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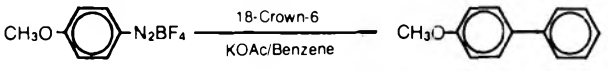

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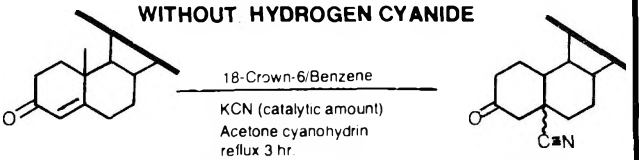

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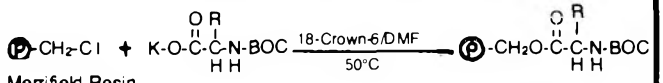

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R. W. Roeske, P. D. Gesellchen, *Tetrahedron Lett.*, **1976** (38), 3369-3372

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J. P. Tam, W. F. Cunningham-Rundles, B. W. Erickson, and R. B. Merrifield, *Tetrahedron Lett.*, *1977*, 4001.

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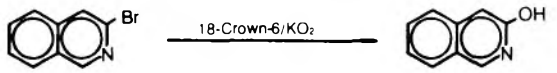

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T. Yamaguchi and H. C. Van der Plas, Rec. Trav. Chim. Pays-Bas, **96** (3), 89(1977).

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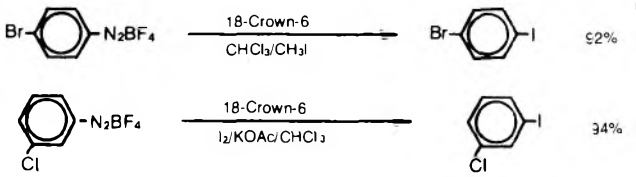

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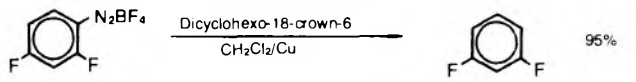

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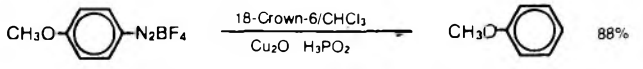

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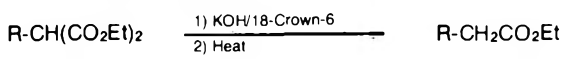

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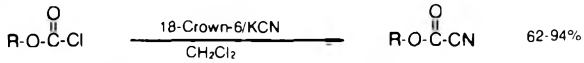

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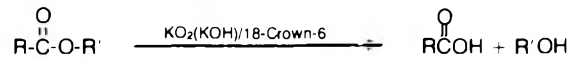

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J. San Filippo, L. J. Ramano, C.I. Chern, and J. S. Valentine, *J. Org. Chem.*, 41 (3) 586 (1976).

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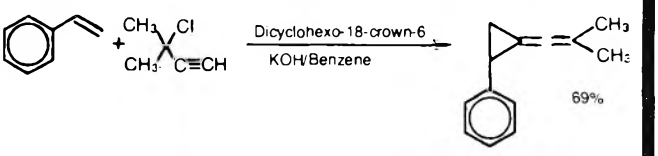

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T. Sasaki, S. Eguchi, M. Ohno and F. Nakata, *J. Org. Chem.*, 41, 2409 (1976)

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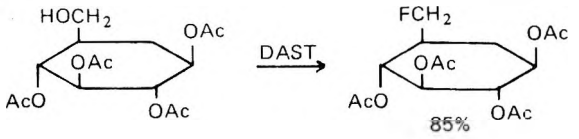
A NEW FLUORINATING REAGENT

DIETHYLAMINOSULFUR TRIFLUORIDE (DAST)

Recently, Middleton[1] and Markovskij and co-workers[2] have shown diethylaminosulfur trifluoride (DAST)[3] to be an excellent reagent for the replacement of the oxygen function in alcohols and carbonyl containing compounds with fluorine.

The use of DAST has several advantages over other fluorinating reagents such as SF_4. The reagent itself is a liquid which can be handled in conventional laboratory glassware. Reactions can be carried out under very mild conditions allowing multi-functional alcohols to be selectively fluorinated. Furthermore, side reactions such as carbonium ion rearrangements and dehydrations are less likely to occur when using DAST.

Primary, secondary and tertiary alcohols can be fluorinated with DAST usually in high yields. Reaction with most substrates is rapid, even at -50°C. DAST is also finding applications in sugar chemistry. It has been utilized in the synthesis of 3-deoxy-3-fluoro-D-glucose[5] and was found to be a mild enough reagent to allow the use of the O-acetyl protecting group in the synthesis of 6-fluoro-6-deoxy-D-glucopyranose[6].



Aldehydes and ketones undergo reaction with DAST, usually at ambient temperature, to give good yields of the *gem*-difluoro derivatives. A particular advantage here is that the reaction can be run under non-acidic conditions rendering it especially useful for acid-sensitive substrates (e.g. pivaldehyde).

$$(CH_3)_3CCHO \xrightarrow[CCl_3F]{DAST} (CH_3)_3CCHF_2 \quad 78\%$$

Carboxylic acids give the acid fluoride[2]. A more recent publication[7] has described the application of DAST to prepare *gem*-difluorosaccharides from sugar aldehydes and ketones in the pyranosyl form.

Tetraalkylthiuran disulfide, triphenylphosphine, triphenylphosphine disulfide and trimethylchlorosilane are also fluorinated with DAST[2].

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1. W. J. Middleton, *J. Org. Chem.*, **40**, 574 (1975).
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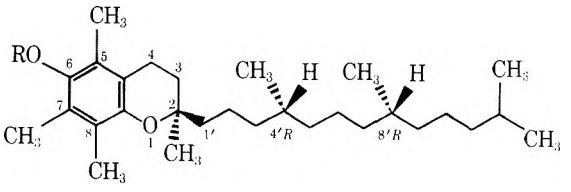
A new synthesis of (2*R*,4′*R*,8′*R*)-α-tocopheryl acetate (**1b**) was achieved by the application of stereoselective [3,3] sigmatropic (Claisen) rearrangement. Treatment of the (*S*)-chromanylacetaldehyde **6** with propynylmagnesium bromide gave two diastereomeric acetylenic carbinols, (*R*)-**15a** and (*S*)-**16a** (~2:1). Orthoester Claisen rearrangement of allylic alcohols (*R*,*E*)-**17** and (*S*,*Z*)-**18**, respectively, yielded the same unsaturated ester, (*R*,*E*)-**19a**, with essentially complete chiral transmission. The ester **19a** was converted into tosylate **24b** by standard transformations. Coupling of **24b** with the optically active nine-carbon synthon **25c** furnished tocopheryl benzyl ether (**1c**). Hydrogenation of **1c** followed by acetylation then afforded **1b** (*vitamin E acetate*). The complete transfer of chirality from (*R*,*E*)-**17** and (*S*,*Z*)-**18** to (*R*,*E*)-**19a** demonstrates the wide potential applicability of this [3,3] sigmatropic process in the synthesis of optically active substances.

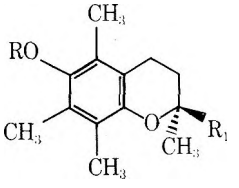
Previous approaches to the synthesis of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**) and the acetate **1b** have involved Wittig reactions between the homologous chromanyl aldehydes **2** and **3** and the optically active side chain synthons **7a**[1] and **7b**,[2] respectively, or alternatively, coupling of the chromanyl tosylate **4** with the Grignard reagent **7c**[3b] (Scheme I). In our recent papers,[3a,4] the preparation of highly enantiomerically pure isoprenoid synthons such as **8a**[4] and **8b**[3a] (precursors to **7**) via [3,3] sigmatropic (Claisen) rearrangements was described. The success of this approach (Scheme II) depends on the complete transfer of chirality from allylic alcohols such as (*R*,*Z*)-**11a** and (*S*,*E*)-**12b** [derived from acetylenic carbinols (*R*)-**10a** and (*S*)-**10b**, respectively] to the optically active product (*S*,*E*)-**13a**.[4] An important feature of this synthesis involves the economical utilization of both antipodal or diastereomeric carbinols (*R*)-**10a** and (*S*)-**10b** for the production of the same target molecule. Furthermore, the absolute configuration of the final product can be manipulated simply by choosing the right combination of absolute configuration and geometry of the allylic alcohols. Thus, allylic alcohols (*R*,*Z*)-**11a** and (*S*,*E*)-**12b** give the optically active (*S*,*E*)-**13a** (path i, Scheme II), whereas the isomers possessing the alternate geometry, namely, (*R*,*E*)-**12a** and (*S*,*Z*)-**11b**, generate the antipodal or diastereomeric (*R*,*E*)-**13b** (path ii). In this manner, it is possible to construct optically active isoprenoid synthons utilizing either a "right-to-left" (path i)[5] or "left-to-right" (path ii)[5] strategy. In the present report, we would like to disclose an alternative synthesis of vitamin E acetate (**1b**), which further demonstrates the versatility of this concept.

Our synthetic plan (Scheme III) was based upon the consideration that the vitamin E molecule could be constructed *starting from the chroman moiety* using a "left-to-right" approach, provided diastereomerically pure carbinols **17** [cf. (*R*,*E*)-**12a**] and **18** [cf. (*S*,*Z*)-**11b**] were readily accessible (Scheme III). We envisioned that the synthon **19a** [cf. (*R*,*E*)-**13b**], resulting from orthoester Claisen rearrangement of these carbinols and possessing the required chirality at the newly secondary methyl center, would be easily elaborated into the target molecule **1**.

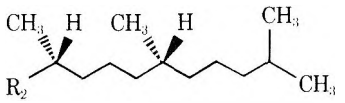
Scheme I



1a, R = H (vitamin E)
b, R = $COCH_3$
c, R = $CH_2C_6H_5$



2a, R = $COCH_3$; R_1 = CHO
b, R = CH_2Ph; R_1 = CHO
3, R = $COCH_3$; R_1 = CH_2CHO
4, R = CH_2Ph; R_1 = $CH_2CH_2OSO_2C_6H_4$-*p*CH_3
5, R = H; R_1 = CH_2COOH
6, R = CH_2Ph; R_1 = CH_2CHO



7a, R_2 = $CH_2CH_2P^+Ph_3Br^-$
b, R_2 = $CH_2P^+Ph_3Br^-$
c, R_2 = CH_2MgBr
8a, R_2 = CH_2CH_2OH
b, R_2 = CH_2OH

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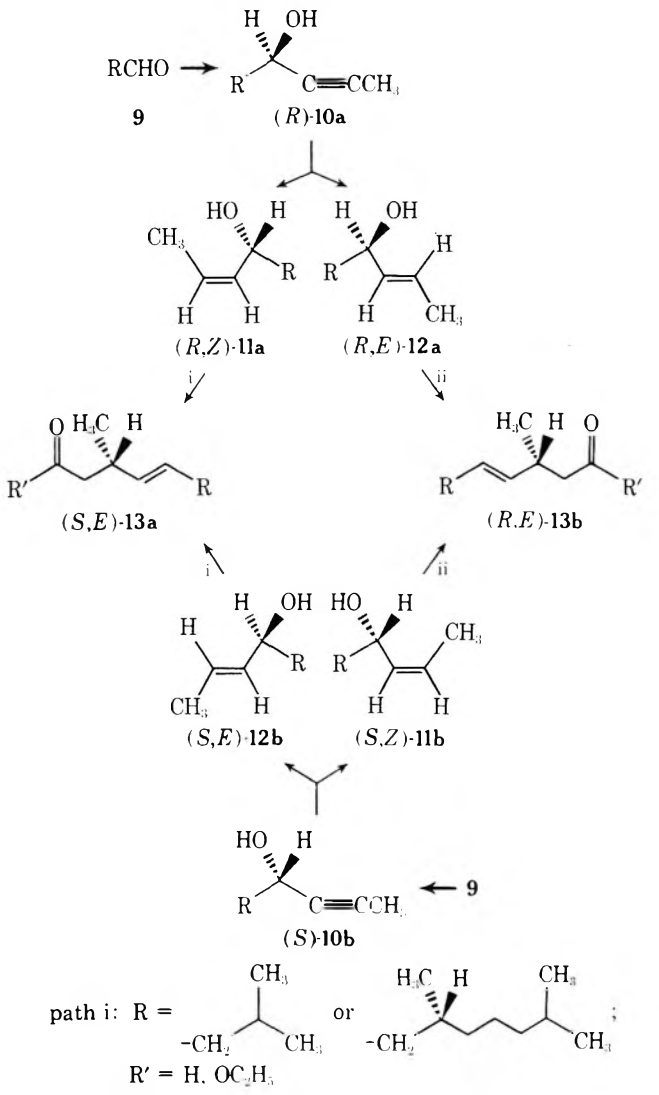
Scheme II[a]



