (25 Torr) [lit.[12] bp 61–62° (17 Torr)], α^{20}_{589} −30.72°.

(−)-(*R*)-2-Bromooctane was synthesized by a procedure similar to that described for the preparation of 1 using anhydrous potassium bromide (1.97 g, 18.0 mmol) and 4.26 g (15.0 mmol) of the tosylate of (+)-(*S*)-2-octanol in 15 ml of triethylene glycol at 65° (0.1 Torr). The reaction was conducted over a period of 2 hr. Direct fractionation of the crude product afforded 1.84 g (63%) of (−)-(*R*)-2-bromooctane, bp 74–76° (14 Torr) [lit.[12] bp 72° (9 Torr)], α^{20}_{589} −41.56°.

(−)-(*R*)-2-Iodooctane was prepared according to the procedure outlined for the preparation of 1 using lithium iodide (0.806 g, 6.00 mmol) and 1.42 g (5.00 mmol) of the tosylate of (+)-(*S*)-2-octanol in 10 ml of tetraethylene glycol. The reaction was carried out under a reduced pressure of 0.1 Torr at a temperature of 90° over a period of 90 min. Direct fractionation of the crude product gave 0.80 g (67%) of (−)-(*R*)-2-iodooctane, bp 54–55° (1.5 Torr) [lit.[12] bp 42° (0.5 Torr)], α^{20}_{589} −19.32°.

(−)-(*R*)-2-Azidooctane was prepared from 2.45 g (50.0 mmol) of lithium azide and 2.84 g (10.0 mmol) of the tosylate of (+)-(*S*)-2-octanol by a procedure analogous to that described for the preparation of 1. Direct fractionation of the crude product yielded 1.11 g (72%) of (−)-(*R*)-2-azidooctane: bp 59–60° (5 Torr) [lit.[13] bp 68° (9 Torr)]; α^{20}_{589} −40.20°; ^{1}H NMR (CCl_4) δ 3.33 (1 H, sextet), 1.9–1.2 (13 H, br, complex multiplets), 0.90 (3 H, t); ir (CCl_4) 2110 cm^{-1} (vs, $-N_3$).

Acknowledgment. We thank Professor Donald B. Denney for a generous gift of optically active 2-octanol.

Registry No.—2-Fluorooctane, 54632-06-3; 2-chlorooctane, 18651-57-5; 2-bromooctane, 5978-55-2; 2-iodooctane, 29117-48-4; (+)-(*S*)-2-octyl tosylate, 34817-25-9; (−)-(*R*)-2-azidooctane, 53475-02-8.

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(7) For a review of these procedures, see H. R. Hudson, *Synthesis*, **1**, 112 (1969).
(8) Yield determined by GLC analysis. The observed rotation for purportedly optically pure 2-azidooctane is $[\alpha]^{20}_{589}$ 38.6° [R. A. Moss and P. E. Schueler, *J. Am. Chem. Soc.*, **96**, 5792 (1974)].
(9) All boiling points are uncorrected. Infrared spectra were determined within sodium chloride cells on a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were determined with a Varian T-60 NMR spectrometer. ^{1}H chemical shifts are reported in parts per million relative to internal tetramethylsilane. All coupling constants are in hertz. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-7E mass spectrometer. Analytical GLC analyses were performed on a Hewlett-Packard Model 5750 flame ionization instrument. Absolute product yields were calculated from peak areas using internal standard techniques with response factors obtained from authentic samples. Reported rotations were recorded as neat liquids in a 1-dm cell using a Perkin-Elmer Model 141 spectropolarimeter. Alkali salts were purchased from Alfa Inorganics. Solvents were distilled immediately prior to use.
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Sodium Bismuthate as a Phenolic Oxidant

Emil Kon and Edward McNelis*

Chemistry Department, New York University, New York, New York 10003

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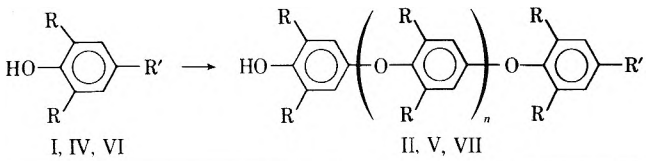
The oxidative polymerization of 2,6-xylenol (I) to its corresponding polyphenylene oxide (II) has been carried out with homogeneous and heterogeneous one-electron oxidants. An excellent catalytic oxidant is the homogeneous cuprous halide–oxygen–pyridine system developed by Hay and coworkers.[1] Heterogeneous oxidants such as silver oxide,[2] activated manganese dioxide,[3] lead dioxide,[3] and nickel peroxide[4] have been reported to be noncatalytic and less effective in achieving with facility the high molecular weights of the Hay system. Nonetheless, studies of these heterogeneous oxidants have been important in eliciting the mechanism of the polymerization and understanding the oxidative capabilities of nonstoichiometric oxides. Despite the disparity of oxidants for this polymerization, the mechanism is a free-radical one characterized by a polycondensation via quinone–ketal intermediate.[3,5,6]

Sodium bismuthate is another interesting and possibly more useful heterogeneous oxidant for the polymerization of I and other phenols (Table I). Scant attention has been given to sodium bismuthate as an oxidant for phenols, even though its potential was indicated by Hewitt, who used it to oxidize the monobenzyl ether of bis-2-hydroxy-1-naphthylmethane to a spironaphthalenone in 90% yield.[7]

Table I
Products of Phenolic Oxidation by Sodium Bismuthate



I, IV, VI II, V, VII

Compd	R	R′	Compd	R	R′
I	CH_3	H	II	CH_3	H
IV	CH_3	CH_3	V	CH_3	CH_3
VI	OCH_3	H	VII	OCH_3	H

When a benzene solution of 2,6-xylenol was refluxed with sodium bismuthate in 2 molar excess, a 74% yield of II was obtained. The polymer's infrared spectrum contained the characteristic peaks at 8.4, 9.8, 10.4, 11.6, and 12.0 μ. The two NMR peaks at 2.1 and 6.5 ppm relative to $(CH_3)_4Si$ were in the ratio of 3:1. In the mass spectrum peaks which were multiples of 120 were displayed. The polymer had an intrinsic viscosity of 0.33, which corresponds to an approximate molecular weight of 1.1×10^4.[8] A comparable experiment with activated manganese dioxide gave a polymer with an intrinsic viscosity of 0.14. An examination of variations of reaction conditions is presented in Table II. A noteworthy point is that reactions at room temperature afford polymers of higher molecular weight than those obtained at temperatures of refluxing solvents. Other points of interest from these variable studies are that polymer viscosities did not change appreciably after 2 hr of reaction time or with an increase of oxidant to phenol molar ratio beyond 6:1.

The bismuthate-mediated polymerization had the polycondensation feature of similar reactions in that when an oily oligomer devoid of monomer was treated with bismuthate at room temperature, a 72% yield of solid polymer melting at 190° was obtained.

The bismuthate reaction mixtures of most polymerizations in benzene contained minor amounts of tail-to-tail products, such as 3,3′,5,5′-tetramethyldiphenoquinone (III). Indeed this product and its reduced precursor were not recovered even when I was in 2 molar excess—in contrast to the activated manganese dioxide reactions.[3] Small amounts of III were formed if these bismuthate mixtures were not refluxed or the reaction solvent was chloroform or the bismuthate was pretreated with a 10% sulfuric acid washing. An oxidation of authentic III with excess bismuthate yielded neither organic products nor starting material. III is quite stable to a similar treatment by activated manganese dioxide. This decomposition of III, however, can be carried out with nickel peroxide. The polymer itself was recovered in 89% yield with no change in viscosity after a 2-hr reflux in benzene over excess bismuthate.

Not all tail-to-tail couplings suffer complete oxidation with bismuthate. 2,6-Di-*tert*-butylphenol was oxidized to the tetra-*tert*-butyldiphenoquinone in 91% yield with a 2-hr refluxing of a benzene solution over a 2 molar excess of bismuthate.

Bismuthate attack on specialized tail-to-tail products was exemplified by the oxidation of mesitol (IV). The principal products were 4-hydroxy-3,5-dimethylbenzaldehyde and that polymeric mixture (V) formed by oxidative dealkylation of mesitol, which was first observed in activated manganese dioxide oxidations.[9] The yields of the aldehyde, which was absorbed on the surface of the bismuthate as a sodium salt, and the polymer were 26 and 30%, respectively, for a 2 molar excess bismuthate oxidation. Only a small amount of mesitol was recovered; copious amounts of CO_2 were evolved upon acidification. In a separate experiment, the aldehyde was recovered in 50% yield after stirring at room temperature for 5 days over 3 molar excess bismuthate.

Carbon dioxide formation was not unique to the mesitol reaction. Acidification of the water washings of bismuthate surfaces from 2,6-xylenol oxidations after extensive benzene washings afforded carbon dioxide. Furthermore, titration of such basic water wishes indicated amounts of base equivalent approximately to the polymer yield. The formation of strongly basic sites on the oxidizing bismuthate surfaces might be implicated in the diphenoquinone breakdown via proton abstraction on the methyl groups. Such anions could be oxidized further or lead to Diels–Alder adducts susceptible to bismuthate degradation.

Another peculiarity of the xylenol oxidation is the appearance of a green coating on the oxidant during the initial stage of the reaction. When the mole ratio of bismuthate to xylenol was more than 1:1, the reaction viscosity gradually decreased and the green color disappeared. With equimolar ratios the thinning out was observed but the residual bismuthate remained green. No color was observed when bismuthate was used to oxidize oligomer to polymer. One source of the green could be the diphenoquinone precursor. When the sodium salt of reduced III was treated with bismuth trinitrate to give a monobismuth salt, the latter turned green upon contact with light and/or air.

Despite its ability to attack tail-to-tail or alkyl groups in the para position of phenols, bismuthate is ineffectual as an oxidant for benzyl alcohol. Even the use of bismuthate which had oxidized partially 2,6-xylenol and hence contained basic sites gave no oxidation. This represents a dis-

Table II
Polymerization of 2,6-Xylenol with Sodium Bismuthate

Wt $NaBiO_3$, g	Benzene, ml	Temp	Reaction time, hr	% yield[a] of polymer	Intrinsic viscosity[b]	Approx mol wt[c]
16.5	100	Ambient	0.33	24	0.07	1.3×10^3
16.5	100	Ambient	2	67	0.15	3.6×10^3
33.0	100	Reflux	2	74	0.33	1.1×10^4
33.0	100	Ambient	2	70	0.59	2.3×10^4
55.0	200	Reflux	2	73	0.49	1.8×10^4
55.0	200	Ambient	2	79	0.59	2.3×10^4

[a] The yield is calculated on initial amount (4.1 g) of 2,6-xylenol. [b] All intrinsic viscosities were determined in benzene at 30°. [c] Molecular weights were estimated from the formula of Price and Chu.[8]

tinct difference from that workhorse of benzylic oxidations, activated manganese dioxide,[10] and its more powerful relative, nickel peroxide.[11]

In order to examine the bismuthate reaction products, 2,4,6-tri-*tert*-butylphenol was treated with sodium bismuthate to give the corresponding stable phenoxyl radical. This reaction with excess of the phenol was used to completely exhaust the oxidizing power of a bismuthate sample. After benzene and water washings, the remaining residue was Bi_2O_3. Titration of the washes indicated amounts of sodium hydroxide almost equivalent to the initial sodium bismuthate. These results suggest that the stoichiometry of bismuthate oxidations is $2NaBiO_3 + 4(H) \rightarrow H_2O + Bi_2O_3 + 2NaOH$. It should be borne in mind that the formula of the bismuthate does not fully express its structure. Commercial bismuthate usually has a 5–6% water content as determined by benzene azeotrope. Bismuthates with or without this water are equally effective in xylenol polymerization. Azetropic distillation has little effect on "chemical hydration" as indicated by ir bands at 2.95 and 5.95 μ.[12] The structure of the bismuthate undergoes a substantial change in refluxing acetic acid, wherein the 2,6-xylenol oxidation products are 2-acetoxy-2,6-dimethylcyclohexadien-3,5-one (63%) and diphenoquinone (III, 15%). No polymer was formed. Without the xylenol the sodium bismuthate in refluxing acetic acid evolves oxygen, as demonstrated by trapping the oxygen by a nitrogen sweep into a separate flask containing the 2,4,6-tri-*tert*-butylphenoxyl radical. Acidity causes a drop in active oxygen content. Commercial sodium bismuthate possesses an active oxygen content of 3.1×10^{-3} g-atoms of oxygen per gram. This is indicative of 91% purity, if correction is made for 5% water. The value for bismuthate treated with 10% sulfuric acid is 1.2×10^{-3} g-atoms of oxygen per gram. The sodium bismuthate, however, does not change in oxidizing power on standing in acetic acid at room temperature for several days.