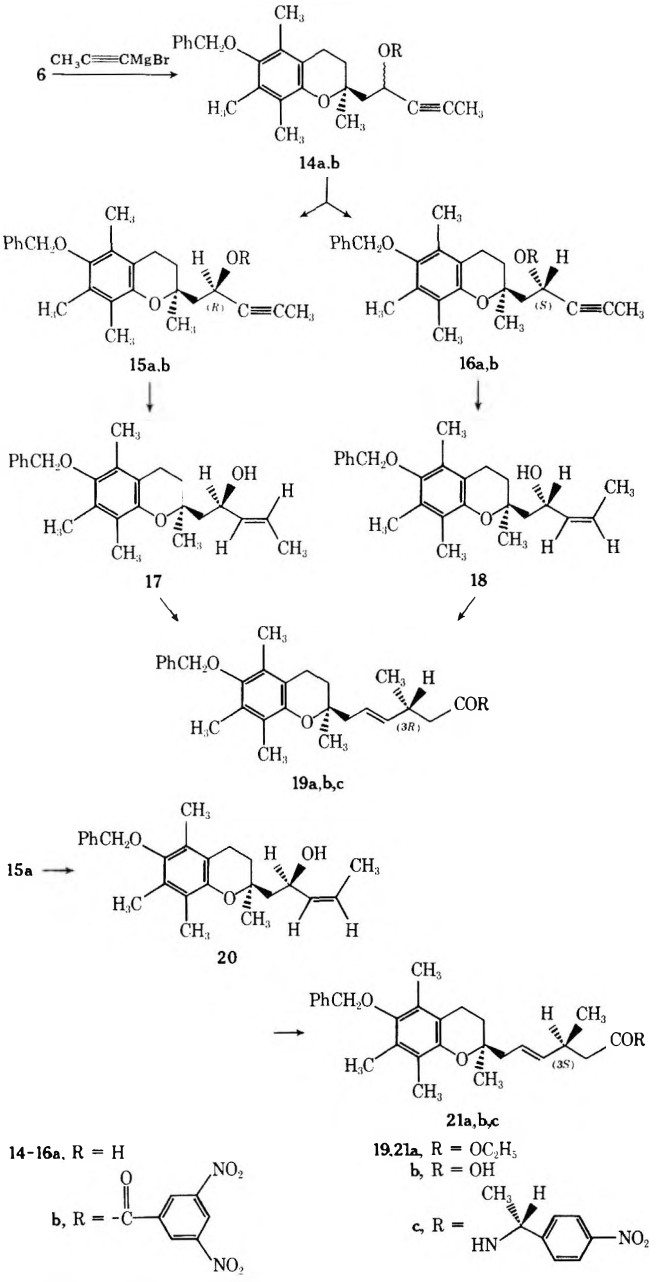
[a] a and b are enantiomeric or diastereomeric pairs.

Results and Discussion

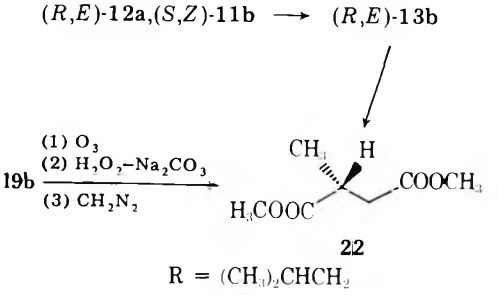
We set as our first goal the preparation of the required diastereomerically pure acetylenic carbinols. The starting material for our synthesis was the readily available optically active 2-chromanylacetaldehyde **6**, easily obtained from (*S*)-chroman-2-acetic acid (**5**)[6] as described previously.[2] Treatment of **6** with propynylmagnesium bromide[4] gave a 2:1 mixture of acetylenic carbinols **14a** (Scheme III). Crystallization of the corresponding mixture of 3,5-dinitrobenzoates **14b** followed by alkaline hydrolysis and further crystallization of the crude hydrolysate afforded the major acetylenic carbinol **15a**. The minor carbinol **16a** was obtained from the mother liquor by recrystallization. The absolute configurations of **15a** and **16a**[7] were assigned to be *R* and *S*, respectively, by chemical transformations described below.

Reduction of **15a** with sodium bis(2-methoxyethoxy)aluminum hydride[4] gave the allylic alcohol (*R,E*)-**17**, whereas partial hydrogenation of **16a** with Lindlar catalyst[8] afforded the (*S,Z*)-**18**. Claisen rearrangement of **17** and **18** with triethyl orthoacetate–propionic acid[4,9] in both cases yielded the same unsaturated ester (3*R*,4*E*)-**19a** [cf. (*R,E*)-**13b** in Scheme II]. On the other hand, partial hydrogenation of **15a** furnished the *R,Z* allylic alcohol **20**, which underwent Claisen rearrangement to give the diastereomeric unsaturated ester (3*S*,4*E*)-**21a** [cf. (*S,E*)-**13a** in Scheme II]. Based on the results of various Claisen rearrangements reported earlier,[4] the absolute configuration of the newly introduced asymmetric center in unsaturated ester **19a** could be assigned to be *R*. This was further confirmed by the following sequence of transformations. Hydrolysis of ester **19a** gave the corresponding unsaturated acid **19b**, ozonolysis of which yielded a mixture of acidic compounds which was then treated with diazomethane. The crude product was purified by column chromatography on silica gel to give (*R*)-(+)-dimethyl 2-methylsuccinate[10] (**22**) (Scheme IV). A reference sample of **22** was further prepared from the unsaturated acid **13b** (R′ = OH), which had been shown to have the *R* configuration[4,11] and was in turn derived via allylic alcohols (*R,E*)-**12a** and (*S,Z*)-**11b**, from the optically

Scheme III



Scheme IV

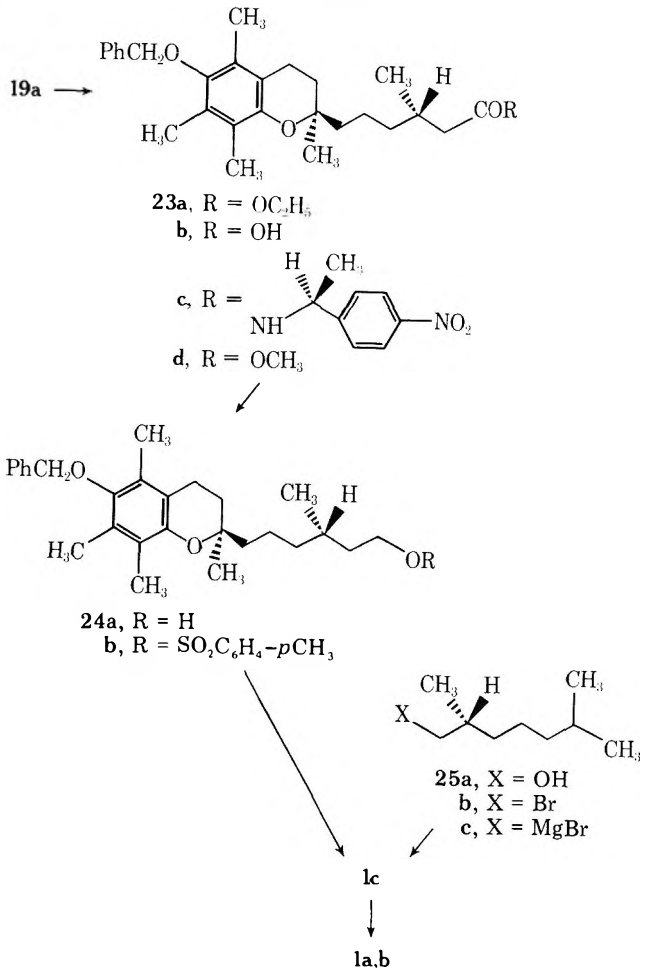


active acetylenic carbinols **10a** and **10b**, respectively.[4] ^{1}H NMR studies of **22** [derived from unsaturated acid **13b** (R′ = OH)] using an optically active shift reagent [tris[((heptafluoroprop-3-yl)hydroxymethylene)-*d*-camphorato]europium(III), Eu(hfbc)$_3$][12] revealed the presence of a singlet signal for the *sec*-carbomethoxy group ($CH_3CHCOOCH_3$) at δ 4.78 (racemic **22** displayed two singlets at δ 4.78 and 4.82, respectively, with equal intensity), while the primary carbomethoxy function (CH_2COOCH_3) of **22** exhibited a singlet at δ 4.69. Comparison of **22** derived from ester **19b** with the reference sample [derived from unsaturated acid (*R*,*E*)-**13b**] thus firmly established the *R* configuration of the *sec*-methyl group in acid **19b**. Based on previous results and the established mechanism[4] of the Claisen rearrangement, these results provide confirmation of the absolute configurational assignment of the starting allylic alcohols (2*R*,3*E*)-**17** and (2*S*,3*Z*)-**18**.

The enantiomeric purity of the new chiral center in **19a** was first estimated to be nearly 100% by NMR studies on **22** as mentioned earlier. The exact enantiomeric compositions at C(3), however, were obtained by LC analysis[4,13] of the corresponding (*R*)-α-methyl-*p*-nitrobenzylamide derivatives **19c** and **21c**: showing 98.9% *R*, 1.1% *S* [**19c** derived from (*R*,*E*)-**17**]; 98.8% *R*, 1.2% *S* [**19c** derived from (*S*,*Z*)-**18**]; and 4% *R*, 96% *S* [**21c** derived from (*R*,*Z*)-**20**], respectively. The transfer of chirality therefore was essentially 100% in going from allylic alcohols (*R*,*E*)-**17** and (*S*,*Z*)-**18** to unsaturated ester (*R*,*E*)-**19a**.