Other phenols which have been polymerized by sodium bismuthate are durenol and 2,6-dimethoxyphenol. The durenol (2,3,5,6-tetramethylphenol) was treated with a 2 molar excess of bismuthate in refluxing benzene for 2 hr to give a 64% yield of a polymer (mp 215–230°) whose ir and NMR spectra were identical with those reported by Price and Nakagawa.[13] A similar treatment of 2,6-dimethoxyphenol afforded a polymer VII which adhered strongly to the bismuthate surface. Soxhlet extraction with chloroform was used to obtain a 66% yield of a polymer melting at 205–210°. Its NMR spectrum had two singlet peaks at 3.7 (6 H) and 6.3 ppm (2 H) relative to $(CH_3)_4Si$. Significant ir bands were at 8.2, 8.35, 10.1, 10.6, 11.3, and 12.1 μ.

Experimental Section

Materials and Instruments. Phenols were obtained from Aldrich Chemical Co. and were used without further purification. Sodium bismuthate was obtained from J. T. Baker Chemical Co., Fisher Scientific Co., and Allied Chemical Co. Spectral determinations were determined as follows: infrared, Perkin-Elmer Model 137; nuclear magnetic resonance, Varian Associates Model A-60; mass spectra, Varian Associates Model M-66. Melting points were determined on a Thomas-Hoover Unimelt apparatus. The thermometer was calibrated against melting point standards supplied by A. H. Thomas Co.

An Oxidation Procedure. Sodium bismuthate (33.0 g, 0.118 mol) was added to a solution of 2,6-xylenol (4.1 g, 0.033 mol) in 100 ml of benzene. The mixture was refluxed for 2 hr with magnetic stirring. After being cooled to 20° the mixture was filtered and the residual sodium bismuthate was washed with 150 ml of benzene. The combined benzene solutions were washed with a 5% solution of NaOH. Acidification of the basic layer did not yield any organic matter. The dried benzene solution was evaporated to give a crude polymer, which was dissolved in 25 ml of chloroform. The latter solution was poured into 200 ml of methanol to coagulate the polymer, which was then filtered and dried. It weighed 3.05 g and melted at 186–215°. The alcoholic mother liquor was concentrated to near dryness and yielded 0.047 g of diphenoquinone (III), as determined by superimposition of its infrared spectrum with that of an authentic sample. A portion of the dried recovered sodium bismuthate–bismuth oxide mixture was dissolved in concentrated hydrochloric acid without any residue.

Registry No.—I, 576-26-1; II repeating unit, 24938-67-8; II homopolymer, 25134-01-4; III, 4906-22-3; IV, 527-60-6; V homopolymer, 30140-67-1; VI, 91-01-1; VII repeating unit, 25667-13-4; VII homopolymer, 25511-61-9; $NaBiO_3$; 12125-43-8; 2,6-di-*tert*-butylphenol, 128-39-2; tetra-*tert*-butyldiphenoquinone, 2455-14-3; 4-hydroxy-3,5-dimethylbenzaldehyde, 2233-18-3; 2-acetoxy-2,6-dimethylcyclohexadien-3,5-one, 7218-21-5; durenol, 527-35-5.

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Ionization Constants of Substituted 2-Aminoacetanilides and Benzylamines. Transmission of Electronic Effects through Amide Links

Frances B. Peters and H. W. Johnson, Jr.*

Department of Chemistry, University of California at Riverside, Riverside, California 92502

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Previous papers in this series have reported the effect of aromatic ring substituents on the rates of reaction at the methylene group adjacent to the carbonyl in substituted anilides.[1] A typical study was the displacement rate of 4-nitrophenoxide with 2-bromoacetanilides.[1d] The reaction center was immediately adjacent to the carbonyl group, and Hammett ρ values[2-7] appeared to indicate efficient transfer of activation effects through the amide link. Two studies have indicated low transmission efficiencies through the amide functionality: the ionization constants of 4-substituted 4′-aminobenzanilides[8] and the ^{19}F chemical shifts in substituted trifluoroacetanilides.[9]

In a continuation of these studies, and because of possible interest from the biochemical area, we have prepared a group of ring-substituted 2-aminoacetanilides and have measured the pK's in water solution. For comparison the pK's of a group of ring-substituted benzylamines have been determined; previous determinations[3,10-12] of the Hammett ρ for these amines gave values ranging from 0.72[3,10] to 1.06[11] to 1.13 (data from ref 12 fit to the Hammett equation in this work; $r = 0.987$). Values of ρ refer to eq 1. It was

$$BH^+ \rightleftarrows B + H^+ \quad (1)$$

thought desirable to remeasure the benzylamines to ensure consistency of measurement with the 2-aminoacetanilides.

The benzylamines and their hydrochlorides are known compounds; they were purchased or prepared by reported

Table I
p*K* Values of the 2-Aminoacetanilide Hydrochlorides in Water at 23 ± 1°

Substituent	p*K*	σ^a
4′-CH_3	7.99	−0.17
4′-H	7.96	0.00
3′-OCH_3	7.92	0.12
4′-Cl	7.88	0.23
3′-Cl	7.89	0.37
4′-CF_3	7.83	0.54
3′-NO_2	7.78	0.71
4′-NO_2	7.76[b]	0.78

$\rho = 0.23$; $r = 0.960$;[c] $s = 0.027$.

[a] Reference 4. [b] Determined at 0.001 *M* because of limited solubility in water. [c] The somewhat low *r* value is caused primarily by the small slope of the regression line when compared with the normal error of ±0.02.

Table II
p*K* Values of the Benzylamine Hydrochlorides in Water at 23 ± 1°

Registry no.	Substituent	p*K* (this study)	p*K* (other work)	σ^d
26177-45-7	4-CH_3	9.74	9.54[a]	−0.17
3287-99-8	4-H	9.54	9.38[a]	0.00
			9.34[b]	
			9.62[c]	
42365-43-5	4-Cl	9.31	9.14[c]	0.23
			9.18[b]	
42365-42-4	3-Cl	9.09	9.01[a]	0.37
			8.99[b]	
18600-42-5	4-NO_2	8.58	8.50[a]	0.78
			8.38[b]	

$\rho = 1.23$; $r = 0.998$; $s = 0.025$.

[a] p*K* values at 25°, ref 11. [b] p*K* values at 25°, ref 12. [c] p*K* at 25°: R. J. Bruehlman and F. H. Verkock, *J. Am. Chem. Soc.*, **70**, 140 (1948). [d] Reference 4.

methods. The 2-aminoacetanilides and their hydrates are known compounds;[13] the hydrochlorides appear to be unreported except for the parent compound.[13a,14] The most common method of synthesis of the 2-aminoacetanilides is the ammonolysis of the 2-chloroacetanilides; it was found most convenient to use the Sheehan–Frank[14] route involving reaction of *N*-phthaloylglycyl chloride with the aniline followed by hydrazinolysis of the protecting group.[15] The 2-aminoacetanilide hydrochlorides had satisfactory infrared spectra and elemental analyses.

The p*K*'s were determined by potentiometric titration of 0.02 *M* amine hydrochloride with 0.08 *M* sodium hydroxide in water at 23 ± 1°.[16] The p*K* values were reproducible to 0.02 p*K* units in different titrations; at least three independent titrations were conducted for each compound, and the average is reported. The p*K* values refer to eq 1. Table I reports p*K* values with the selected Hammett σ constant[4] for the eight 2-aminoacetanilide hydrochlorides used in this work. Table II reports identically determined p*K* values and σ constants for five benzylamine hydrochlorides; Table II also contains previous workers' p*K* values.

The p*K* values for the 2-aminoacetanilide hydrochlorides gave a ρ value of 0.23 ($r = 0.960$).[3] Irrespective of model compound comparison, the ring substituent has only a small effect on the dissociation constant of the ammonium group. Presumably the same low effect would be noted for differing substituents in peptides if steric and/or secondary–tertiary structural effects are absent.

The ρ value for dissociation of the benzylamine hydrochlorides from this work was 1.23 ($r = 0.998$)[3] using five compounds in water at 23 ± 1°. This value is near the 1.13 calculated from the data of Litvinenko et al.,[12] somewhat higher than the 1.06 of Blackwell et al.,[11] and substantially higher than the first report of 0.72.[3] In this equilibrium reaction the amide link is transmitting substituent effects with 20–25% efficiency, measured by ρ(anilide)/ρ(benzylamine). In the reactions where kinetics were used as the probe and where the reactive site was adjacent to the carbonyl group, the transmission efficiencies appeared to be 70–100%.[1]

This work suggests that the amide group functions as a relatively efficient transmitter of substituent effects when the reactive site or transition state has the potential to conjugate with the carbonyl carbon atom. The p*K* measurements of Kadin[17] on 2-methyl-1,3(2*H*,4*H*)-dioxoisoquinoline-4-carboxanilides (ρ 1.25), the ^{19}F NMR measurements of Pews[18] on 3- and 4-substituted 4′-fluorobenzanilides as contrasted with our measurements of trifluoroacetanilides,[9] as well as our previous kinetic results[1] fit the pattern. The p*K* measurements of Menger[8] with 4-substituted 4′-aminobenzanilides ($\rho = 0.06$) remain to be explained unless a directional effect[18] is operative. The work of Pews[17] and Kadin[18] seems to eliminate ground-state vs. transition-state substituent sensitivity as the major contributor to the explanation.

Experimental Section

General. Melting ranges were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 621 spectrophotometer. Titration curves were obtained using a Corning Model 7 pH meter (No. 475007) with glass electrode (No. 476022) and reference electrode (No. 476002).

Mallinckrodt BuffAR standard buffer solutions, pH at 25° of 4.01, 7.00, and 10.00, were used to standardize the pH meter prior to each run.

Microanalyses were performed by C. F. Geiger, Ontario, Calif., and Elek Microanalytical Laboratories, Harbor City, Calif.

Chemicals. The benzylamines, benzyl chlorides, *N*-phthaloylglycine, and thionyl chloride used in this study were obtained from Aldrich Chemical Co. The anilines and hydrazine hydrate were obtained from Mallincrodt Chemical Works, Matheson Coleman and Bell, and Sigma Chemical Co.

Preparation of the 2-Aminoacetanilide Hydrochlorides. The general method is a modification of a literature procedure[14,15] and can be illustrated by the preparation of 2-aminoacetanilide hydrochloride.

Thionyl chloride (24.0 g, 0.2 mol) and *N*-phthaloylglycine (20.5 g, 0.1 mol) were refluxed together for 2.5 hr. Excess $SOCl_2$ was removed in a stream of N_2. The crude product was dissolved in benzene to make 200 ml of solution. Phthaloylglycyl chloride (100 ml benzene solution, 0.05 mol) was slowly added to 500 ml of benzene solution containing aniline (9.2 g, 0.1 mol). The precipitate of crude phthaloylglycine anilide was collected, rinsed with water, and recrystallized twice from absolute methanol, yield 11.4 g (0.04 mol), 80%. Phthaloylglycine anilide (5.6 g, 0.02 mol) as a slurry in 250 ml of absolute ethanol was refluxed for 1.5 hr with 99% hydrazine hydrate (1.19 g, 0.022 mol). Ethanol was removed from the reaction mixture using a Roto-vap evaporator. The residue was treated with 150 ml of 2 *N* HCl and the mixture was heated at 60° for 15 min and allowed to cool to room temperature. Phthalhydrazide (3.2 g, 0.02 mol dry material) was removed by filtration. Water and HCl were removed on the Roto-vap, yield of crude product 3.4 g (0.018 mol), 82%. The solid was crystallized from ethanol into three fractions. The middle fraction (mp 190–195°) was recrystallized from ethanol and used for p*K* determinations (mp 190–250° dec). Melting ranges of the 2-aminoacetanilide hydrochlorides are included in Table III. All the compounds except for the 4′-NO_2 and 3′-NO_2 derivatives evolve gas, melt, and decompose over a long temperature range.

Preparation of the Benzylamine Hydrochlorides. Five benzylamine hydrochlorides were prepared from the amines and HCl or by reaction of phthalimide, K_2CO_3, and the appropriate substi-

Table III
Melting Characteristics of the 2-Aminoacetanilide Hydrochlorides[a]

Registry no.	Substituent	Melting range, °C
4801-39-2	H	190–250 dec
54643-64-0	4′-CH_3	200–260 dec
54643-65-1	4′-NO_2	273–274 (darkens 250)
54643-66-2	3′-NO_2	246–248 (darkens 240)
54643-67-3	4′-Cl	235–290 dec
54643-68-4	3′-Cl	210–280 dec
54643-69-5	3′-OCH_3	210–225 dec
54643-70-8	4′-CF_3	235–245 dec

[a] Satisfactory analytical data for C, H, Cl (±0.35%) were reported for the compounds in this table. Ed.

tuted benzyl chloride, followed by hydrazinolysis. Two recrystallizations of the crude products from ethanol yielded the benzylamine hydrochlorides melting with some decomposition: 4-methylbenzylamine, mp 240–243° (lit. mp 235°);[19a] benzylamine, mp 263–264° (lit. mp 260°);[19b] 4-chlorobenzylamine, mp 263–265° (lit. mp 259°);[19c] 3-chlorobenzylamine, mp 225–227° (lit. mp 225°);[19c] 4-nitrobenzylamine, mp 269–270° with decomposition from 260° (lit. mp 256° dec).[19c]

Potentiometric Determination of p*K* Values. Solutions (0.02 *M*) of each of the 2-aminoacetanilide hydrochlorides and benzylamine hydrochlorides in water were prepared. Three 25.0-ml aliquots of each were titrated at 23.0 ± 1° with 0.08 *M* NaOH and the pH of the solutions was measured at intervals using glass and saturated calomel electrodes.[16,20,21] Values of p*K* were computed from the equation p*K* = pH + log [BH^+]/[B]. The ionic strength was constant (0.02) throughout each titration. The p*K*'s determined are the so-called "mixed" constants.[10] Scatter within individual runs ranged from 0.02 to 0.09 p*K* units, depending upon the purity of the compound. Agreement between average p*K* values among the three titrations for each compound ranged from 0.00 to 0.02.

Values of ρ were determined from p*K* values and the respective σ constants[4] using an Olivetti Underwood Programma 101 least-squares program.[22]

Registry No.—Thionyl chloride, 7719-09-7; *N*-phthaloylglycine, 4702-13-0; phthaloylgylcyl chloride, 6780-38-7; phthaloylglycine anilide, 2017-94-9.

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The Capability and Nature of the Amide Bond as a Transmitter of Electronic Effects[1]

John P. Idoux* and Rudolfo Zarrillo

Department of Chemistry, Florida Technological University, Orlando, Florida 32816

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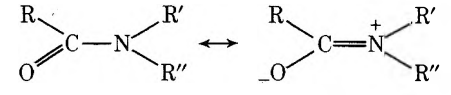
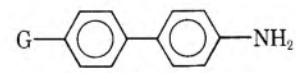
The planarity and restricted rotation which has been observed about amide bonds has been attributed to the importance of a dipolar resonance contributor such as II, and, in fact, based on contribution from such a form, Pauling[2]

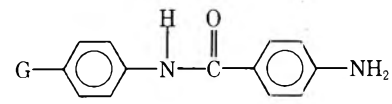


I II

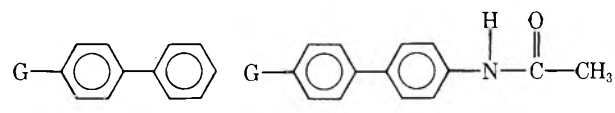
has estimated that this carbon–nitrogen bond should have ca. 40% double-bond character. As a result, it has been assumed for some time that the amide bond can function as a transmitter of conjugative effects. Recently, however, a number of conflicting reports have appeared[3–8] concerning the amide bond's capability as a transmitter of electronic effects, and in particular questions have arisen relative to the manner and magnitude of this transmission[5–8] and of its dependence on the location of a substituent relative to the amide nitrogen.[7,8] In an effort to clarify some of these questions and to investigate the validity of using either a nonreaction property (in the form of NMR chemical shifts) or a reaction property (in the form of pK_a data) as a probe of substituent effects, we report here studies on the transmission of electronic effects through two closely related amide bond containing systems. These studies involve comparisons of pK_a data for a simple monosubstituted biphenylamine system (III) with those for a related, perturbed biphenylamine system (IV) and NMR chemical shift data for 4-substituted biphenyls (V) and 4′-substituted 4-biphenylacetanilides (VI). Since the 1,1′ bond in biphenyl can conjugatively transmit electronic effects, although at a much diminished intensity relative to a single benzene ring,[9–12] we felt that comparisons of reaction and nonreaction properties of biphenyl and perturbed biphenyl systems would provide a rather severe test of the amide bond's conjugative ability.



III



IV



V VI

Table I
pK_a's for 4′-Substituted 4-Aminobenzanilides (IV)[a]

Registry no.	4′ substituent	pK_a
891-35-0	OCH_3	2.99
955-96-4	CH_3	2.96
782-45-6	H	2.94
955-97-5	Cl	2.75
31366-39-9	NO_2	2.34

[a] The pK_a values, determined spectrophotometrically in 1.6% acetonitrile–water at 23°, represent the average of at least five determinations.

Table II
Substituent Chemical Shift (SCS in Hertz) for Amide Group Methyl Protons in 4′-Substituted 4-Biphenylacetanilides (VI)[a]

Registry no.	4′ substituent	SCS
4075-79-0	H	124.5
54643-71-9	Br	124.2
398-32-3	F	124.3
28533-02-0	NO_2	125.8
2221-22-9	CH_3O	123.7
54643-72-0	CO_2CH_3	125.0
3366-61-8	NH_2	123.6

[a] The SCS values, determined vs. TMS at 37° in 10% DMSO-d_6, represent the average of at least three determinations.

Results and Discussion

The pK_a's for IV are reported in Table I and the substituent chemical shifts (SCS) for the amide group methyl protons of VI are given in Table II. Corresponding pK_a data for III and carbon-13 SCS's (of the 4′ carbon) for V have been reported previously.[11,12]

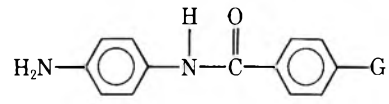
In order to obtain a quantitative assessment of the electronic effect transmission in III and IV, the pK_a data were subjected to correlation analysis[13-15] via the Hammett equation to give eq 1 for III and eq 2 for IV. Included for comparison is the correlation equation (eq 3) for a series of 4-substituted anilines.[18] Of particular interest in comparing these equations is to consider the magnitude of the ρ values, since this offers a measure of the susceptibility of the reaction center to changes in electron density as caused by the various substituents and thus provides an indication of the electronic effect transmission in one system relative to another. The ρ values of −0.67 for III and −0.64 for IV compared to that of −2.89 for the 4-substituted anilines indicates, as expected, that the electronic effect transmission in III and IV is much diminished relative to that for the anilines. Of greater significance, however, is the fact that the ρ values for III and IV are essentially identical, which indicates that the electronic effect transmission in III and IV is essentially identical and that the amide bond must, therefore, be functioning as an effective transmitter of electronic effects. The nature of this transmission is perhaps better revealed via a dual substituent parameter equation analysis.[19] This approach for the aniline-related series III and IV yields eq 4 for III and eq 5 for IV.[20] The relatively small differences in the ρ_I and ρ_{R^-} values for III and IV are an indication of the similarity in electronic effect transmission in these two series. In particular, the relative magnitude of the ρ_{R^-} values provides evidence that the amide bond is capable of functioning as a transmitter of conjugative effects and that it is about 80% as effective as the 1,1′ bond in biphenyl. In effect, the amide bond as substituted in IV does not substantially impede the normal conjugative transmitting ability of the 1,1′ bond in biphenyl. In addition, this effect is not altered by introduction of the amide bond at a position following the 1,1′ bond in biphenyl or by the use of a nonreaction property as a monitor of electronic effect transmission. For example, correlation analysis of NMR data yields eq 6 for the carbon-13 SCS's of the 4′ carbon in V and eq 7 for the amide group methyl protons in VI.

$$pK_a = 4.21 - 0.67\sigma_p,\ r = 0.930,\ s = 0.12 \quad (1)$$
$$pK_a = 2.87 - 0.64\sigma_p,\ r = 0.984,\ s = 0.06 \quad (2)$$
$$pK_a = 4.70 - 2.89\sigma_p,\ r = 0.994,\ s = 0.13 \quad (3)$$
$$pK_a = 4.30 - 0.63\sigma_I - 0.60\sigma_{R^-},\ R = 0.995,\ s = 0.04 \quad (4)$$
$$pK_a = 2.92 - 0.56\sigma_I - 0.46\sigma_{R^-},\ R = 0.995,\ s = 0.04 \quad (5)$$
$$SCS = 0.98 - 1.50\sigma_p,\ r = 0.675,\ s = 0.83 \quad (6)$$
$$SCS = 124.4 + 1.53\sigma_p,\ r = 0.926,\ s = 0.32 \quad (7)$$

While eq 6 for V is not statistically significant,[21] it is important to note the essential identity in absolute magnitude for the ρ values in eq 6 and 7. This suggests that the electronic effect transmitted to the 4′ carbon in V or VI is relayed rather efficiently to the methyl group in VI via the amide bond. In addition, a dual substituent parameter equation analysis (eq 8 for V and eq 9 for VI) indicates that

$$SCS = 1.27 - 1.92\sigma_I - 1.96\sigma_{R^-},\ R = 0.963,\ s = 0.34 \quad (8)$$
$$SCS = 124.1 + 1.00\sigma_I + 1.64\sigma_{R^-},\ R = 0.971\ s = 0.23 \quad (9)$$

this transmission is due in part to a conjugative effect. That is, the ρ_{R^-}(VI)/ρ_{R^-}(V) ratio is essentially identical with the corresponding ratio for III and IV and indicates a conjugative transmission in VI via the amide bond equal to about 80% of that in V. However, the amide bond's ability to function as a transmitter of electronic effects does depend on the location of substituents relative to the amide nitrogen. This point is rather clear when one considers the pK_a data reported by Menger and coworkers[5] for 4-substituted 4′-aminobenzanilides (VII), a series isomeric with IV.