Having accomplished the synthesis of the desired key intermediate **19a** (cf. compound **13b** as shown in Scheme II) with 99% *R* purity at C(3), we then proceeded to construct the target molecule **1**. Hydrogenation of unsaturated ester **19a** using 5% palladium on carbon gave the saturated ester **23a**

Scheme V



(Scheme V). ^{1}H NMR studies of the corresponding methyl ester **23d**, using a chiral shift reagent, indicated the enantiomeric composition at C(3) to be approximately 90% *S* and 10% *R*. Thus, racemization had occurred to a certain extent during hydrogenation using palladium as catalyst.[4a] On the other hand, hydrogenation of **19a** with Raney nickel at 25 °C, 30 psi, resulted in partial cleavage of the benzyl ether group; therefore, the crude product of hydrogenation was treated with benzyl chloride–potassium carbonate to give the desired saturated ester **23a** in good yield. This material was converted to the corresponding (*R*)-(+)-α-methyl-*p*-nitrobenzylamide **23c**, having an enantiomeric composition at C(3) of 96.1% *S* and 3.9% *R* by LC analysis. Clearly, Raney nickel catalyst is preferred, although the reaction conditions for the hydrogenation step have not yet been optimized. Reduction of saturated ester **23a** (derived from **19a** by hydrogenation using palladium catalyst)[14] with sodium bis(2-methoxyethoxy)-aluminum hydride afforded the optically active chromanyl alcohol **24a**, which was then converted to the corresponding tosylate **24b** in the usual manner.[20] With this optically active tosylate **24b** in hand, the stage was set to achieve the final goal, which could be accomplished by coupling of **24b** with an optically active nine-carbon synthon derived from **25a**. To this end, the nine-carbon Grignard reagent **25c**,[3a] prepared from alcohol **25a**[3a,15] via the bromide **25b**,[3a] was allowed to react with the tosylate **24b** in the presence of Li_2CuCl_4[3a,16] to give (2*R*,4′*R*,8′*R*)-α-tocopheryl benzyl ether (**1c**)[3a] (69% yield), which was then converted to the corresponding acetate **1b**,[17] shown to be identical (IR, NMR, and MS spectroscopy, GC, and TLC) with an authentic sample.[2]

In summary, a new synthesis of vitamin E (**1b**) was achieved by the application of stereoselective [3,3] sigmatropic rearrangement. It was further demonstrated that both *R* and *S* allylic alcohols (*R*,*E*)-**17** and (*S*,*Z*)-**18** [cf. (*R*,*E*)-**12a** and (*S*,*Z*)-**11b**, Scheme II] could be utilized productively to give the same optically active synthon (**19a**), and the transfer of chirality in this [3,3] sigmatropic process was essentially 100%. These findings, together with our earlier reports[3,4] and results of other groups,[18] demonstrate the wide potential applicability of these Claisen rearrangements in the synthesis of optically active substances.[19]

Experimental Section

General. Melting points were determined on a Reichert micro-melting point apparatus and are uncorrected. Spectral and gas chromatographic measurements were performed by members of the Physical Chemistry Department of Hoffmann-La Roche Inc. using the following instruments: IR, Beckmann IR 9 or Perkin-Elmer 621 spectrophotometers; UV, Cary Model 14 spectrometer; NMR, Varian A-60 and HA-100 spectrometers with tetramethylsilane as an internal standard; GC, Becker 409 or Hewlett-Packard 5700 instruments with a flame ionization detector; $[\alpha]_D$, Perkin-Elmer 141 polarimeter. LC separations were carried out as described previously.[4,13] Column chromatography was performed using Merck (Darmstadt) silica gel, 0.063–0.2 mm. Unless otherwise noted, the "usual workup" procedure involves dilution of the reaction mixture with water or brine followed by three extractions with the specified solvent. The organic extracts were then combined, washed when appropriate with H_2O, 1 N HCl, saturated $NaHCO_3$, and/or saturated brine, dried over $MgSO_4$, filtered, and concentrated under water aspirator pressure at 30–40 °C on a rotary evaporator.

(2*S*,2*R)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-benzopyran-2-yl)-3-pentyn-2-ol (15a) and (2*S*,2*S**)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-benzopyran-2-yl)-3-pentyn-2-ol (16a).** A solution of the aldehyde **6**[2] (64 g, 0.19 mol) in 1.0 L of dry ether was added dropwise at ~4 °C with mechanical stirring under argon to a suspension of propynylmagnesium bromide (~2.5 mol; preparation described previously[4]) in ~1.0 L of ether. When the addition was complete, the reaction mixture was further stirred at ~4 °C for 0.5 h and then at 25 °C for 0.5 h. The reaction mixture was poured in small portions into 500 mL of saturated aqueous NH_4Cl solution. It was worked up with ether to give 74 g of the crude product **14a** (mixture of isomers ca. 2:1). This material (70

g, 0.185 mol) was dissolved in 300 mL of dry pyridine, and the resulting solution was added at 4 °C to a solution of 73.6 g (0.37 mol) of *p*-toluenesulfonyl chloride and 39 g (0.19 mol) of 3,5-dinitrobenzoic acid in 300 mL of dry pyridine.[20] The mixture was stirred at ~4 °C for 4 h. It was worked up with $CHCl_3$ as usual, and the crude dinitrobenzoate **14b** was crystallized from CH_3OH–$CHCl_3$ (~3:1) to give 63 g (59.4%) of **15b** as yellow crystals (~84% **15b** and 16% **16b** by NMR). A small sample was recrystallized from CH_3OH–$CHCl_3$ for analysis: mp 150–156 °C; $[\alpha]^{25}_D$ +24.9° (*c* 4.39, $CHCl_3$); MS *m/e* 572 (M^+); ^1H NMR ($CDCl_3$) δ 1.34 (s, C(2) CH_3, ~95% of **15b**), 1.44 (s, C(2) CH_3, ~5% of **16b**), 1.80 (d, C≡CCH_3), 1.9–2.0 (m, CH_2), 2.04, 2.14, and 2.16 (s, 3ArCH_3), 2.34 (d, CH_2CH), 2.63 (t, ArCH_2CH_2), 4.58 (s, PhCH_2O, minor isomer), 4.63 (s, PhCH_2O, major isomer), 5.95 (m, CHC≡C), 8.95 (m, 3,5-NO_2Ph, minor **16b**), 7.4 (m, **Ph**CH_2O), 9.12 (s, 3,5-NO_2Ph). Anal. Calcd for $C_{32}H_{32}N_2O_8$: C, 67.12; H, 5.63; N, 4.87. Found: C, 66.81; H, 5.67; N, 4.80.

The above dinitrobenzoate (60 g) was dissolved in 150 mL of methanol and 100 mL of 6 N NaOH. It was refluxed for 2.0 h and worked up with ether as usual to give 41.0 g of yellow oily material after chromatography on 150 g of silica gel (ether–petroleum ether 2:3 as eluent). This mixture of acetylenic carbinols **15a** and **16a** was then crystallized from ether–petroleum ether (30–60 °C) to give 27.5 g (38.5% from **6**) of the major carbinol **15a**: mp 89–91 °C; $[\alpha]^{25}_D$ −16.2° (*c* 5.05, $CHCl_3$); MS *m/e* 378 (M^+); IR (KBr) 3450 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3, C(2) CH_3), 1.81 (d, C≡CCH_3), 2.07, 2.19, and 2.14 (3s, 9, 3ArCH_3), 2.63 (t, CH_2), 3.08 (d, CHOH), 4.66 (s, ArCH_2O–), 4.75 (m, **CH**OH), 7.4 (m, **Ar**CH_2–). Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.20; H, 7.89.

The mother liquor from the first crystallization, yielding a mixture of 63 g of **15b** and **16b**, was evaporated to dryness at reduced pressure to give an oily residue. This was quickly filtered through 400 g of Florisil. Elution with $CHCl_3$ afforded 36 g of oily material which was dissolved in 100 mL of CH_3OH containing 50 mL of 6 N NaOH. It was refluxed for 1.5 h and worked up with ether as usual. The crude product was filtered through 100 g of silica gel. Elution with ether–petroleum ether (2:3) gave 20 g of oily material consisting of approximately 26% of **15a** and 74% of **16a** (by NMR). Crystallization of this material twice from ether-hexane gave 5.01 g (7% from **6**) of acetylenic alcohol **16a** as white crystals: mp 74–76 °C; $[\alpha]^{25}_D$ −42° (*c* 5.01, $CHCl_3$); MS *m/e* 378 (M^+); IR (KBr) 3450 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3, C(2) CH_3), 1.81 (d, C≡CCH_3), 2.07, 2.21, and 2.14 (3s, 9, 3ArCH_3), 2.61 (t, CH_2), 3.30 (d, CHOH), 4.65 (s, $C_6H_5CH_2O$), 4.82 (m, **CH**OH), 7.4 (m, **Ar**CH_2–). Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.41; H, 8.13.

(2*S*,2*R,3*E*)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-penten-2-ol (17).** The acetylenic alcohol **15a** (5.0 g, 13.2 mmol) was dissolved in 50 mL of dry ether and treated dropwise with a solution of 4.1 mL (29 mg-atom of hydrogen) of sodium bis(2-methoxyethoxy)aluminum hydride (Aldrich Red-Al, 70% in benzene) in 10 mL of ether. The resulting solution was refluxed for 17 h under argon and then cooled in an ice bath. A solution of 10% (by volume) aqueous H_2SO_4 (100 mL) was carefully added. The mixture was filtered and washed with ether and water. The aqueous phase was again extracted with ether. The combined ether phases were washed with saturated aqueous $NaHCO_3$ solution and water and dried over $MgSO_4$. Evaporation of ether to dryness at reduced pressure yielded 5.21 g of crude product which was crystallized from petroleum ether to give 4.23 g of **17** as white needles: mp 68–70 °C; $[\alpha]^{25}_D$ −24.0° (*c* 5.00, $CHCl_3$); MS *m/e* 380 (M^+); Raman (5145 Å, neat) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 3, C(2) CH_3), 1.66 (d, C=CCH_3), 1.79–2.02 (m, 2CH_2), 2.06, 2.13, and 2.18 (3s, 9, 3ArCH_3), 2.63 (m, CH_2), 3.06 (s, OH), 4.42 (m, **CH**OH), 4.65 (s, ArCH_2O–), 5.58 (m, (*E*)-CH=CH, *J* = 15.5 Hz) 7.4 (m, **Ar**CH_2–). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 79.12; H, 8.63.

(2*S*,2*S,3*Z*)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-penten-2-ol (18).** A mixture of 2.5 g (6.60 mmol) of acetylenic alcohol **16a**, 0.25 g of Lindlar catalyst, and 0.1 mL of quinoline in 15 mL of ethyl acetate–hexane (2:1) was hydrogenated at 23 °C for 4.0 h. The catalyst was removed by filtration and washed with ethyl acetate. The solvent was evaporated to dryness in vacuo, and the oily residue was dissolved in diethyl ether (300 mL), washed with 1 N HCl and water, and dried over anhydrous $MgSO_4$. Evaporation of ether to dryness in vacuo gave 2.51 g of yellow oil which upon crystallization from pentane afforded 2.05 g of 18 as white crystals: mp 84–86 °C; $[\alpha]^{25}_D$ −30.6° (*c* 5.04, $CHCl_3$); Raman (5145 Å, neat) 1675 [(*Z*)-C=C] cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3, C(2) CH_3), 1.73 (d, C=CCH_3), 2.11, 2.18, and 2.23 (3s, 9, 3ArCH_3), 4.69 (s, ArCH_2O), 5.50 (m, (*Z*)-CH=CH, *J* = 7.5 Hz), 7.43 (m, C_6H_5). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 78.69; H, 8.39.

(2*S*,3*R,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid Ethyl Ester (19a). (A) From Allylic Alcohol 17.** A mixture of 4.42 g (0.0116 mol) of (*R*,*E*)-**17**, 13.1 g (0.081 mol) of triethyl orthoacetate, and 85.5 mg (1.16 mmol) of propionic acid in a flask equipped with a short distilling column was degassed, placed under argon, and heated in an oil bath at 140 °C. The ethanol that formed was removed by distillation, and the solution was refluxed for 4.0 h. The excess of reagent was removed under vacuum, and the resulting oily product was quickly chromatographed on 125 g of silica gel. Elution with 1:4 ether–petroleum ether (30–60 °C) afforded 4.86 g (92% yield) of unsaturated ester **19a** as a colorless oil: $[\alpha]^{25}_D$ +0.9° (*c* 5.05, $CHCl_3$); MS *m/e* 450 (M^+); Raman (5145 Å, neat) 1680, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, *J* = 6 Hz, $CHCH_3$), 1.17 (s, 3, C(2) CH_3), 1.19 (t, $COOCH_2CH_3$), 1.78 (broad s, CH_2), 2.07, 2.13, and 2.17 (3s, 9, 3ArCH_3), 2.82–2.52 (m, 3), 4.05 (q, $COOCH_2CH_3$), 4.64 (s, ArCH_2O), 5.52 (m, (*E*)-CH=CH, *J* = 15.5 Hz), 7.4 (m, C_6H_5). Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.16; H, 8.51. Found: C, 77.30; H, 8.50.

(B) From 18. A mixture of 500 mg of *S*,*Z* allylic alcohol **18**, 1.48 g of triethyl orthoacetate, and 9.7 mg of propionic acid was allowed to react as described above. After purification of the crude product by column chromatography on silica gel, 479 mg (81% yield) of the unsaturated ester **19a** was obtained as a colorless oil: $[\alpha]^{25}_D$ +0.5° (*c* 4.2, $CHCl_3$); IR and NMR spectra were identical with those described above in A.