VII

These data indicate that the various substituents in VII have virtually no effect on the pK_a of the amino group. For example, the pK_a of the nitro-substituted compound in VII, which for aromatic amines is normally a much weaker base than the parent amine, differs by only 0.07 pK units from that of the unsubstituted compound, while the corresponding difference in IV is 0.60 pK units. In addition, the range in pK for VII is only 0.14 compared to 0.65 for IV. As expected, correlation analysis of the pK_a data for VII does not yield a significant relation (eq 10) and indicates a ρ value approaching zero.

$$pK_a = 4.55 - 0.09\sigma_p,\ r = 0.772,\ s = 0.04 \quad (10)$$

The results of this study and the comparisons with previous studies indicate that the amide bond is capable of functioning as a transmitter of substituent conjugative effects but can do so effectively only on a one-way basis by way of substitution on the amide nitrogen.

Experimental Section

The 4′-substituted 4-aminobenzanilides were prepared as previously described in the literature.[22,23] The 4′-substituted 4-biphenylacetanilides were prepared by glacial acetic acid–acetic anhydride acetylation of the corresponding 4′-substituted 4-aminobiphenyls.[12]

The pK_a's reported in Table I for the 4′-substituted 4-aminobenzanilides represent the average of at least five determinations

and were determined as described previously[12] with the following exceptions. Spectral solutions were 3×10^{-5} *M* and buffered solutions were prepared using citric acid–Na_2HPO_4. The maximum deviation from the mean of replicate pK_a values did not exceed 2.5% for any of the compounds studied.

The substituent chemical shifts (SCS) in hertz for the amide group methyl protons of 4′-substituted 4-biphenylacetanilides were measured on a Varian T-60 spectrometer vs. TMS at 37° in a 10% DMSO-d_6 solution. These values are reported in Table II and represent the average of at least three determinations. The maximum deviation from the mean of replicate SCS values did not exceed 0.5% for any of the compounds studied.

Acknowledgment. This work was supported in part by the National Science Foundation Institutional Grants for Science Program (GU-3297).

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(21) Correlation analysis of the carbon-13 data[11] using Δ SCS (i.e., substituent chemical shift of the substituted derivative − substituent chemical shift of parent compound) instead of SCS yields a highly statistically significant relation. No difference in correlation significance is obtained for VI when ΔSCS is used.
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An Investigation of the Scope and Limitations of the Cornforth Rearrangement

Michael J. S. Dewar* and Ignatius J. Turchi

Department of Chemistry, The University of Texas, Austin, Texas 78712

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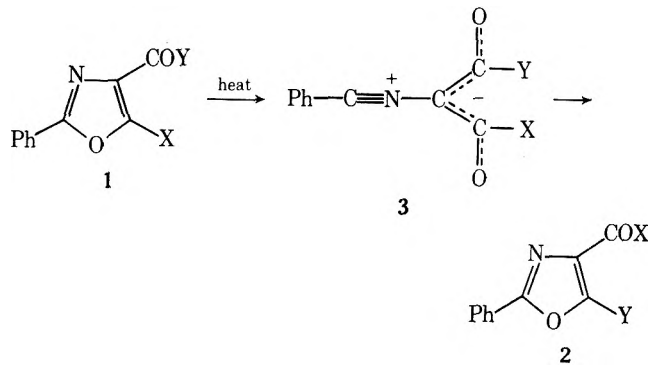
The thermal rearrangement of 4-carbonyl substituted oxazoles was first observed by Cornforth.[1] We have investigated the mechanism of this reaction by experimental[2a,b] and theoretical techniques.[3] The results of these studies suggest the intermediacy of the nitrile ylide **3** in the reaction of **1** → **2**.



a, X = OEt; Y = —N△

b, X = OEt; Y = —N⬭O

c, X = OEt; Y = —N⬭N

d, X = OEt; Y = —N⬭N, Me

e, X = OEt; Y = N, N

f, X = OMe; Y = SPh-*p*-Me

g, X = OEt; Y = F

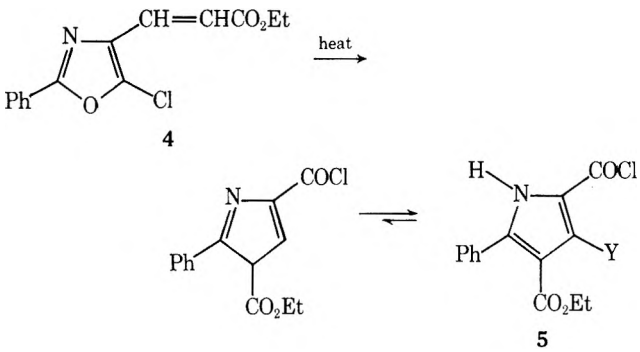
Cornforth found that 2-phenyl-5-ethoxyoxazole-4-carboxamide (**1**, X = OEt; Y = NH_2) rearranged on heating to ethyl 2-phenyl-5-aminooxazole-4-carboxylate (**2**, X = OEt; Y = NH_2).[1] We have now carried out similar rearrangements of several secondary and tertiary alkyl and aryl oxazole-4-carboxamides to the corresponding secondary and tertiary 5-aminooxazoles.[2b] We have also found that this rearrangement occurs in yields of >90% when the amide nitrogen is part of a heterocyclic ring system (**1a–e** → **2a–e**).

Trideuteriomethyl 2-phenyl-5-methoxyoxazole-4-carboxylate (**1**, X = OMe; Y = OCD_3) rearranged on heating to give a 1:1 equilibrium mixture of **1** and the corresponding rearranged ester **2** (X = OMe; Y = OCD_3).[2b] The thiol ester **1f** underwent thermal isomerization to the corresponding 5-thiooxazole **2f** in good yield under similar conditions. Prior to this investigation there was, to our knowledge, only one other method for preparing 5-thiooxazole-4-carboxylates, i.e., the reaction of 4-benzamido-1,2-dithiol-3-thione with KOH and methyl iodide to give 2-phenyl-5-methylthiooxazole-4-carbodithioate.[4] Thus the Cornforth rearrangement of 5-alkoxyoxazole-4-thiocarboxylates is a potentially general method for the synthesis of 5-thiooxazole-4-carboxylic esters.

While **1** (X = OEt; Y = Cl) rearranges to **2** (X = OEt; Y = Cl),[1] the corresponding fluoro derivative **1g** failed to rearrange.

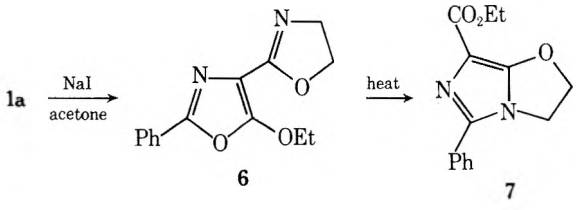
These reactions all involve compounds where a heteroatom is attached to the 5 position. One rearrangement has been reported[5] where the group X in **1** is alkyl or aryl, i.e., the interconversion of 2,5-diphenyl-4-acetyloxazole and 2-phenyl-4-benzoyl-5-methyloxazole; the reactions were, however, very slow even at 220°.

When the 4-carbonyl group of **1** was replaced by an α,β-unsaturated ester functionality, the resulting compound (**4**) failed to rearrange to the corresponding pyrrole derivative **5**, even after boiling under reflux for 17 hr in toluene.



Attempts to prepare 2-phenyl-5-ethoxyoxazole-4-carboxylic acid thioamide by the reaction of the corresponding oxazole-4-cyanide with H_2S–NaOEt failed to yield any identifiable products. Rearrangement of this thioamide should lead to ethyl 2-phenyl-5-aminothiazole-4-carboxylate.

The reaction of the aziridinyl amide **1a** with sodium iodide in acetone gave 2-(2-phenyl-5-ethoxyoxazolyl)-Δ^2-oxazoline (**6**) in 60% yield. Thermolysis of **6** in boiling toluene gave 5-phenyl-7-carboethoxyimidazo[5,1-*b*]-2,3-dihydrooxazole (**7**) in 97% yield.



Whether or not rearrangement of 1 occurs in any given case seems to depend solely on the equilibrium between reactant and product. For example, oxazole-4-carboxamides rearrange irreversibly to 5-aminooxazoles at temperatures above 90°. 5-Methoxyoxazole-4-carboxamide is calculated (by the MINDO/3 MO method[6]) to be some 6 kcal/mol less stable than the rearranged methyl 5-aminooxazole-4-carboxylate.[3]

The 5-aminooxazoles prepared via the Cornforth rearrangement could possess interesting and useful biological properties. Tests of the biological activity of several of these new compounds are now in progress.

Experimental Section

Melting points are uncorrected. NMR spectra were recorded on a Varian A-60 instrument using solutions approximately 15% w/v in deuteriochloroform. Ir spectra were determined with a Beckman IR-8 spectrophotometer (KBr disk). Mass spectra were measured with 70-eV electrons. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., and Heterocyclic Chemical Corp., Harrisonville, Mo.

General Procedure for the Preparation of 2-Phenyl-5-ethoxyoxazole-4-carboxamides (1a–e). A solution of 2-phenyl-5-ethoxyoxazole-4-carboxylic acid chloride[1] (0.005 mol) in benzene (20 ml) was added to a solution of the corresponding amine (0.005 mol) and triethylamine (0.5 g, 0.005 mol) in benzene (40 ml) at 0°. The mixture was then stirred for 3 hr at room temperature, filtered, washed with water, and dried ($MgSO_4$) and the benzene was evaporated. The resulting amides were recrystallized several times from petroleum ether (bp 60–70°).

1a: yield 80%; mp 82–83°; ir 2970–3000 (w), 1660 (s, C=O), 1600 cm^{-1} (s, C=N); NMR δ 8.0 (m, 2 H, phenyl), 7.6 (m, 3 H, phenyl), 4.6 (q, 2 H, ethoxymethylene), 2.4 (s, 4 H, aziridine), 1.5 (t, 3H, methyl); mass spectrum *m/e* (rel intensity) 258 (21), 212 (6), 188 (12), 131 (15), 105 (100).

Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.29; H, 5.67; N, 11.05.

1b: yield 93%; mp 83–84°; ir 2720–2920 (m), 1645 (s, C=O), 1605 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.55 (q, 2 H, ethoxymethylene), 3.9 (broad m, 8 H, morpholine protons), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 303 (21), 302 (100), 216 (11), 188 (39), 172 (15), 105 (66). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.79; H, 6.00; N, 9.20.

1c: yield 78%; mp 105–107°; ir 3160 (w), 2960 (w), 1700 (s, C=O), 1600 cm^{-1} (s, C=N); NMR δ 8.75 (d, 1 H, J = 3 Hz, 3-pyrazole proton), 7.9 (m, 3 H, phenyl and 5-pyrazole protons), 7.45 (m, 3 H, phenyl), 6.45 (dd, 1 H, 4-pyrazole proton), 4.65 (q, 2 H, methylene), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 283 (76), 256 (19), 255 (100), 238 (19), 188 (46). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.85; H, 4.75; N, 14.64.

1d: yield 92%; mp 98–100° dec; ir 3180 and 2990 (m), 1685 (s, C=O), 1600 cm^{-1} (s, C=N); NMR δ 8.3 (d, 1 H, J = 1.5 Hz, 4-imidazole proton), 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 6.9 (d, 1 H, J = 1.5 Hz, 5-imidazole proton), 4.65 (q, 2 H, methylene), 2.75 (s, 3 H, imidazole methyl), 1.55 (t, 3 H, ethoxymethyl); mass spectrum *m/e* (rel intensity) 297 (35), 216 (60), 188 (45), 110 (100), 95 (53). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; 5.09; N, 14.13. Found: C, 64.78; H, 5.16; N, 14.06.

1e: yield 88%; mp 156° dec; ir 3150 (m), 2950 (w), 1685 (s, C=O), 1590 cm^{-1} (s, C=N); NMR δ 8.4 (m, 1 H, 2-benzimidazole proton), 7.9 (m, 3 H, phenyls), 7.4 (m, 6 H, phenyls), 4.7 (q, 2 H, methylene), 1.6 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 333 (100), 216 (63), 188 (73), 146 (77), 131 (95). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.68; H, 4.69; N, 12.50.

General Procedure for the Preparation of Ethyl 2-Phenyl-5-aminooxazole-4-carboxylates (2a–e). The corresponding amides **1a–e** were heated under reflux for 17 hr in dry toluene. The solvent was then removed and the residue recrystallized from petroleum ether. Yields of >90% of pure materials were obtained.

2a: mp 118–119°, ir 3170 (w), 2950 (m), 1710 (s, C=O), 1580 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.4 (q, 2 H ethoxymethylene), 2.6 (s, 4 H, aziridine), 1.4 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 258 (100), 216 (33), 188 (73), 160 (32). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.88; H, 5.32; N, 10.74.

2b: mp 85–86°; ir 2700–2920 (m), 1685 (s, C=O), 1610 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.4 (q, 2 H, ethoxymethylene), 3.8 (m, 8 H, morpholine), 1.4 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 302 (100), 216 (11), 188 (42), 160 (25). Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.62; H, 6.13; N, 9.37.

2c: mp 99–101°; ir 3150 and 2950 (w), 1710 (s, C=O), 1630 cm^{-1} (s, C=N); NMR δ 8.55 (d, 1 H, J = 3 Hz, 3-pyrazole proton), 8.15 (m, 2 H, phenyl), 7.9 (d, 1 H, J = 2 Hz, 5-pyrazole proton), 7.45 (m, 3 H, phenyl) 6.55 (dd, 1 H, 4-pyrazole proton), 4.45 (q, 2 H, methylene), 1.3 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 283 (100), 255 (99), 226 (17), 188 (37). Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.49; H, 4.53; N, 14.70.

2d: mp 149–150°; ir 3130 and 2950 (w), 1740 (s, C=O), 1645 cm^{-1} (m, C=N); NMR δ 8.1 (m, 2 H, phenyl), 7.5 (m, 3 H, phenyl), 7.2 (d, 1 H, J = 1 Hz, 4-imidazole proton), 7.05 (d, 1 H, J = 1 Hz, 5-imidazole proton), 4.35 (q, 2 H, methylene), 2.45 (s, 3 H, imidazole methyl), 1.3 (t, 3 H, ethoxymethyl); mass spectrum *m/e* (rel intensity) 297 (14), 216 (76), 188 (100), 160 (52). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.47; H, 5.01; N, 13.96.

2e: mp 189–190°; ir 3170 and 2950 (w), 1710 (s, C=O), 1610 cm^{-1} (s, C=N); NMR δ 8.65 (broad s, 1 H, 2-benzimidazole proton), 7.8 (m, 9 H, phenyls), 4.4 (q, 2 H, methylene), 1.3 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 333 (13), 216 (3), 188 (2), 176 (15), 161 (100). Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46, H, 4.54; N, 12.61. Found: C, 68.64; H, 4.60; N, 12.45.

***p*-Tolyl 2-Phenyl-5-methoxyoxazole-4-thiocarboxylate (1f).** A solution of 2-phenyl-5-methoxyoxazole-4-carboxylic acid chloride[2b] (0.005 mol, 1.19 g) in benzene (40 ml) was added to a solution of *p*-thiocresol (0.005 mol, 0.62 g) and triethylamine (0.005 mol, 0.5 g) in benzene (40 ml) at 0°. The mixture was then stirred at room temperature for 15 hr and worked up as in the preparation of **1a–e** (1.5 g, 95%): mp 104–105°; ir 2930 (w), 1670 (s, C=O), 1605 cm^{-1} (s, C=N); NMR δ 8.0 (m, 2 H, phenyl), 7.4 (m, 7 H, phenyls), 4.25 (s, 3 H, methoxymethyl), 2.4 (s, 3H, Ph-*p*-**Me**); mass spectrum *m/e* (rel intensity) 326 (12), 325 (52), 220 (100), 174 (27), 146 (12). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.64; H, 4.80; N, 4.31.

Methyl 2-phenyl-5-*p*-tolylthiooxazole-4-carboxylate (2f) was prepared in the same manner as **2a–e**: yield 94%; mp 94–95°; ir 3040, 2850–2950 (w), 1735 (s, C=O), 1550 cm^{-1} (m, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.35 (m, 7 H, phenyls), 4.0 (s, 3 H, methoxy-

methyl), 2.45 (s, 3 H, Ph-*p*-Me); mass spectrum *m/e* (rel intensity) 326 (20), 325 (81), 203 (15), 202 (100), 174 (24). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.36; H, 4.49; N, 4.18.

2-Phenyl-5-ethoxyoxazole-4-carboxylic Acid Fluoride (1g) (Prepared by a Modification of the Method of Olah et Al.[7]). A solution of cyanuric fluoride (0.004 mol, 0.54 g) in acetonitrile (20 ml) was added dropwise to a stirred solution of 2-phenyl-5-ethoxyoxazole-4-carboxylic acid[1] (0.01 mol, 2.33 g) and pyridine (0.01 mol, 0.79 g) in acetonitile (50 ml). (Before the addition of the cyanuric fluoride, the acid–pyridine–acetonitrile mixture was warmed on a water bath to dissolve the acid.) The reaction mixture was allowed to stand at room temperature for 3 hr. After the completion of the reaction the mixture was poured onto ice water, extracted with ether, and dried (Na_2SO_4) and the solvent was removed. The residue was recrystallized several times from petroleum ether to remove traces of the starting acid: 1.1 g (48%); mp 88–90°; ir 2990 (w), 1805 (s, C=O), 1630 cm^{-1} (s, C=N); NMR δ 7.9 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.6 (q, 2 H, methylene), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 236 (5), 235 (27), 188 (36), 187 (100), 105 (42). Anal. Calcd for $C_{12}H_{10}NO_3F$: C, 61.28; H, 4.28; N, 5.95. Found: C, 61.13; H, 4.24; N, 5.80.

Ethyl β-(2-Phenyl-5-chlorooxazole-4)acrylate (4). A solution of 2-phenyl-5-chlorooxazole-4-carboxaldehyde[1] (0.0048 mol, 1.0 g) and (carboethoxymethylene)triphenylphosphorane (0.0072 mol, 2.55 g) in ethanol (50 ml) was allowed to stand for 3 days at room temperature. The mixture was then filtered and the solvent removed. The residue was recrystallized several times from petroleum ether to remove triphenylphosphine oxide and starting material (1.2 g, 90%): mp 90–91°; ir 3060 (w), 2900–2950 (m), 1710 (s, C=O), 1640 (s, C=N), 1600 cm^{-1} (m, C=C–C=O); NMR δ 8.0 (m, 2 H, phenyl), 7.5 (m, 4 H, phenyl and part of AB quartet of vinyl protons), 6.85 and 6.6 (1 H, part of AB quartet of vinyl protons, $J_{AB} \simeq 16$ Hz), 4.3 (q, 2 H, methylene), 1.35 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 279 (17), 278 (18), 277 (64), 249 (28), 242 (37), 232 (22), 220 (100). Anal. Calcd for $C_{14}H_{12}NO_3Cl$: C, 60.55; H, 4.36; N, 5.04. Found: C, 60.46; H, 4.28; N, 5.07.

2-(2-Phenyl-5-ethoxyoxazolyl)-Δ²-oxazoline (6). A solution of **1a** (0.012 mol, 3.0 g) and NaI (22.5 g) in acetone (300 ml) was stirred at room temperature for 24 hr. The solvent was removed; the residue was extracted with hot benzene, filtered, and dried ($MgSO_4$) and the benzene was removed, leaving an oil which crystallized on standing. Recrystallization from pentane gave 1.8 g (60%) of **6**: mp 66–67°; ir 2720–2980 (m), 1665 and 1635 cm^{-1} (s, C=N); NMR δ 8.0 (m, 2 H, phenyl), 7.4 (m, 3 H, phenyl), 4.4 (m, 6 H, oxazoline and ethoxymethylenes), 1.5 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 258 (100), 213 (39), 186 (50), 156 (44), 130 (54). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.88; H, 5.51; N, 11.04.

5-Phenyl-7-carboethoxyimidazo[5,1-*b*-]-2,3-dihydrooxazole (7). A solution of **6** (0.0077 mol, 2.0 g) in dry toluene was heated under reflux for 17 hr. The solvent was removed and the solid residue was recrystallized from benzene (1.94 g, 97%): mp 166–167°; ir 3160 (w), 2900–2975 (m), 1695 (s, C=O), 1590 cm^{-1} (s, C=N); NMR δ 7.7 (m, 2 H, phenyl), 7.3 (m, 3 H, phenyl), 5.2 broad t, 2 H, NCH_2), 4.3 (m, 4 H, OCH_2 of oxazoline ring and ethoxymethylene protons), 1.35 (t, 3 H, methyl); mass spectrum *m/e* (rel intensity) 259 (18), 258 (100), 213 (24), 186 (26), 156 (25), 130 (74). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.23; H, 5.63; N, 11.09.

Acknowledgments. This work was supported by the Air Force Office of Scientific Research (Contract No. F44620-71-C-0119) and the Robert A. Welch Foundation (Grant F-126). The calculations were carried out using the CDC 6400/6600 computer at the University of Texas Computation Center.

Registry No.—**1a**, 54643-95-7; **1b**, 54643-96-8; **1c**, 54643-97-9; **1d**, 54643-98-0; **1e**, 54643-99-1; **1f**, 54644-00-7; **1g**, 54644-01-8; **2a**, 54644-02-9; **2b**, 54644-03-0; **2c**, 54644-04-1; **2d**, 54644-05-2; **2e**, 54644-06-3; **2f**, 54644-07-4; **4**, 54644-08-5; **6**, 54644-09-6; **7**, 54644-10-9; aziridine, 151-56-4; morpholine, 110-91-8; 1*H*-pyrazole, 288-13-1; 2-methyl-1*H*-imidazole, 693-98-1; 1*H*-benzimidazole, 51-17-2; 2-phenyl-5-methoxyoxazole-4-carboxylic acid chloride, 54644-11-0; *p*-thiocresol, 106-45-6; cyanuric fluoride, 675-14-9; 2-phenyl-5-ethoxyoxazole-4-carboxylic acid, 54644-12-1; 2-phenyl-5-chlorooxazole-4-carboxaldehyde, 54644-13-2; 2-phenyl-5-ethoxyoxazole-4-carboxylic acid chloride, 54644-14-3.

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A Convenient Preparation of Simple Optically Active Phosphinate Esters and Derivatives from the Corresponding Menthyl Esters. Solvolysis of Menthoxyphosphonium Salts in Trifluoroacetic Acid

Kenneth E. DeBruin* and D. Edward Perrin

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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Optically active phosphinate esters with chirality at phosphorus are important intermediates in the synthesis of other classes of chiral phosphorus compounds such as phosphine oxides[1,2] and phosphines,[3] phosphinamidates,[4] and phosphinothioates.[5] At present, preparation of the menthyl esters and separation of diastereomers provides the easiest route to these phosphinate esters. The use of the menthyl esters, however, suffers from certain limitations. Often, as is the case for the widely used $(S)_P$ menthyl methylphenylphosphinate, only one diastereomer is easily obtained in high optical purity. The chiral menthyl ligand, however, requires access to both epimers at phosphorus before the stereospecificity of a reaction can be established. In addition, the steric bulk of the menthyl ligand hinders transformations which involve a nucleophilic displacement at phosphorus.[2]

We would like to report a convenient stereospecific conversion of menthyl phosphinates to the more simply substituted methyl or ethyl phosphinates, which have their sole center of chirality at phosphorus and have the opposite stereochemical configuration at phosphorus than the starting menthyl esters. Thus, the limitations of the menthyl esters can be circumvented and the procedure broadens their usefulness. In addition, an extension of the method for the conversion of menthyl phosphinothionates to alkyl phosphonothiolates was found.