(2*S*,3*R,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid (19b).** A solution of 2.0 g (4.4 mmol) of unsaturated ethyl ester **19a** ($[\alpha]^{25}_D$ +0.9°) in 7 mL of methanol and 2 mL of 6 N aqueous NaOH was refluxed for 2.0 h. The solution was diluted with water and extracted with ether. The aqueous alkaline phase was cooled in an ice bath and then acidified with concentrated hydrochloric acid. It was worked up with ether in the usual manner to give 1.57 g of unsaturated acid **19b** as a colorless oil (84% yield): $[\alpha]^{25}_D$ −2.7° (*c* 3.18, $CHCl_3$); MS *m/e* 422 (M^+); IR (neat) 3000–3400, 1710 (COOH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, 3, $CHCH_3$), 1.21 (s, 3, C(2) CH_3), 1.75 (t, CH_2), 2.08, 2.15, and 2.21 (3s, 9, 3ArCH_3), 2.56 (t, CH_2), 4.64 (s, ArCH_2O), 5.48 (m, (*E*)-CH=CH, *J* = 15.5 Hz), 7.4 (m, C_6H_5), 9.95 (broad, COOH). Anal. Calcd for $C_{27}H_{34}C_4$: C, 76.75; H, 8.12. Found: C, 76.85; H, 8.09.

(2*S*,3*R,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid (*R*)-α-Methyl-*p*-nitrobenzylamide (19c).** A solution of 38 mg of unsaturated acid **19b** (derived from *R*,*E* allylic alcohol **17** via ester **19a**) and 203 mg of oxalyl chloride in 5 mL of dry benzene was refluxed for 1.0 h and worked up with ether in the usual manner to give 38 mg of the corresponding acid chloride. This material was treated with 49.8 mg of (*R*)-α-methyl-*p*-nitrobenzylamine as reported before[13] to give the corresponding amine **19c** which was analyzed by LC using conditions as described previously.[13] The enantiomeric composition at C(3) was shown to be 1.1% *S* (*k'* 13.5) and 98.9% *R* (50 × 0.45 cm column packed with Partisil 10; eluent 20% THF in heptane, at 3 mL/min).

Similarly, the unsaturated acid **19b**, which was derived from *S*,*Z* allylic alcohol **18**, was transformed into the corresponding amide **19c** as a viscous oil: LC 1.2% 3*S* (*k'* 13.5) and 98.8% 3*R*; MS *m/e* 570 (M^+); IR (neat) 3300 (NH), 1647 (amide CO) cm^{-1}.

(2*S*,2*R,3*Z*)-1-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-penten-2-ol (20).** A mixture of 5.0 g (13.2 mmol) of acetylenic alcohol **15a**, 0.5 g of Lindlar catalyst, and 0.3 mL of quinoline in 150 mL of hexane–ethyl acetate (1:2) was stirred in an atmosphere of hydrogen at 25 °C until 1 equiv of hydrogen was consumed. Workup as described above for 18 gave a yellow oil which upon crystallization from petroleum ether in a dry ice–acetone bath afforded 3.41 g of **20** as a white semisolid substance: mp 31–33 °C; $[\alpha]^{25}_D$ −27.4° (*c* 3.67, $CHCl_3$); MS *m/e* 380 (M^+); ^1H NMR (100 MHz, $CDCl_3$) δ 1.30 (s, 3, C(2) CH_3), 1.67 (d, 3, C=CCH_3), 2.11, 2.18, and 2.22 (3s, 9, 3ArCH_3), 2.96 (s, OH), 4.69 (s, 2, ArCH_2O), 4.82 (m, 1, **CH**OH), 5.51 (m, 2, (*Z*)-CH=CH), 7.43 (m, 5, C_6H_5). Anal. Calcd for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48. Found: C, 79.00; H, 8.44.

(2*S*,3*S,4*E*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid Ethyl Ester (21a).** A mixture of 4.0 g (10.5 mmol) of the *R*,*Z* allylic alcohol **20**, 77.3 mg (1.05 mmol) of propionic acid, and 11.8 g (73.5 mmol) of triethyl orthoacetate was refluxed for 3.0 h, while the ethanol that formed was removed by distillation. The mixture was worked up as described earlier. The crude product was chromatographed on 125 g of silica gel. Elution with ether–petroleum ether (1:4) gave 4.72 g (98% yield) of unsaturated ester **21a** as a colorless oil: $[\alpha]^{25}_D$ +19.6° (*c* 5.02, $CHCl_3$); MS *m/e* 450 (M^+); IR (neat) 1735 ($COOC_2H_5$) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.05 (d, $CHCH_3$), 1.20 (s, 3, C(2) CH_3), 1.20 (t, 3, $COOCH_2CH_3$), 2.08, 2.14, and 2.19 (3s, 9, 3ArCH_3), 2.57 (m, 2, $CH_2COOC_2H_5$), 4.08 (q, 2, $COOCH_2CH_3$), 4.67 (s, 2, ArCH_2O), 5.45

(m, 2, CH=CH), 7.42 (m, C_6H_5). Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.16; H, 8.51. Found: C, 77.43; H, 8.50.

(2S,3S*,4E)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methyl-4-hexenoic Acid (21b). A mixture of unsaturated ester **21a** (1.5 g, 3.34 mmol), 2 mL of 6 N NaOH, and 10 mL of methanol was refluxed for 2.0 h. Workup as usual gave 1.33 g (94% yield) of the unsaturated acid **21b** as a colorless oil: $[\alpha]^{25}_D$ + 22.4° (*c* 2.67, $CHCl_3$); MS *m/e* 422 (M^+); IR (neat) 3000–3400, 1710 (COOH) cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.02 (d, 3, $CHCH_3$), 1.15 (s, 3, C(2) CH_3), 2.06, 2.12, and 2.17 (3s, 9, $3ArCH_3$), 4.65 (s, 2, $ArCH_2$), 5.45 (m, 2, CH=CH), 7.38 (m, C_6H_5), 10.90 (COOH). Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.75; H, 8.12. Found: C, 76.64; H, 8.07.

The acid **21b** was converted, as described earlier, to the corresponding (*R*)-α-methyl-*p*-nitrobenzylamide **21c,** whose enantiomeric composition at C(3) was shown by LC (conditions the same as described for **19c**) to be 96% 3*S* and 4% 3*R*.

(R)-(−)-(E)-3,7-Dimethyl-4-octenoic Acid [13b; R' = OH]. A mixture of 4.0 g of (*S,Z*)-6-methyl-2-hepten-4-ol (**11b**) [prepared from (*S*)-6-methyl-2-heptyn-4-ol (**10b**) of 93.6% *S* and 6.4% *R* by Lindlar hydrogenation as reported previously[4]], 226 mg of propionic acid, and 36.6 g of triethyl orthoacetate was refluxed for 16 h, while the ethanol that formed was removed by distillation. Workup as described earlier gave 3.67 g of the unsaturated ester (*R,E*)-**13b** (R' = OC_2H_5) as a colorless oil, $[\alpha]^{25}_D$ −18.1° (neat). A 2.0-g sample of this ester was refluxed in 5 mL of methanol and 3 mL of 6 N NaOH for 2 h. Workup in the usual manner afforded 1.54 g of unsaturated acid **13b:** bp 99–100 °C (0.6 mm) (Kugelrohr); $[\alpha]^{25}_D$ −2.7° (neat); homogeneous by GC analysis (conditions described previously[4]). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.11; H, 10.42.

Similarly, the unsaturated acid **13b,** $[\alpha]^{25}_D$ −2.6° (neat), was also prepared from (*R,E*)-6-methyl-2-hepten-4-ol (**12a**) [95.9% *R* and 4.1% *S* prepared from (*R*)-6-methyl-2-heptyn-4-ol (**10a**) as reported previously[4]].

(R)-(+)-Dimethyl 2-Methylsuccinate (22). (A) From Unsaturated Acid 19b. A solution of the unsaturated acid **19b** (1.03 g) in 20 mL of ethyl acetate was cooled in a dry ice–acetone bath. A stream of ozone (3%) was slowly bubbled through until the solution became blue (~20 min). Most of the ethyl acetate was removed in vacuo, and the reaction mixture was heated with 25 mL of 10% aqueous sodium carbonate and 15 mL of 30% H_2O_2 at 80 °C for 3 h. It was cooled in an ice bath, acidified with concentrated hydrochloric acid, and finally saturated with NaCl. Extraction with ether and workup in the usual manner gave 715 mg of product which was dissolved in 10 mL of ether and treated with a solution of ethereal diazomethane (25 mL) at 23 °C for ~1.0 h. Evaporation of ether gave 645 mg of a yellow liquid which was chromatographed on 30 g of silica gel. Elution with ether–petroleum ether (1:4) gave 129 mg of material which was further purified by Kugelrohr distillation at 100 °C (20 mm) to give 114 mg of (*R*)-(+)-dimethyl 2-methylsuccinate (**22**) as a colorless liquid: $[\alpha]^{25}_D$ +4.2° (*c* 5.42, $CHCl_3$) [lit.[10] $[\alpha]^{25}_D$ +6.1°]; GC (10% OV-101, GCQ 100/200, 80–250 °C) retention time, 26 (67.6% of **22**), 33.6 (21.1% of unknown with molecular weight 174), and 39.8 min (3.3% of unknown with molecular weight 186). GC–IR showed the major component to be completely identical with a sample of racemic dimethyl 2-methylsuccinate: ^1H NMR ($CDCl_3$) δ 1.24 (d, $CHCH_3$), 2.35–3.1 (m, $CHCH_3$ and CH_2COOCH_3), 3.69 (s, CH_2COOCH_3), 3.71 (s, $COOCH_3$); ^1H NMR [100 MHz, $CDCl_3$, 20 mg of sample and 40 mg of Eu(hfbc)$_3$] δ 2.38 (d, $CHCH_3$), 4.69 (s, CH_2COOCH_3), 4.78 (s, $CH_3CHCOOCH_3$). Comparison of this material with racemic dimethyl 2-methylsuccinate and a reference sample of (*R*)-(+)-dimethyl 2-methylsuccinate prepared from 3(*R*),7-dimethyl-4(*E*)-octenoic acid (**13b**) firmly established its *R* configuration and showed no detectable *S* enantiomer present.

(B) From Unsaturated Acid 13b. The unsaturated acid **13b** (250 mg, $[\alpha]^{25}_D$ −2.6°) was ozonized as described above to give 209 mg of partly crystalline acidic substance. This was treated with cold $CHCl_3$ and filtered to remove the isovaleric acid that formed. The $CHCl_3$ filtrate was evaporated, and the residue was dissolved in ether and treated with 10 mL of ethereal diazomethane. Evaporation of ether afforded 108 mg of **22** as a slightly yellow liquid: $[\alpha]^{25}_D$ +1.6° (*c* 2.52, $CHCl_3$); GC (97.6% pure) (conditions the same as in A) retention time, 26.2 min; ^1H NMR (20 mg of sample and 40 mg of Eu(hfbc)$_3$ in $CDCl_3$, 100 MHz) δ 2.43 (d, $CHCH_3$), 4.72 (s, CH_2COOCH_3), 4.82 (s, $CH_3CHCOOCH_3$, 90% *R*), 4.88 (s, $CH_3CHCOOCH_3$, ~10% *S*).

Racemic Dimethyl 2-Methylsuccinate. A 5.0-g (0.044 mol) sample of methyl succinic anhydride in 30 mL of methanol containing 1 mL of concentrated H_2SO_4 was refluxed for 16 h. It was diluted with water and extracted with ether. The ether extract was washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. Evaporation of ether to dryness in a rotary evaporator at 25 °C and purification of the crude product by Kugelrohr distillation [110–115 °C (20 mm)] afforded 5.94 g of racemic dimethyl 2-methylsuccinate: MS *m/e* 129 (M^+ − 31); ^1H NMR (100 MHz, $CDCl_3$) δ 1.21 (d, $CHCH_3$), 2.3–3.05 (m, $CHCH_3$ and CH_2COOCH_3), 3.65 (s, CH_3COOCH_3), 3.66 (s, $COOCH_3$); ^1H NMR [100 MHz, $CDCl_3$, 31 mg of sample and 62 mg of Eu(hfbc)$_3$] δ 2.4 (d, $CHCH_3$), 4.69 (s, CH_2COOCH_3), 4.78 (s, (*R*)-$CH_3CHCOOCH_3$), 4.82 (s, (*S*)-$CH_3CHCOOCH_3$).

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexanoic Acid Ethyl Ester (23a). (A) Hydrogenation with Palladium Catalyst. A mixture of 3.36 g of unsaturated ester **19a** and 350 mg of 5% palladium on carbon was hydrogenated in 20 mL of ethyl acetate at 23 °C and atmospheric pressure until 1 equiv of hydrogen was consumed (4 h). Workup gave 3.07 g of ester **23a** as a colorless oil: $[\alpha]^{25}_D$ −0.2 ° (*c* 4.14, $CHCl_3$); MS *m/e* 452 (M^+), 437, 407, 362 (base peak); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, $CHCH_3$), 1.23 (s, C(2) CH_3), 1.23 (t, $COOCH_2CH_3$), 1.4–1.85 (m, 6, CH_2), 2.08, 2.14, and 2.19 (3s, $ArCH_3$), 2.00–2.4 (m, CH_2COO), 2.58 (t, CH_2CH_2), 4.10 (q, $COOCH_2CH_3$), 4.67 (s, $ArCH_2O$), 7.4 (m, $ArCH_2O$).

(B) Hydrogenation with Raney Nickel. The unsaturated ester **19a** (1.0 g, 2.22 mmol) was hydrogenated with ~200 mg of Raney nickel in ethyl acetate (25 mL) at 25 °C (30 psi) for 4.0 h. The catalyst was filtered off and washed well with ethyl acetate. Evaporation of ethyl acetate in vacuo gave 1.0 g of colorless oil which was dissolved in DMF (10 mL) and treated with 532 mg (3.8 mmol) of anhydrous potassium carbonate and 435 mg (3.8 mmol) of benzyl chloride at 25 °C for 60 h. The reaction mixture was diluted with water and extracted with ether. Workup in the usual manner gave 930 mg of crude product which was purified by thick-layer chromatography on silica gel (ether–petroleum ether 2:3) to give 650 mg of saturated ester **23a** as an oil: $[\alpha]^{25}_D$ −1.4 ° (*c* 4.97, $CHCl_3$); IR, MS, and NMR spectra were identical with the material described in A.

The ester **23a** (200 mg) was hydrolyzed in aqueous NaOH–MeOH to give 189 mg of the acid **23b** which was then converted into the corresponding amide **23c** as described for the preparation of **19c.** LC analysis indicated the enantiomeric composition at C(3) to be 96.1% *S* and 3.9% *R* (two 50 cm × 4.5 mm columns in series, Partisil 10, R-19, flow rate at ~3 mL/min, eluted with 1:4 THF–heptane, monitored at 254 nm; retention volume 182 mL for *R* and 194 mL for *S*).

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexanoic Acid (23b). A mixture of 600 mg of ethyl ester **23a** (prepared from Pd/C hydrogenation of **19a**) and 2 mL of 6 N NaOH in 10 mL of methanol was refluxed for 2.0 h. Workup in the usual manner gave the crude oily acid, which was quickly filtered through a column of silica gel (10 g). Elution with $CHCl_3$ yielded 510 mg (90% yield) of the acid **23b** as a colorless oil: $[\alpha]^{25}_D$ −1.7° (*c* 1.93, $CHCl_3$); MS *m/e* 424 (M^+); IR (neat) 3000–3400, 1705 (COOH) cm^{-1}. Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.18; H, 8.67.

The enantiomeric purity at C(3) was determined by NMR analysis of the corresponding methyl ester **23d** [30 mg of **23d,** 80 mg of Eu(fod)$_3$, and 5 μL of CH_3OD in $CDCl_3$]: δ 9.30 (s, $COOCH_3$, 10% 3*R*), 9.33 (s, $COOCH_3$, 90 ± 2% 3*S*).

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexan-1-ol (24a). The ester **23a** (2.2 g, 4.85 mmol; prepared from **19a** by Pd/C hydrogenation) in 20 mL of dry ether was treated dropwise with a solution of 1.81 mL (13 mmol) of sodium bis(2-methoxyethoxy)aluminum hydride (70% in benzene) in 2 mL of ether. The resulting solution was refluxed for 3.0 h and then cooled to 0 °C, and the excess of hydride was destroyed by careful addition of 10 mL of 1.0 N H_2SO_4 followed by 100 mL of water. The precipitate was filtered and washed well with ether. The aqueous phase was separated from the ether layer and was extracted again with ether. Workup of the ether phase in the usual manner gave 2.18 g of crude product which was chromatographed on 100 g of silica gel. Elution with 3:7 ether–petroleum ether afforded 1.55 g (78% yield) of the alcohol **24a** as a colorless oil: $[\alpha]^{25}_D$ −0.6° (*c* 1.01, $CHCl_3$); IR (neat) 3350 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, $CHCH_3$–), 1.22 (s, C(2) CH_3), 1.3–1.5 (m, $CHCH_3$ and $3CH_2$), 1.8 (t, 2, CH_2), 2.08, 2.14, and 2.19 (3s, $ArCH_3$), 2.62 (t, 2, CH_2), 3.62 (t, CH_2OH), 4.66 (s, $ArCH_2O$), 7.4 (m, C_6H_5). Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.91; H, 9.23.

(2R,3S*)-6-(3,4-Dihydro-6-benzyloxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)-3-methylhexan-1-ol *p*-Toluenesulfonate (24b). A solution of 1.23 g (2.98 mmol) of alcohol **24a** in 4 mL of dry pyridine (dried and distilled over barium oxide) was treated in portions with 1.14 g (5.96 mmol) of *p*-toluenesulfonyl chloride at ~0 °C.[20] The resulting solution was stirred at 0 °C for 3.0 h and then kept at −10 °C for 16 h. The mixture was poured into 100 mL of ice water and

acidified with 3 N HCl (ca. 50 mL). It was extracted with ether, and the combined ether extracts were washed with water and dried over anhydrous potassium carbonate–sodium sulfate (~1:1). Evaporation of ether in vacuo yielded 1.80 g of **24b** as a yellow oil: $[\alpha]^{25}_D$ +1.4° (*c* 2.06, $CHCl_3$); MS *m/e* 564 (M^+); IR (neat) 1365 ($-OSO_2$) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, $CHCH_3$), 1.22 (s, C(2) CH_3), 1.3–1.6 (m, 7), 1.77 (t, CH_2), 2.08, 2.16, and 2.21 (3s, $ArCH_3$), 2.42 (s, CH_3Tos), 2.58 (t, $ArCH_2$), 4.04 (t, CH_2SO_3-), 4.67 (s, $ArCH_2O$), 7.4 (m, $ArCH_2$ and $CH_3C_6H_4SO_3$), 7.78 (d, $CH_3C_6H_4SO_3$).

(2*R*,4′*R*,8′*R*)-α-Tocopherol Benzyl Ether (1c). A solution of 1.24 g (6.0 mmol) of (*R*)-2,6-dimethylheptyl 1-bromide (**25b**) (prepared from (*S*)-(+)-β-hydroxyisobutyric acid via the C(9) alcohol **25a**)[3] in 3 mL of dry ether was added dropwise at 23 °C with stirring under argon to a suspension of 195 mg (8 mmol) of powdered magnesium in 3 mL of ether. The resulting mixture was refluxed with stirring under argon for 3.0 h and then was further stirred at 25 °C for 1.0 h. It was then cooled to −75 °C in a dry ice–acetone bath. To this mixture 0.1 mL of Li_2CuCl_4 was first added followed by a solution of 0.64 g (1.14 mmol) of the *p*-toluenesulfonate **24b** in 10 mL of THF. The resulting reaction mixture was stirred at −75 °C for 10 min, and then it was allowed to warm to 25 °C and stirred for 17 h under argon. The mixture was then treated with 5 mL of 1 N aqueous H_2SO_4 and worked up by ether extraction in the usual manner to give 1.03 g of crude product. This material was purified by thick-layer chromatography on silica gel, and elution with ether–hexane (5:95) afforded 409 mg of (2*R*,4′*R*,8′*R*)-α-tocopherol benzyl ether (**1c**; 69% yield), $[\alpha]^{25}_D$ +0.4° (c 4.19, benzene) [lit.[3a] $[\alpha]^{25}_D$ +0.7° (c 1.95, benzene)]. Anal. Calcd for $C_{36}H_{56}O_2$: C, 83.02; H, 10.84. Found: C, 82.98; H, 10.95.

(2*R*,4′*R*,8′*R*)-α-Tocopheryl Acetate (1b). A mixture of **1c** (326 mg, 0.63 mmol) and 600 mg of 5% palladium on carbon in 5 mL of THF containing two drops of concentrated HCl was hydrogenated at 25 °C and atmospheric pressure for 1.5 h. Workup gave 239 mg of (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**) as a light yellow oil which was treated with 2 mL of dry pyridine and 2 mL of acetic anhydride at 25 °C for 16 h. The mixture was poured into ice water and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were successively washed with aqueous 1 N HCl, saturated $NaHCO_3$ solution, and H_2O and dried over $MgSO_4$. Evaporation of solvent in vacuo gave 250 mg of crude product which was purified by thick-layer chromatography on silica gel (ether–petroleum ether 1:4) to yield 188 mg (64%) of **1b** as a light yellow oil: $[\alpha]^{25}_D$ +2.6° (*c* 2, C_2H_5OH) [lit.[2] $[\alpha]^{25}_D$ +3.2° (C_2H_5OH)]; MS *m/e* 472 (M^+); 97.8% pure by GC (OV-101, GCQ 100/120, 6 ft × 4 mm column, 250 °C; retention time, 52.3 min); IR, NMR, and UV spectra were identical with an authentic sample (Eastman Kodak, highest purity). Anal. Calcd for $C_{31}H_{52}O_3$: C, 78.76; H, 11.09. Found: C, 78.82; H, 11.17.

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Registry No.—**1a**, 59-02-9; **1b**, 58-95-7; C(4′)-(*S*)-**1b**, 66900-46-7; **1c**, 59965-06-9; **6**, 58846-73-4; **11b**, 66900-47-8; **12a**, 66900-48-9; **12b**, 59983-79-8; **13b** (R′ = OH), 66900-49-0; **13b** (R′ = OEt), 66842-31-7; **15a**, 64704-95-6; **15b**, 66842-32-8; **16a**, 64765-29-3; **16b**, 66842-33-9; **17**, 64704-96-7; **18**, 60919-74-6; **19a**, 64704-97-8; **19b**, 64704-98-9; **19b** acid chloride, 66842-34-0; **19c**, 66842-35-1; C(3)-(*S*)-**19c**, 66900-50-3; **20**, 66842-36-2; **21a**, 66842-37-3; **21b**, 66842-38-4; (*R*)-(+)-**22**, 22644-27-5; (±)-**22**, 21307-96-0; **23a**, 64704-99-0; **23b**, 64705-00-6; **23c**, 66900-51-4; C(3)-(*R*)-**23c**, 66842-29-3; **23d**, 66842-30-6; **24a**, 64705-01-7; **24b**, 64705-02-8; **25b**, 60610-07-3; (*S*)-(−)-3,7-dimethyloctanoic acid, 55509-77-8; (*R*)-α-methyl-*p*-nitrobenzylamine, 22038-87-5.

References and Notes

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(5) The "right-to-left" (path i) strategy has been demonstrated in the synthesis of optically active 10- and 15-carbon isoprenoids starting from isoveraldehyde.[4] The "left-to-right" (path ii) strategy has been applied to the synthesis of the 14-carbon synthon **8b** starting from (*S*)-(+)-3-hydroxy-2-methylpropanoic acid.[3a]

(6) We thank Dr. J. W. Scott for providing us with this compound.

(7) The absolute configurations of these carbinols could not be assigned based on their spectral properties. Both carbinols showed free and bonded hydroxy absorptions at 3620 and 3530 cm^{-1} (IR in dilute CCl_4), respectively. In the ^1H NMR spectrum of **15a** the tert-C(2) CH_3 appeared as a sharp singlet at δ 1.29, while in the minor diastereoisomer **16a** this signal was found at δ 1.34 (s). Both **15a** and **16a** were essentially optically pure.