The general method for the above conversions is indicated in Scheme I. A general procedure applied to the examples in Table I is given in the Experimental Section. Invariably, the yields for the overall conversions of 1 to 3 were greater than 90%. The use of the trialkyloxonium *hexafluorophosphate* alkylating agents was found to be far superior to using either the tetrafluoroborate or hexachloroantimonate salts. The oxonium tetrafluoroborates are hygroscopic and usually result in phosphonium salts (**2**, $ML_n = BF_4$) which are oils and difficult to handle. While the phosphonium salts (**2**, $ML_n = SbCl_6$) resulting from alkylation with the less hygroscopic oxonium hexachloroantimonates are usually solids, the solvolysis of these phosphonium salts to the desired products (**3**) results in the formation of an insoluble mass and greatly complicates work-up. When the alkylating agent is the oxonium hexafluorophosphate, all of the above advantages and none of the disadvantages occur

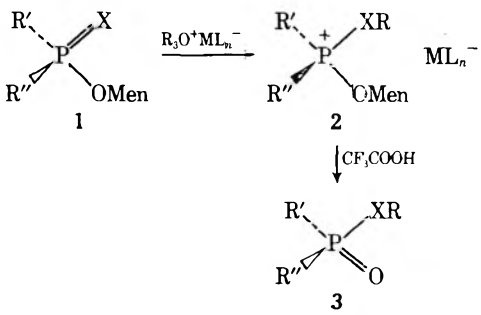
Table I
Products and Stereochemistry of Menthyl Phosphinate and Phosphinothionate Ester Transformations

Menthyl ester, R'R''P(X)OMen					$R_3O^+PF_6^-$	Product, R'R''P(O)XR			
(S):(R)[a]	R'	R''	X	Registry no.	R	Conf	$[\alpha]D$[b]	Optical purity, %	Registry no.
100:0	Ph	Me	O	16934-93-3 (S)	Me[h]	R[c]	+56°	100	34647-07-9
44:56	Ph	Me	O	16934-92-2 (R)	Me	S[c]	−6.2°	11	34647-06-8
100:0	Ph	Me	O		Et[i]	R[d]	+49°	100	34638-79-4
44:56	Ph	Me	O		Et	S[d]	−6.0°	12	33642-98-7
20:80	Ph	β-Np	O	21232-92-8 (S)	Me	S[e]	−22°	(60)[e]	54632-62-1
20:80	Ph	β-Np	O	21232-91-7 (R)	Et	S[e]	−17°	(60)[e]	54632-63-2
0:100[f]	Ph	Me	S	54142-41-5 (R)	Me	R[g]	+158°	100	38605-11-7

[a] Configuration at phosphorus. Established by ^1H NMR.[6] [b] Rotations in benzene (ca. 4 g/100 ml). [c] Reference 7. [d] Reference 8. [e] Assumed from this work. Np = naphthyl. [f] References 9 and 10. [g] Reference 11. [h] Registry no., 12116-05-1. [i] Registry no., 17950-40-2.

except that the solution darkens to a reddish color but remains clear.

Scheme I



R', R'' = aryl or alkyl
R = Me or Et
X = O or S
ML_n = PF_6, BF_4, or $SbCl_6$
Men = *l*-menthyl

Since the second step in the above conversion appears to involve the solvolysis of a menthyl compound with a *neutral* leaving group (phosphinate ester), we decided to study the kinetics and activation parameters of the reaction. The reaction was easily followed by ^1H NMR and the data obtained are given in Table II. There appears to be little effect by varying substituents on phosphorus or by using a different anion on the rate of the solvolysis. The menthyl fragment of the solvolysis exists primarily as menthyl trifluoroacetate with minor amounts of elimination products.[12]

The rate constant for the solvolysis of menthoxymethoxymethylphenylphosphonium hexafluorophosphate (1.5×10^{-3} sec^{-1}) in trifluoroacetic acid at 40° is of the same order of magnitude as that observed for the solvolysis of cyclohexyl tosylate (1.3×10^{-3} sec^{-1}) under the same conditions. If the rather tentative assumption is made that cyclohexyl tosylate and menthyl tosylate solvolyze at similar rates in trifluoroacetic acid as they do in acetic acid,[13] it follows that the neutral phosphinate ester is of comparable leaving ability to the anionic tosylate leaving group. This observation might suggest using the readily accessible methyl diphenylphosphinate leaving group resulting from the solvolysis of alkoxy diphenyl methoxyphosphonium salts [$Ph_2(MeO)P^+OR$, PF_6^-] to probe, in comparison to the tosylates, such factors as internal return and solvent on solvolysis reactions.

The activation parameters obtained from the data in Table II are $\Delta G^\ddagger$ = 22 kcal/mol, $\Delta H^\ddagger$ = 19 kcal/mol, and $\Delta S^\ddagger$ = −11 eu (25°). The similarity in the entropy to that for cyclohexyl tosylate ($\Delta S^\ddagger$ = −13 eu)[14] is particularly striking.[15]

Table II
Solvolysis of Phosphonium Salts[a] in Trifluoroacetic Acid

$Ph(R)P^+(XR')OMen\ ML_n^-$				Temp,	
R	XR'	ML_n	Registry no.	°C[b]	10^3 k, sec^{-1}
Me	OMe	BF_4	54656-82-5	40	0.90[c]
Me	OMe	PF_6	54656-83-6	40	1.5[c]
				38	1.4[c]
				30	0.48[c]
				18	0.15[c]
Me	OEt	BF_4	54632-64-3	40	0.62[c]
Me	SMe	PF_6	54656-85-8	40	0.5[d]
β-Np	OMe	PF_6	54632-66-5 (R)	40	1.5[e]
			54656-87-0 (S)		

[a] Concentration ca. 0.6 *M*. [b] Obtained using standard methanol or ethylene glycol calibration curves. [c] $(S)_P$ isomer. [d] $(R)_P$ isomer. [e] 80:20 $(R)_P$:$(S)_P$. Diastereomers reacted at similar rates.

Experimental Section

Conversion of Menthyl Esters (1) to Phosphonium Salts (2). Equal molar amounts of the trialkyloxonium salt and menthyl ester (1) are added to dichloromethane (10 ml/g of ester) at room temperature. (Note: the trimethyloxonium salts are insoluble and dissolve as they react). After 5 hr of stirring, the reaction is usually complete and can be investigated by ^1H NMR on a sample directly removed from the reaction mixture. The dichloromethane is removed under vacuum *without heating* and the colorless residue can be retained in the reaction flask and used in the next step without purification.

If purification of the phosphonium salt 2 is desired, it is most easily accomplished by redissolving the residue in a minimal amount of dichloromethane to make the sample less viscous. This solution is then rapidly added to a tenfold volume of anhydrous ether with a disposable pipette, causing an oil or white solid to come out of solution as the phosphonium salt. If an oil forms, it can usually be made to solidify if the ether mixture is cooled to Dry Ice–acetone bath temperature.

Conversion of the Phosphonium Salts (2) to the Corresponding Esters (3). Decomposition of the phosphonium salt to the desired ester is accomplished by adding trifluoroacetic acid (5 ml/g of starting ester 1) to the residue obtained above and stirring at room temperature for 5 hr. The reaction is worked up by diluting 20-fold with dichloromethane and extracting twice with water and once with a saturated aqueous sodium bicarbonate solution. Drying and concentrating the organic layer affords approximately equal volume amounts of the desired ester 3 and products derived from the menthyl fragment. Purification is best accomplished by elution chromatography on silica gel with hexane eluting the menthyl products and chloroform eluting the phosphorus ester. Rapid short-path distillation affords the desired ester in greater than 90% yield.

Kinetic Procedure. The progress of the solvolysis of 2 is easily followed by ^1H NMR on a sample directly removed from the reaction mixture as prepared above. The protons on the ester product are upfield from the corresponding protons on the phosphonium salt. Since the reaction is quantitative, integration provides a direct measure of the progress of the reaction. Good pseudo-first-order plots can be obtained over the entire reaction.

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Gas Phase Thermolysis of Sulfonyl Azides

W. B. Renfrow* and Manoharran Devadoss

Department of Chemistry, Oberlin College, Oberlin, Ohio 44074

Received January 2, 1975

Prior information about the gas phase thermolysis of a sulfonyl azide is restricted to a report by Reichle,[1] who obtained azobenzene (17%) and tar from benzenesulfonyl azide (1) at 625° and 0.5 Torr.

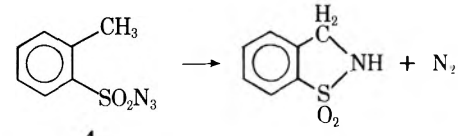
It was of interest to us to determine whether or not gas phase thermolysis of 1 in the presence of benzene would produce products obtainable from the same reactants in the liquid phase. The liquid phase thermolysis of sulfonyl azides has been studied extensively.[2] Thermolysis of 1 in benzene solution produces[3] nitrogen gas, *N*-phenylbenzenesulfonamide (2), benzenesulfonamide (3), and tar. A sulfonylnitrene, $C_6H_5SO_2N$, is generally considered[2] to be an intermediate in these reactions. In agreement with the earlier work, we have isolated from liquid phase thermolysis a 64% yield of 2 and 6% yield of 3.

$$\underset{1}{PhSO_2N_3} + PhH \longrightarrow \underset{2}{PhSO_2NHPh} + \underset{3}{PhSO_2NH_2} + N_2 + tar$$

Products and yields from gas phase thermolysis of 1 in the presence/absence of benzene were as follows: sulfur dioxide, 65/71%; azobenzene, 32/27%; 3, 2/2%; diphenylamine, 1/3%; and biphenyl, 2/1%. Fluorescent material, probably a mixture of *N*-phenylbiphenylamines and triphenylamine, was formed in about 1% yield in the absence of benzene and in less amount in the presence of benzene. No insertion product into benzene (2) could be detected among the products formed in the presence of benzene.

Phenylnitrene (C_6H_5N) is a likely intermediate in the gas phase thermolysis of 1 because azobenzene is also the major organic product (72%) from gas phase thermolysis of phenyl azide.[4] Phenylnitrene could be formed by a Curtius-type rearrangement[5] of benzenesulfonylnitrene, followed by loss of sulfur dioxide. Decomposition products in the reaction zone of the hot tube probably include phenyl radicals, hydrogen atoms, singlet and triplet forms of benzenesulfonylnitrene, and phenylnitrene. Aniline was not detected among the products. The fact that the yield of diphenylamine was greater in the absence than in the presence of benzene is evidence against an insertion reaction of phenynitrene into benzene.

With 2-methylbenzenesulfonyl azide (4), the intramolecular insertion product, benzylsultam (5), was obtained in 21% yield from gas phase thermolysis in the absence of



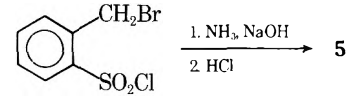
4 5

benzene and in 13% yield with benzene present. This result is readily explained in terms of a sulfonylnitrene intermediate which inserts into the adjacent methyl group. No 2,2′-dimethylazobenzene was found among the products from gaseous 4.