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Two New Vitamin D Isomers. Formation of (3S,10R)-(Z,Z)-9,10-Secocholesta-5,7,14-trien-3-ol and Its 10S-Epimer from *cis*-Isotachysterol$_3$ via Facile [1,7] Sigmatropic Rearrangements

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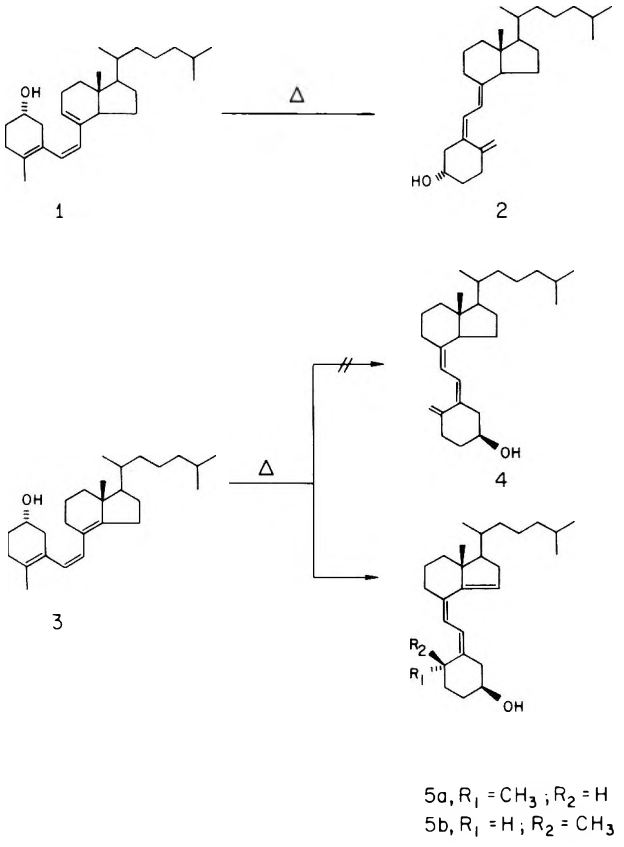
Warming a solution of (3S)-(Z)-9,10-secocholesta-5(10),6,8(14)-trien-3-ol (*cis*-isotachysterol$_3$) in decane produced two new isomers of vitamin D_3: (3S,10S)-(Z,Z)-9,10-secocholesta-5,7,14-trien-3-ol (**5a**) and (3S,10R)-(Z,Z)-9,10-secocholesta-5,7,14-trien-3-ol (**5b**). The reaction has been shown to be reversible, and to occur via an intramolecular [1,7] hydrogen transfer. Stereochemistry at C-10 was assigned by chemical correlation with dihydrotachysterol, and double bond geometry was deduced from NMR data and mechanistic considerations. Activation parameters for the reactions to **5a** and **5b**, calculated from kinetic data, are $\Delta H^{\ddagger} = 23.0 \pm 1.2$ kcal/mol, $\Delta S^{\ddagger} = -16.3 \pm 3.3$ eu and $\Delta H^{\ddagger} = 23.2 \pm 1.2$ kcal/mol, $\Delta S^{\ddagger} = -17.1 \pm 3.4$ eu, respectively.

For the past decade work in our laboratories has focused on the isolation and characterization of biologically active vitamin D metabolites. Since metabolite identification depends heavily on spectral correlations, we have, as part of our general program, prepared most of the known triene isomers of vitamin D, for which required spectral data were often not available, because their original syntheses[1,2] predated the advent of modern spectroscopic techniques. One of these compounds, *cis*-isotachysterol, was originally described by Verloop et al.[3] who noted that prolonged heating (60 °C) of a methanol solution of this compound produced a shift of the UV absorption maximum from 253 to 265 nm and an increase in absorption intensity. A spectral change of this kind is reminiscent of that occurring in the thermal isomerization of previtamin D (**1**) to vitamin D (**2**) via a [1,7]sigmatropic shift. In the case of *cis*-isotachysterol$_3$ (**3**), an exactly analogous rearrangement (C-19 → C-14 H migration) would yield the new and unusual vitamin D isomer(s) **4** (C-14 stereochemistry *R* or *S*, or both) featuring (5Z,7Z) double-bond geometry. A reinvestigation of this reaction has now shown that *cis*-isotachysterol$_3$ (**3**) undergoes an alternative sigmatropic rearrangement involving intramolecular hydrogen transfer from C-15 to C-10 and resulting exclusively in (3S,10S)-(Z,Z)-9,10-secocholesta-5,7,14-trien-3-ol (**5a**) and its (10R)-epimer (**5b**).

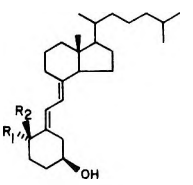


5a, $R_1 = CH_3$; $R_2 = H$
5b, $R_1 = H$; $R_2 = CH_3$

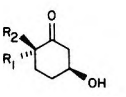
Results and Discussion

In refluxing toluene, *cis*-isotachysterol$_3$ (**3**) was smoothly converted to two products (**5a,b**) which were separated by preparative TLC. High resolution mass spectrometry showed them to be isomers of the starting material ($C_{27}H_{44}O$) and both exhibited the UV absorption maximum of a conjugated triene chromophore (273 nm). The NMR spectra indicated three olefinic protons (two as an isolated AB pattern, the third coupled to two other protons) and an additional secondary methyl instead of the olefinic methyl of the starting material. Given the structure of **3** and the conditions of its conversion to **5a** and **5b**, the spectral evidence required that both products be $\Delta^{5,7,14}$-trienes differing in configuration at C-10. Stereochemistry at C-10 was established by chemical correlation to dihydrotachysterol$_2$ (DHT_2),[4] an historically important reduction product of vitamin D_2. Ozonolysis of **5a** gave β-hydroxy ketone **7a**, identical (as determined by combined GC/MS) with the ozonolysis product obtained from DHT_2 for which the (10S) configuration has been established.[5,6] Ozonolysis of **5b**, on the other hand, furnished hydroxy ketone **7b**, exhibiting a mass spectrum nearly identical to that of **7a**, but clearly distinguished from the latter by GC retention time. These correlations establish the (10S) and (10R) configurations for **5a** and **5b**, respectively, and confirm the C-5 terminus of the triene system for both isomers.

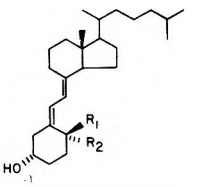
The major difference between the strikingly similar ^{1}H-NMR spectra of the two new isomers is that between the chemical shifts of the 3α protons. This difference allowed assignment of the stereochemistry of the 5,6-double bond by spectral correlation with dihydrovitamins **6a,b** and **8a,b**. The 3α proton of **5a** occurs at δ 4.05, very similar to that found for **8a** (4.02 ppm),[6] but not to that observed for **6a** (3.61 ppm).[6] Analogously, the 3α proton of **5b** resonates at δ 3.52, similar



6a, $R_1 = CH_3$; $R_2 = H$
6b, $R_1 = H$; $R_2 = CH_3$



7a, $R_1 = CH_3$; $R_2 = H$
7b, $R_1 = H$; $R_2 = CH_3$



8a, $R_1 = CH_3$; $R_2 = H$
8b, $R_1 = H$; $R_2 = CH_3$

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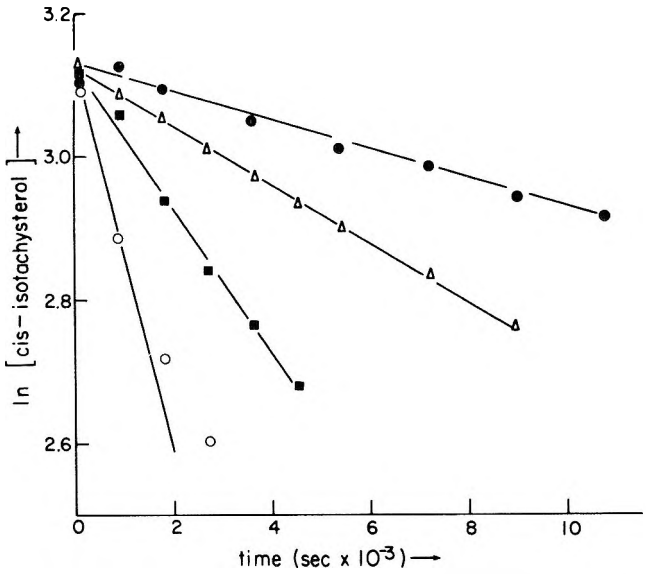


Figure 1. Kinetics of the decrease of *cis*-isotachysterol$_3$ concentration with time at 80 (●), 90 (△), 100 (■), and 110 °C (○). The reaction was run in decane under nitrogen gas; the ordinate represents the natural log of the starting material concentration in arbitrary units.

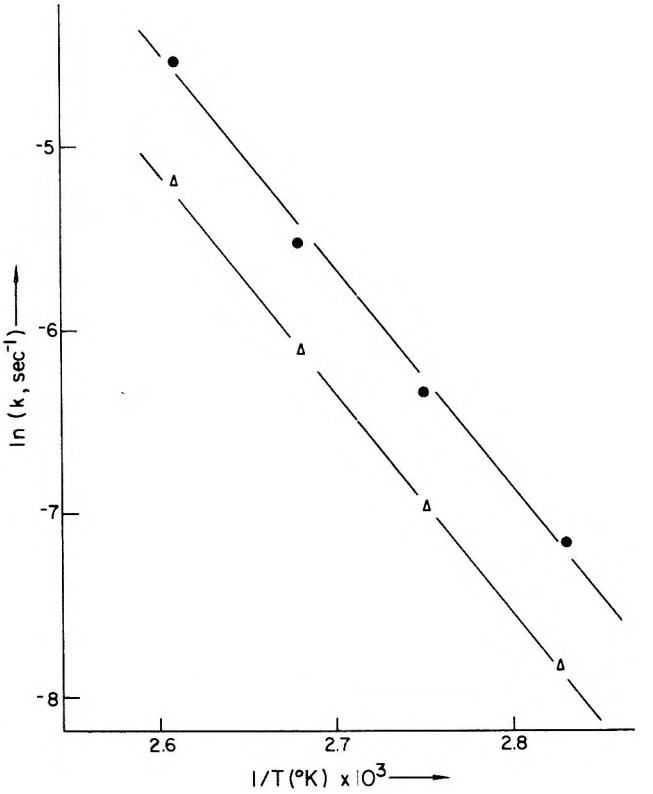


Figure 2. Arrhenius plot of rate constants for formation of isomer **5a** (●) and isomer **5b** (△) from *cis*-isotachysterol$_3$ in decane solutions at 80, 90, 100, and 110 °C.

to that found for **8b** (3.57 ppm),[6] but not to that observed for **6b** (3.82 ppm).[6] These comparisons indicate (5*Z*) stereochemistry for both triene isomers. Since both products arise by intramolecular hydrogen migration (see next paragraph), the known geometric requirement for an antarafacial transition state in [1,7]sigmatropic rearrangements[7] dictates the (7*Z*) geometry for the central double bond in both compounds; structures **5a** and **5b,** therefore, define the reaction products.

To examine the mechanism of the rearrangement, *cis*-isotachysterol$_3$ was heated in CH_3OD. Products **5a** and **5b** were isolated by preparative TLC, and the isotopic composition of their molecular ions was determined by mass spectrometry. As expected for an intramolecular hydrogen transfer, no deuterium was incorporated into the products (Table I). The reversibility of the reaction was demonstrated by heating a solution of **5a** in xylene and isolating **3** and **5b.**

Table I. Mass Spectral Intensities[a] of M, M + 1, and M + 2 for Trienes 5a and 5b Formed Thermally from 3 in CH_3OD

m/e	*cis*-isotachysterol$_3$ (3)	triene **5a**	triene **5b**
384	100.0	100.0	100.0
385	30.8	3/5	30.7
386	5.7	5.5	5.7

[a] Each value represents the mean of three measurements with the intensity of *m/e* 384 taken as 100.

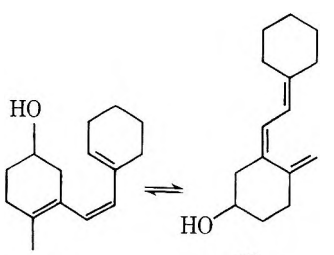
Table II. Comparison of Kinetics of Thermal Rearrangements.

rearrangement	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
3 → **5a**[f]	23.0 ± 1.2[a]	−16.3 ± 3.3[a]
3[d] → **5b**[g]	23.2 ± 1.2[a]	−17.1 ± 3.4[a]
1[e] → **2**[h]	18.5 ± 0.1[b]	−21.8 ± 0.4[b]
9 → **10**	21.6 ± 0.2[c]	−17.2[c]

[a] Calculated for 95 °C. [b] Calculated from data in ref 10 for 70 °C. [c] Reference 11. [d] Registry no. 66966-15-2. [e] Registry no. 1173-13-3. [f] Registry no. 66901-52-8. [g] Registry no. 66966-16-3. [h] Registry no. 67-97-0.

The kinetics of the reaction were examined at 80, 90, 100, and 110 °C in decane solutions. The decrease in starting material concentration (Figure 1) followed first-order kinetics except at later times for the higher temperatures where the influence of back reaction was evident. Triene isomer **5a** was formed 1.9–2.0 times faster than triene isomer **5b.** The activation parameters (Table II) show that the formation of isomer **5a** is favored over **5b** kinetically. Isomer **5b** is, however, the major product. At 120 °C, the equilibrium mixture in decane consists of 24% of **5a,** 36% of **3,** and 40% of **5b.** Thus isomer **5b** is thermodynamically preferred over **5a** by 0.4 kcal/mol ($\Delta F°$). For both isomers, the C-10 methyl would be almost exclusively axial to minimize the severe steric interaction between the C-19 and C-7 protons. This conformational bias has been experimentally confirmed for compounds **8a** and **8b.**[6] Thus, the C-3 hydroxyl would be forced into an axial orientation in **5a** and an equatorial one in **5b,** accounting for the thermodynamic stability of the latter. The *A* value of 0.5 kcal/mol for the equatorial preference of an hydroxyl substituent on a cyclohexane ring in nonpolar solvents supports this interpretation.[8]

The activation parameters for the conversion of **3** → **5a** + **5b** calculated from our kinetic results are in accord with data for other [1,7]sigmatropic rearrangements in analogous systems. Table II lists the corresponding values for the previtamin D_3 (**1**) to vitamin D_3 (**2**) reaction, one of the earliest



9 **10**

known [1,7]sigmatropic isomerizations,[9,10] and for the reaction of triene **9** to its isomer **10,** studied by Schlatmann et al.[11] The large negative entropy of activation reflects the high degree of order in the transition state. Since the activation parameters for the isomerization of **1** → **2** and **9** → **10** compare so closely to those found for the formation of trienes **5a** and **5b** from **3,** it is reasonable to assume that the same type of mechanism applies to each case. Unlike the reaction from **3** to **5a** and **5b,** however, the conversion of **1** to **2** involves two transition states (transfer of one of the C-19 hydrogens to either the α or the β face of the 8,9-double bond in **1**) that lead to the same product.[12]

Experimental Section

Mass spectra were obtained on an AEI Model MS-902 mass spectrometer at 70 eV using a direct probe for introduction of samples (source temperature, 110–130 °C above ambient); high resolution mass spectra were measured on the same instrument coupled to an AEI Model DS-50 data system and using perfluorokerosene as an internal mass standard. UV absorption spectra were recorded on a Beckman Model 25 instrument. NMR spectra were taken on a Bruker 270 MHz FT spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. GC–MS was carried out on a Varian Model 2740 gas chromatograph coupled to a Dupont 21-491 B mass spectrometer. For analytical TLC, air-dried silica gel G plates (5 × 20 cm, 0.25 mm thick) were used. For preparative TLC, 20 × 20 cm plates covered with a 0.75 mm thick layer of silica gel H and silica gel PF-254 (1:1) were used. HPLC was performed on a Dupont 830 liquid chromatograph with a Waters Model U6K injector and 254 nm detector; a Partisil-10 column (0.46 × 50 cm, Whatman) was operated at 800 psig which gave a flow rate of 2.2 mL/min using 1% 2-propanol in hexane as solvent. Ozone was produced with a Supelco microozonator. Commercial Skellysolve B was distilled and the fraction boiling between 67 and 69 °C was used. Dihydrotachysterol$_2$ was a generous gift from the Philips Duphar Co., Amsterdam; methanol-d_1 (99% D) was purchased from Stohler Isotope Chemicals.

***cis*-Isotachysterol$_3$ (3).** An ether solution (200 mL) of 56.7 mg of isotachysterol$_3$ [(3*S*)-(*E*)-9,10-secocholesta-5(10),6,8,(14)-trien-3-ol, prepared from vitamin D_3 (**2**) by the procedure of Murray et al.[13]] was irradiated under N_2 for 35 min using an ice bath, vigorous stirring, Vycor filter, water-cooled quartz irradiation apparatus, and a mercury-arc lamp (Hanau TQ 150 Zz). The solvent was removed by evaporation and the resulting residue was purified on a 20 × 20 cm silica gel preparative TLC plate. After developing the plate four times with 10% ethyl acetate in Skellysolve B two bands were eluted with ethyl acetate. The bottom band was starting material (identical to isotachysterol$_3$ by UV, MS, GC, and TLC) while the top zone, after flash evaporation of solvent, gave 14 mg (25%) of *cis*-isotachysterol$_3$ (*3*) as a clear oil: UV (EtOH) λ_{max} 253 nm (ϵ 13 000); NMR ($CDCl_3$) δ 5.83 and 5.80 (AB, J = 12.7 Hz, 2 H, C-6,7), 3.90 (m, 1 H, C-3), 1.80 (s, 3 H, C-19), 0.94 (d, J = 6.3 Hz, 3 H, C-21), 0.88 (s, 3 H, C-18), 0.87 (d, J = 6.6 Hz, 6 H, C-26,27); mass spectrum, *m/e* (relative intensity) 384 (M^+, 100), 369 (21), 271 (51), 253 (25), 217 (22), 199 (18), 81 (40); M^+, *m/e* calcd for $C_{27}H_{44}O$ 384.3393, found 384.3380; homogeneous on TLC (R_f 0.54, 15% ethyl acetate in Skellysolve B) and LC (t_R = 4.90 min); two peaks are observed on GC[14] (Lit. UV (ether) λ_{max} 253 nm (ϵ 15 000)[3]).

Preparation of Isomers 5a and 5b. A solution of 9.5 mg of *cis*-isotachysterol$_3$ (**3**) in 10 mL of toluene was refluxed under nitrogen for 3 h. The solvent was removed by flash evaporation and the resulting oil was purified by preparative silica gel TLC. The plate was developed with 15% ethyl acetate in Skellysolve B and two bands were eluted with ethyl acetate. The top band gave triene isomer **5a** (1.8 mg, 19%) as an oil: UV (EtOH) λ_{max} 273 nm (ϵ 18 000); NMR ($CDCl_3$) δ 6.21 and 6.13 (AB, J = 11.4 Hz, 2 H, C-6 and C-7), 5.48 (dd, J = 2.9 and 1.8 Hz, 1 H, C-15), 4.05 (m, 1 H, C-3), 1.10 (d, J = 7 Hz, 3 H, C-19), 0.93 (d, J = 6.3 Hz, 3 H, C-21), 0.88 (d, J = 6.3 Hz, 6 H, C-26,27), 0.87 (s, 3 H, C-18); mass spectrum, *m/e* (relative intensity) 384 (M^+, 100), 369 (18), 351 (13), 271 (40), 253 (22), 244 (33), 159 (22), 145 (23), 133 (40); M^+, *m/e* calcd for $C_{27}H_{44}O$ 384.3393, found 384.3375; homogeneous on TLC (R_f 0.77, 15% ethyl acetate in Skellysolve B) and LC (t_R = 2.71 min); GC[14] gave two peaks. The bottom band was reapplied to a silica gel preparative TLC plate which was developed three times using 10% ethyl acetate in Skellysolve. B. Two zones were eluted with ethyl acetate. The upper zone gave 2.7 mg (28%) of starting material (identical to authentic *cis*-isotachysterol$_3$ by UV, TLC, and NMR), and the lower zone gave triene isomer **5b** (2.9 mg, 31%) as an oil: UV (EtOH) λ_{max} 273 nm (ϵ 19 000); NMR ($CDCl_3$) δ 6.14 and 6.05 (AB, J = 11 Hz, 2 H, C-6 and C-7), 5.49 (dd, J = 3 and 2 Hz, 1 H, C-15), 3.52 (m, 1 H, C-3), 1.08 (d, J = 7 Hz, 3 H, C-19), 0.93 (d, J = 6 Hz, 3 H, C-21), 0.88 (d, J = 6 Hz, 6 H, C-26,27), 0.86 (s, 3 H, C-18); mass spectrum, *m/e* (relative intensity) 384 (M^+, 100), 369 (19), 351 (13), 271 (42), 253 (22), 244 (20), 159 (22), 145 (23), 133 (28); M^+, *m/e* calcd for $C_{27}H_{44}O$ 384.3393, found 384.3387; homogeneous on TLC (R_f 0.51, 15% ethyl acetate in Skellysolve B) and LC (t_R = 5.51 min); GC gave two peaks.[14]

Ozonolysis of Compounds 5a, 5b, and DHT$_2$.[4] A sample (20 μg) of each compound was dissolved in 50 μL of dichloromethane containing 100 μg of pyridine, cooled with a dry ice/2-propanol bath, and ozonized to excess. After sparging with nitrogen, the samples were directly examined by combined GC–MS using a 2 mm × 1 m glass column packed with 3% OV-225 on Varaport 30, 100/120 mesh, operated isothermally at 90 °C at a He flow rate of 27 mL/min. From DHT_2, β-hydroxy ketone **7a** was obtained [t_R = 7.4 min; *m/e* (relative intensity) 128 (M^+, 10), 110 (2), 82 (12), 74 (100), 71 (30)]. Triene isomer **5a** also gave **7a** [t_R = 7.4 min; *m/e* (rel intensity) 128 (M^+, 12), 110 (1), 82 (10), 74 (100), 71 (32); 70% yield relative to the amount of **7a** formed from DHT_2]. The more polar isomer **5b** gave **7b** [t_R = 8.5 min; *m/e* (rel intensity) 128 (M^+, 17), 110 (3), 82 (11), 74 (100), 71 (38); 85% yield relative to the amount of **7a** formed from DHT_2].[15] Under the GC conditions chosen, only the most volatile degradation products (i.e., **7a,b**) are eluted; the higher molecular weight products formed by ozonolysis of **5a,b** or DHT_2 require elevated temperatures for elution. Coinjection of ozonolysis products from **5a** and DHT_2 gave a single peak with t_R = 7.4 min, while coinjection of the products from **5b** and DHT_2 gave two peaks (t_R's = 7.5 and 8.7 min).

Deuterium Incorporation Study. To a Pyrex tube was added 1.0 mg of *cis*-isotachysterol$_3$ (**3**) in 0.30 mL of CH_3OD. After freezing the solvent in liquid nitrogen, the tube was sealed and heated to 110 °C for 3 h. The solvent was removed and 0.3 mL of CH_3OH was added and then evaporated. The products were purified by preparative TLC as described above. This gave, as evidenced by UV absorption, 0.21 mg of isomer **5a,** 0.16 mg of starting material (**3**), and 0.23 mg of isomer **5b.** Mass spectral analysis of these two products and a sample of starting material that had never been exposed to CH_3OD is summarized in Table I.

Reaction Reversibility. Isomer **5a** (1.8 mg) was dissolved in 1.0 mL of xylene and heated to 125 °C for 2.5 h. After evaporation of solvent, the residue was purified by preparative TLC as described above. This gave 0.31 mg of starting material **5a,** 0.47 mg of **3,** and 0.43 mg of **5b.** Product identity was confirmed by UV, TLC, and NMR; product amounts were quantitated by UV.