The main product from gas phase thermolysis of 4 was a clear yellow gum. On TLC the gum gave a yellow band and several bands which fluoresced under 350-nm light. Attempts to obtain identifiable pure substances from the yellow and fluorescent bands were unsuccessful because of spontaneous conversion to nonvolatile, presumably polymeric products. Smolinsky[4] obtained a polymeric product from gas phase thermolysis of 2,6-dimethylazidobenzene and suggested that a quinoid compound was a likely intermediate. The same type of intermediate is probably formed from 4.

Liquid phase thermolysis of 4 in benzene gave the insertion product into the solvent, *N*-phenyl-2-methylbenzenesulfonamide (63%), and 2-methylbenzenesulfonamide (8%). No 5 was found. The stereochemical restriction which allows intermolecular C–H insertion to predominate over intramolecular insertion in the liquid phase thermolysis of 4 is obscure. Some sulfonyl azides that can either cyclize or insert into solvent have been studied by Abramovitch and coworkers,[5,6] who found a range of behaviors.

A preparation of 5 in very low yield from *N*,*N*-dichloro-2-methylbenzenesulfonamide has been reported,[7] and 5 has been obtained as a reduction product of saccharin used as a brightener in electroplating.[8] We have prepared 5 in 50% yield from 2-bromomethylbenzenesulfonyl chloride (6). Ammonia and sodium hydroxide react with 6 to produce a salt of 5 which is converted to 5 by acidification.



6

Experimental Section

Mass spectra were obtained with a Hitachi Perkin-Elmer RMS-4 at 70 eV. Preparative TLC was performed using E. Merck No. 7747 silica gel PF-254 in 1-mm layers on 20 × 20 cm glass plates. Ratios of solvent mixtures are v/v. Bands of sorbent from TLC plates were placed in small columns and eluted with chloroform–methanol (9:1) to remove products. Development of TLC plates carrying azobenzene was done in the dark to avoid photochemical cis–trans interconversion[9]. Only *trans*-azobenzene was isolated. In calculating percentage yields all products are considered to have resulted exclusively from sulfonyl azides.

2-Methylbenzenesulfonyl chloride was purified by partial crystallization from its melt until a product was obtained containing less than 0.5% of the 4-methyl isomer by ^1H NMR analysis. Benzenesulfonyl azide (1), bp 61° (0.05 Torr), and 2-methylben-

zenesulfonyl azide (4), bp 70° (0.05 Torr), were prepared[10] from the corresponding sulfonyl chlorides and sodium azide in aqueous acetone.

Gas Phase Pyrolyses.[4] Reactions were carried out in a vertical tube, 12 mm i.d., of which a 120-mm length was maintained at 360 ± 5° by an external electric heater. A mercury thermometer with the bulb in the center of the reaction zone was used to measure temperature. A loose plug of Pyrex glass wool (0.15 g) was inserted immediately beneath the thermometer bulb. The tube was cleaned and the glass wool replaced after each run.

Samples entered the reaction zone through a side arm and short portion of the top of the reaction tube maintained at 110°. The side arm was attached to a vertical 8-mm i.d. tube surrounded by a water bath. A volume of about 0.5 ml could be held at the bottom of the 8-mm tube below the side arm. Pure sulfonyl azides (about 100 mg) were placed in the bottom of the 8-mm tube, a stream of nitrogen or benzene vapor regulated by a capillary was passed over the surface, and the water bath was maintained at a temperature (70–100°) selected to give a desired time (100–5 min) for complete distillation. An alternative method was routinely used for introducing sulfonyl azides plus benzene that avoided distilling the potentially explosive[11] pure azides: a solution of the sulfonyl azide in benzene was introduced through a fine capillary into the bottom of the 8-mm tube with the bath near the temperature of boiling water. Pressure in the system increased with rate of throughput and was usually in the range 0.05–0.2 Torr.

Products were collected in a trap cooled by liquid nitrogen. At the conclusion of a run and after the vacuum was broken a tube containing 0.100 *N* sodium hydroxide was attached to the trap containing products. Nitrogen was passed through the reaction tube and trap and bubbled through the standard base while the reactor tube cooled and the trap warmed to room temperature. The base was titrated to a phenolphthalein end point with hydrochloric acid. Confirmation that the volatile acid was sulfur dioxide was provided by further titration with 0.100 *N* iodine solution. Milliequivalents of base and of iodine consumed were practically the same.

Benzene was added to the trap to bring the liquid volume to about 2 ml and refluxed into the formerly heated reaction tube. Azobenzene and unreacted sulfonyl azide dissolved while tar or gum and benzenesulfonamide deposited beyond the hot zone of the reactor did not dissolve. The benzene solution was assayed for unchanged azide by measuring the intensity of absorption at 2150 cm^{-1}, after which the benzene was evaporated. Tar and sulfonamide remaining in the reaction tube were dissolved in refluxing chloroform–methanol (4:1), the residue from the benzene solution was added, and the solution was streaked onto a TLC plate. The plate was developed in benzene–ethyl acetate (3:1). R_f values for products isolated at this stage follow: benzenesulfonamides and **5**, 0.3–0.4; benzenesulfonanilides, 0.65–0.75. Materials with R_f greater than 0.8 were eluted, streaked onto a fresh TLC plate, and developed with benzene–hexane (1:1). R_f values of products isolated at this stage follow: sulfonyl azides, 0.3; diphenylamine, 0.5; *trans*-azobenzene, 0.7; a fluorescent substance of uncertain structure, 0.8; biphenyl, 0.9. Diphenylamine was the only substance of known structure which fluoresced under 350-nm light. All products of known structures gave dark bands under 254-nm light.

The ir spectra of products isolated from TLC plates were often the same as the spectra of authentic materials, and yields reported were determined at this stage unless otherwise specified. Solid products were further purified by distillation (0.02 Torr) and crystallization, and melting points were compared with those of authentic samples.

Benzenesulfonyl azide (**1**, 121 mg) plus benzene (1.25 g) pyrolyzed in the gas phase during 45 min gave unchanged **1** (15 mg by ir, 11 mg isolated), *trans*-azobenzene (17 mg, 32%), **3** (2 mg, 2%), diphenylamine (0.5 mg, 1%), biphenyl (1 mg, 2%), and sulfur dioxide (0.38 mmol, 65%). A small fluorescent band between azobenzene and biphenyl gave insufficient material for characterization. In the absence of benzene **1** (98 mg) pyrolyzed during 15 min gave no unchanged **1**, *trans*-azobenzene (12.6 mg, 27%), **3** (1.6 mg, 2%), diphenylamine (1.5 mg, 3.5%), biphenyl (0.4 mg, 1%), and sulfur dioxide (0.39 mmol, 71%). A fluorescent band between azobenzene and biphenyl gave on elution 1 mg of brown oil. The mass spectrum of the oil was as follows: *m/e* (rel intensity) 245 (100), 77 (55), 51 (40), 154 (33), 244 (33), 167 (29).

2-Methylbenzenesulfonyl azide (**4**, 104 mg) pyrolyzed alone in the gas phase during 10 min gave no unchanged **4**, 18.5 mg (21%) of **5** after sublimation to clean up the ir spectrum, and sulfur dioxide (0.33 mmol, 62%). Pyrolysis of **4** (95 mg) plus benzene (900 mg) during 100 min gave 4 mg of unchanged **4** and 10 mg (13%) of **5** after sublimation. The first TLC plate from each run showed a yellow band and five fluorescent bands under 350-nm lights. Attempts to purify the yellow and fluorescent materials by further chromatography or distillation led to chromatographically immobile and nonvolatile products.

Liquid Phase Thermolyses. The reactants in glass tubes were frozen, and the tubes were evacuated, sealed, and heated at 145–155° for 8 hr. From **1** (125 mg) in benzene (1.23 g) there was obtained 0.1 mg of unchanged **1**, 102 mg (64%) of **2**, and 6.5 mg (6%) of **3**. From **4** (113 mg) in benzene (1.13 g) there was obtained 89.5 mg (63%) of *N*-phenyl-2-methylbenzenesulfonamide and 8 mg (8%) of 2-methylbenzenesulfonamide.

2-Bromomethylbenzenesulfonyl Chloride (**6**). A solution of 2-methylbenzenesulfonyl chloride (7.7 g) in 50 ml of carbon tetrachloride was cooled and irradiated with a 450-W mercury lamp while a solution of bromine (7.4 g) in carbon tetrachloride (50 ml) was run in during 30 min. A fraction (8.2 g), bp 95–110° (0.1 Torr), crystallized and was recrystallized from petroleum ether to yield 3.6 g of **6**: mp 58–60° (lit.[12] mp 48–55°); mass spectrum *m/e* (rel intensity) 268 (100), 270 (130), 272 (37).

Benzylsultam (**5**). Solutions of **6** (270 mg) in 10 ml of dimethoxyethane and of 2.5 *N* sodium hydroxide (1.5 ml) and 15 *N* ammonia (0.3 ml) in 10 ml of dimethoxyethane were cooled in an ice bath. The first solution was poured with good mixing into the second. The solution was swirled for 10 min in the ice bath and allowed to stand overnight at room temperature. The solvent was removed, the residue was dissolved in 3 ml of water, and the solution was acidified with 0.5 ml of 12 *N* hydrochloric acid. The precipitate was extracted into 5 ml of dichloromethane, washed twice with water, dried ($MgSO_4$), concentrated, and streaked onto a TLC plate. The plate was developed with benzene–ethyl acetate (3:1). The band of R_f 0.4 was eluted with chloroform–methanol (9:1), sublimed at 0.02 Torr, and the sublimate crystallized from carbon tetrachloride–95% ethanol (5:1). The yield of **5** was 90 mg (53%): mp 111–113° (lit.[7] mp 113°); ir 3220, 1270, 1150, 742 cm^{-1}; mass spectrum *m/e* (rel intensity) 169 (100), 78 (96), 77 (76), 104 (72), 149 (62), 168 (55); ^1H NMR δ 4.47 and 4.56 (s, 2, CH_2 not equivalent), 5.3 (broad, 1, NH), 7.2–7.9 (m, 4, ArH).

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Registry No.—**1**, 938-10-3; **4**, 13222-19-0; **5**, 936-16-3; **6**, 34981-56-1; 2-methylbenzenesulfonyl chloride, 133-59-5; benzenesulfonyl chloride, 98-09-9; sodium azide, 12136-89-9.

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Photolysis of Diethyl Mercurybisdiazoacetate and Ethyl Diazoacetate in Chloroalkanes[1a]

Summary: A comparison of the reaction products from the title photolytic reactions allows the preclusion of significant carboethoxycarbene participation in the carboethoxymethyne reaction.

Sir: Photolytic decomposition of diethyl mercurybisdiazoacetate[2] (1) at wavelengths shorter than 290 nm has been shown to be a complicated but useful source of carboethoxymethyne (A).[3]

$$\underset{1}{Hg(N_2CCO_2C_2H_5)_2} \longrightarrow 2N_2 + Hg + 2\underset{A}{:\dot{C}CO_2C_2H_5}$$

We have studied the photolysis reaction of 1 in several chloroalkanes and compared the reaction products with those from the photolysis of ethyl diazoacetate (2), a precursor to carboethoxycarbene (B),[4] in the same chloroalkanes. We now communicate the results of these studies.

$$\underset{2}{N_2CHCO_2C_2H_5} \longrightarrow N_2 + \underset{B}{:CHCO_2C_2H_5}$$

Photolysis of 1 in chloroalkanes (2.5 g in 500 ml, 450-W medium-pressure mercury lamp with a Vycor filter, 30 min at room temperature with continuous nitrogen flushing) gave the products shown in Table I.[5] Mercuric chloride, not mercury, was isolated in nearly quantitative yield. Small amounts of mercury-containing products were observed by mass spectrometry. Decomposition of these products may partially account for the formation of mercuric chloride. Products resulting from carbon–hydrogen insertion were not observed. Photolysis of 2 (same conditions as 1) gave the products reported in Table II.[4]

Inspection of the tables shows that the major products from 1 are C–Cl insertion products leading to ethyl chloroacetate and ethyl chloroacrylate derivatives. Control experiments indicate that the unsaturated products are probably artifacts resulting from loss of chlorine from the original saturated insertion products occurring under our isolation techniques.[6]

The reaction products from 2 show little similarity to those from 1 with the only C–Cl insertion product resulting from 1,1,1-trichloroethane. No C–H insertion products were observed and most products appear to result from free-radical reactions.[7,8]

Carboethoxymethyne (A) in chloroalkanes could conceivably abstract either a hydrogen atom giving carboethoxycarbene (B) or abstract a chlorine atom giving carboethoxychlorocarbene ($ClC\dot{C}CO_2C_2H_5$, C) with the resulting products then arising from reaction of B or C with the chloroalkanes. However, the marked differences in reaction products from 1 as compared with 2 gives strong support for the absence of any B in the photolysis of 1. The results from Table I suggest that A may be produced from 1 in yields from 63 to 83% (combined yields of ethyl chloroacetate and insertion products). This is contingent on the absence of any intervention of C or mercury-containing carboethoxycarbenes.

Table I
Diethyl Mercurybisdiazoacetate–Chloroalkane Photolysis Products

Chloroalkane[a]	Products[b]	% yield[c]
CCl_4	$Cl_2C{=}(Cl)CO_2C_2H_5$	41
	$Cl_3CC(Cl)_2CO_2C_2H_5$	12
	Cl_3CCCl_3	52
	Unidentified	~2
CH_3CCl_3	$CH_3C(Cl){=}C(Cl)CO_2C_2H_5$[d]	35
	$CH_3C(Cl)_2CH(Cl)CO_2C_2H_5$	37
	$CH_2{=}CCl_2$[e]	18
	Unidentified (2)	~10
$(CH_3)_2CCl_2$	$(CH_3)_2C{=}C(Cl)CO_2C_2H_5$	18
	$(CH_3)_2C(Cl)CH(Cl)CO_2C_2H_5$	7
	$ClCH_2CO_2C_2H_5$	35
	$CH_3C(Cl){=}CH_2$[e]	24
	Unidentified	~16
$(CH_3)_3CCl$	$ClCH_2CO_2C_2H_5$	83
	$CH_2{=}C(CH_3)_2$[e]	22

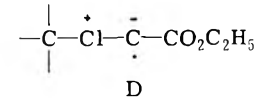
[a] Commercial reagent grade chloroalkanes were used. [b] Product identity was determined from spectral data, elemental analyses, and comparison with authentic samples when possible. [c] Product yields were determined using internal standards. [d] *E*:*Z* ratio 2.2:1: M. Verny and R. Vessiere, *Bull. Soc. Chim. Fr.*, 746 (1970). [e] Isolated as bromine addition product.

Table II
Ethyl Diazoacetate–Chloroalkane Photolysis Products

Chloroalkane[a]	Products[b]	% yield[c]
CCl_4	$Cl_2C{=}C(Cl)CO_2C_2H_5$	80
CH_3CCl_3	$CH_3C(Cl){=}CHCO_2C_2H_5$	40
	Cl_2CHCH_2Cl	45
$(CH_3)_2CCl_2$	$ClCH_2CO_2C_2H_5$	30
	$ClCH_2CHCl_2$	22
	Cl_3CCCl_3	26
	$[CH_3C(Cl)_2CH_2]_2$ or isomer	22
$(CH_3)_3CCl$	13 components	

[a] Commercial reagent grade chloroalkanes were used in all cases. [b] Product identity was determined from spectral data, elemental analyses, and comparison with known samples when possible. [c] Product yields were determined using internal standards.

Using an analogy from the suggested mechanism for carbon–halogen insertion reactions for carbenes,[4] one can speculate on a novel ylide-radical intermediate (D) in the reactions of A with chloroalkanes. Intermediate D could



D

undergo C–Cl insertion or β elimination to give the observed products.

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(5) Compound **1** in tetrachloromethane at room temperature in the absence of light showed after 40 min the precipitation of mercuric chloride and the appearance of a singlet at ca. δ 2.0 in the NMR spectrum. This reaction did not interfere with the photolysis reactions. No product containing this NMR signal was observed.

(6) Preparative GLC was accomplished on a Varian A-90 gas chromatograph using either a 5 ft by 0.25 in. 20% QF-1 column or a 10 ft by 0.12 in. 10% QF-column. Yields were based on relative integration areas assuming unity response ratios for the various peaks. The injection port temperature of 185–200° required for good separation was high enough to effect elimination in the saturated insertion products. Ethyl 2,3,3-trichlorobutanoate decomposed appreciably to ethyl 2,3-dichloro-2-butenoate under these conditions. We thank Dr. H. D. Roth for bring this to our attention.

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Department of Chemistry
Southern Illinois University
Edwardsville, Illinois 62025

Timothy B. Patrick*
George H. Kovitch

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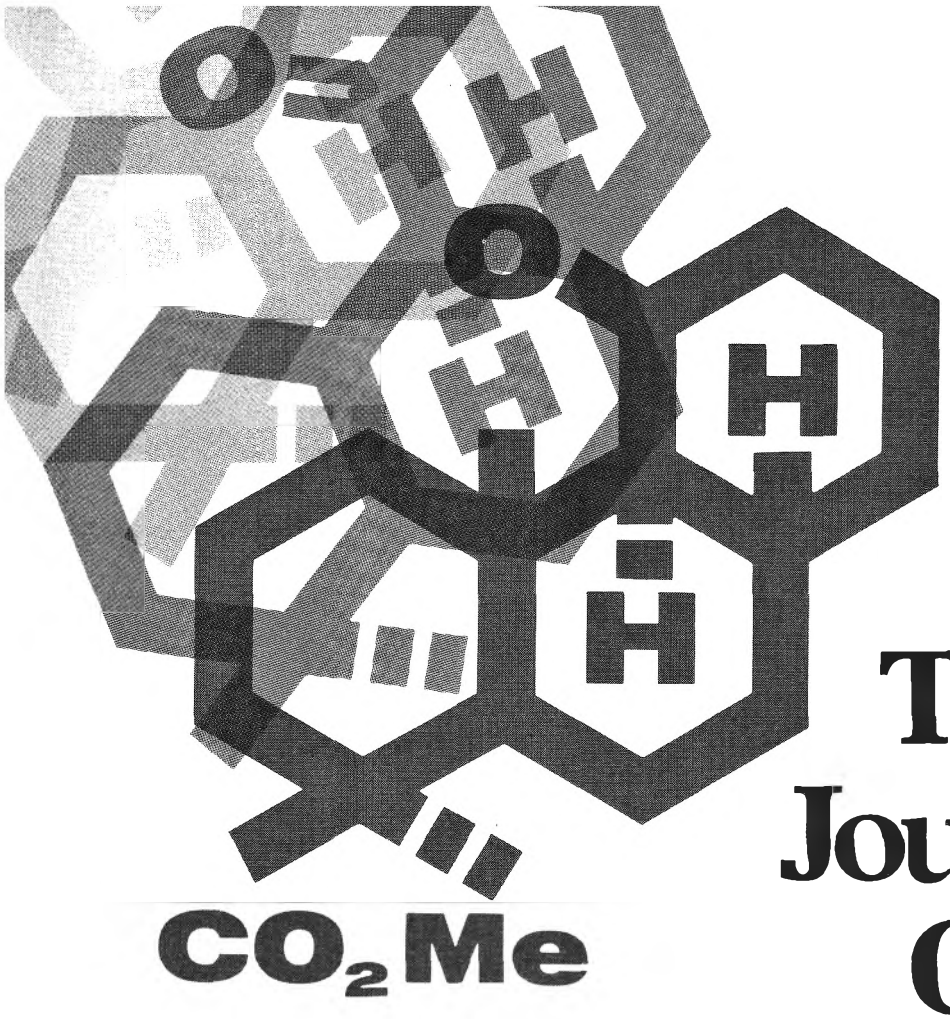

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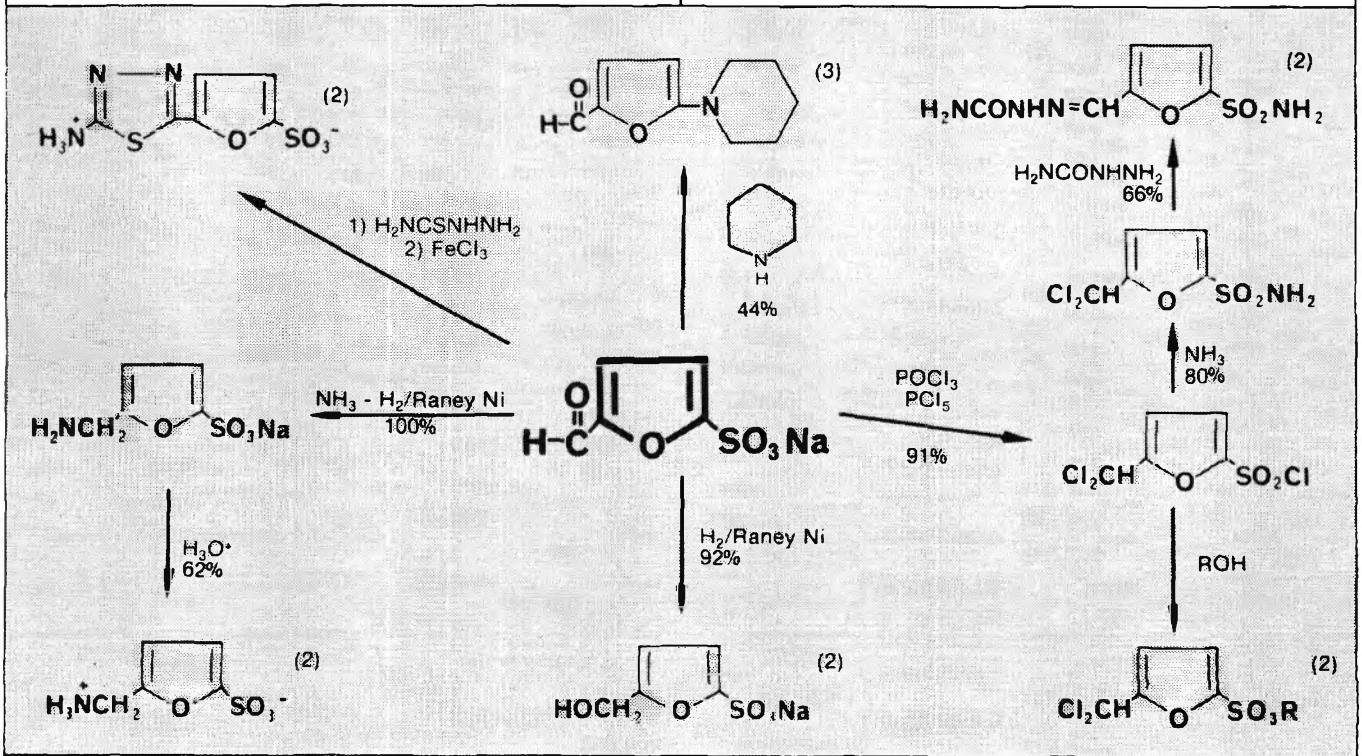

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