Kinetic Experiments. A solution of *cis*-isotachysterol$_3$ (**3**) in *n*-decane was diluted twentyfold with *n*-decane preheated to the desired temperature. The reaction was maintained under nitrogen; temperature was controlled with an oil bath and thermostat. The starting material concentration was initially 0.05 mg/mL. At the indicated times (Figure 1) an aliquot was removed, cooled, then analyzed by LC as described above. The decrease in the peak height of *cis*-isotachysterol$_3$ on the LC trace was followed versus time. Semilogarithmic plots of these data were made (Figure 1), and the slope of the resulting line for each temperature gave the sum of the forward rate constants. The LC trace was calibrated with standards of **5a** and **5b** of known concentration. This allowed measurement of the ratio of the amounts of **5a** to **5b** (based on peak heights of **5a** and **5b** on LC traces of aliquots taken at early time points) and directly gave the ratio of the two forward rate constants.[16] Knowing the ratios and the sums, the two rate constants were calculated for each temperature and fitted to a linear equation (Figure 2). Slopes, intercepts, and the errors in these measurements were determined by the method of Cleland.[17] Thermodynamic parameters (Table II) were derived from the slopes and intercepts as done by Havinga and co-workers.[11]

Acknowledgments. This work was supported by research and training grants from the National Institutes of Health (No. Am-14881 and GM-00236BCH, respectively) and by the Harry Steenbock Research Fund.

Registry No.—**7a,** 66901-50-6; **7b,** 66901-51-7; DHT_2, 67-96-9; isotachysterol$_3$, 22350-43-2.

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(14) Isomerization of vitamin D trienes under GC conditions is a common observation. GC of **3** (2 mm × 2 m glass column packed with 3% OV-101 on Chromosorb 30 100/120 mesh; nitrogen flow rate 30 mL/min; oven held isothermally at 260 °C) gave two peaks with retention times of 3.2 and 8.0 min. Interestingly, GC of either **5a** or **5b** gave the same trace as found for **3**. In all three traces, the ratio of peak heights of the 3.2 to the 8.0 min peak was about 2.5/1. GC–MS of **3** showed that both peaks were isomers of nominal parent mass 384. The early peak showed *m/e* (rel intensity) 384 (M^+, 18), 351 (36), 309 (41), 283 (35), 145 (35), 124 (32), 43 (100). The late peak gave 384 (M^+, 47), 369 (20), 271 (48), 253 (42), 199 (35), 81 (85), 43 (100).
(15) A minor component at t_R = 6.7 min was also found in this sample; its parent ion at *m/e* 110 and fragmentation pattern suggest that it is methylcyclohexenone, the dehydration product of **7b**.
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Effective Biomimetic Route to D(+)-Pantothenate Using Asymmetric Hydrogenation Catalyzed by a Chiral Rhodium Complex in the Key Step

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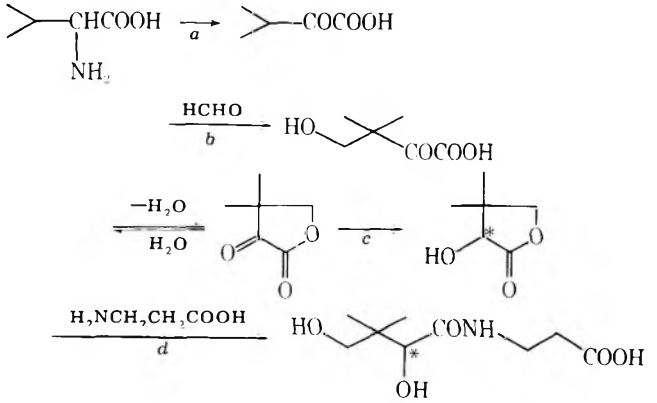
Asymmetric synthesis of D(+)-pantothenate from ketopantoyl lactone following a biomimetic route using asymmetric hydrogenation in the key step is described. The asymmetric hydrogenation of ketopantoyl lactone was effectively catalyzed by a rhodium complex with BPPM as chiral ligand to afford D(−)-pantoyl lactone with 86.7% optical purity under optimum conditions. This was further recrystallized to give the pure lactone in good yield. The pure D(−)-pantoyl lactone thus obtained was converted to ethyl D(+)-pantothenate by reacting with β-alanine ethyl ester.

Pantothenic acid is a member of the B complex vitamins and is an important constituent of Coenzyme A. Pantothenic acid is converted to pantetheine, which further reacts with adenosine triphosphate (ATP) to form Coenzyme A. The biosynthesis of pantothenic acid from valine has been postulated to involve[1,2] (a) the oxidative deamination of valine to α-ketoisovaleric acid, (b) the hydroxymethylation of this acid to form ketopantoyl lactone, (c) the asymmetric reduction of ketopantoyl lactone to pantoyl lactone, and (d) the coupling of pantoyl lactone with β-alanine to give pantothenic acid (Scheme I). Among these processes, step c is the most significant since only D(+)-pantothenic acid derived from D(−)-pantoyl lactone has biological activity.[3] Although the biological synthesis of D(+)-pantothenic acid has been reported using microbial reduction of ketopantoyl lactone to pantoyl lactone,[4] no attempts have been made on the chemical asymmetric synthesis of this substance following the biosynthetic route. We have found that a rhodium complex with a chiral pyrrolidinodiphosphine, (2*S*,4*S*)-*N*-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine (BPPM),[5] displays a high chiral recognition ability comparable to that of microorganisms, and thus the chiral rhodium complex can be considered as a functional biomimetic model of the ketopantoyl lactone reductase. We wish to present here an effective biomimetic route to D(+)-pantothenic acid using a catalytic asymmetric hydrogenation in the key step as an application of the successful hydrogenation of α-keto esters catalyzed by neutral rhodium complexes with phosphine ligands.[6]

Scheme I



[a] Transaminase. [b] Ketopantoaldolase. [c] Reductase. [d] Pantothenate synthetase.

One of the key compounds in the biosynthetic route is ketopantoyl lactone since the asymmetric reduction of this compound is the characteristic process in biological systems. This eliminates the need for the optical resolution of racemic pantoyl lactone as employed in the commercial synthesis of D(+)-pantothenic acid derivatives.[7] As the formation of ketopantoyl lactone is not restricted to enzymatic process but a simple aldol condensation, we started the asymmetric synthesis from ketopantoyl lactone.

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Table I. Asymmetric Hydrogenation of Ketopantoyl Lactone to D(−)-Pantoyl Lactone Catalyzed by the BPPM–Rhodium(I) Complex

Solvent	Initial H_2 pressure, atm	Conditions[a]	Conversion[b] %	$[\alpha]^{25}_D$,[c] deg	Optical purity,[d] % ee
Benzene	50	10 °C, 48 h	95.4	−23.4	46.2
Benzene	50	20 °C, 48 h	99.2	−43.4	85.5
Benzene	50	30 °C, 48 h	100.0	−44.0	86.7
Benzene	50	50 °C, 24 h	100.0	−43.0	84.8
THF[e]	50	0 °C, 70 h	46.1	−13.4	26.4
THF[e]	50	15 °C, 48 h	69.7	−41.9	82.6
THF[e]	50	30 °C, 48 h	99.5	−40.9	80.7
Chlorobenzene	50	50 °C, 48 h	94.5	−32.2	63.5
Toluene	50	50 °C, 48 h	99.6	−39.4	77.7

[a] A 0.99–1.06 mol % amount of the catalyst was employed; [BPPM]/[Rh] = 1.12–1.17. [b] Determined by GLC analysis. As the reaction does not involve any side reactions at all, this value corresponds to the chemical yield. [c] Measured in water; c = 2.010–2.098. [d] Optical purity was calculated on the basis of the maximum rotation of the pure enantiomer, $[\alpha]^{25}_{D\ max}$ −50.7° (c 2.05, H_2O) (ref 3). [e] THF = tetrahydrofuran.

The asymmetric hydrogenation of ketopantoyl lactone was carried out by means of a homogeneous rhodium complex having BPPM as the chiral ligand. This gave D(−)-pantoyl lactone with an optical purity of 86.7% in almost quantitative yield under optimum conditions.[8] The results obtained in the asymmetric hydrogenation under a variety of conditions are summarized in Table I. The corresponding asymmetric hydrogenation using (−)-DIOP[9] as the chiral ligand in tetrahydrofuran at 20 °C resulted in only a 35% enantiomeric excess.

As Table I shows, (i) the optical yield is affected by the solvent employed, with benzene affording the best results as far as we have examined, and (ii) a remarkable effect of the reaction temperature on the optical yield is observed. It is of interest that the extent of asymmetric induction decreases precipitously at temperatures below ca. 10 °C. This phenomenon could be caused by either (i) a change in the rate-determining step or (ii) an exchange of one mechanism for another, provided the reaction proceeds via two parallel mechanisms. A configurational change of the chiral ligand in the coordination sphere of the rhodium complex could be also suggested.

As to the direction of asymmetric induction, *R* configuration is found to be extremely favored, thus leading to the formation of the naturally occurring D(−)-pantoyl lactone which has been shown to have the *R* configuration.[3b] Thus, the direction of asymmetric induction realized in the present reaction is the same as that observed in the asymmetric hydrogenation of pyruvates using either (−)-DIOP or BPPM as the chiral ligand.[6]

The pantoyl lactone thus obtained was easily purified to give the pure D isomer by recrystallization from *n*-hexane–benzene. Accordingly, a pure sample of D(−)-pantoyl lactone was obtained in at least 70% yield from ketopantoyl lactone. The pure sample of D(−)-pantoyl lactone was converted in 77% yield to the ethyl ester of D(+)-pantothenic acid by reacting with β-alanine ethyl ester. The transformations of ethyl D(+)-pantothenate to D(+)-pantothenic acid and to pantetheine are known processes.[3,10] Synthesis of calcium pantothenate from D(−)-pantoyl lactone, β-alanine, and calcium metal or ions has been established.[7]

As the optical yield attained in a microbial reduction of ketopantoyl lactone using baker's yeast has been reported to be ca. 72%,[4] our chiral rhodium catalyst is shown to be superior to baker's yeast in this reaction. Although Lanzilotta et al. recently have found that specific strains of an ascomycete, *Byssochlamys fulva*, can achieve exceedingly high optical yield production of the D isomer,[4] the isolation procedure from aqueous media, i.e., extraction, recovery of raw materials, and purification, is very troublesome because of the high solubility of the product in water. Thus, the present reaction has some advantages from a synthetic point of view; i.e., (i) conversion of the reaction is virtually 100%, and (ii) the isolation of the product is quite simple and convenient since the reaction is carried out in small amounts of nonaqueous media.

Further studies on achieving high stereoselectivity using a variety of chiral ligands are actively under way.

Experimental Section

Measurements. Melting points and boiling points are uncorrected. The infrared spectra were measured on a Hitachi EPI-G3 spectrophotometer using samples as neat liquid or in KBr disks. The nuclear magnetic resonance spectra were obtained using a Varian XL-100, HA-100, or T-60 spectrometer with Me_4Si as an internal standard. Analytical gas chromatography (GLC) was carried out on a Shimadzu GC-3BF using a column packed with 3% PEG-20M.

Materials. [Rh(cycloocta-1,5-diene)Cl]$_2$ was prepared from rhodium trichloride trihydrate and cycloocta-1,5-diene.[11] BPPM was prepared from L-4-hydroxyplorine in accordance with a previously reported method.[5] Ketopantoyl lactone was prepared by the oxidation of DL-pantoyl lactone with *N*-bromosuccinimide in 85% yield by a modified method of Broquet and Bedin.[12] The shift reagent for NMR measurements, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(facam)$_3$], was commercially available from Willow Brook Laboratories, Inc.

Preparation of the Catalyst Solution. The optically active catalyst was prepared in situ by the reaction of [Rh(cycloocta-1,5-diene)Cl]$_2$ with the chiral diphosphine in a degassed solvent at ambient temperature. In a typical experiment, 24.4 mg (4.95×10^{-5} mol) of [Rh(cycloocta-1,5-diene)Cl]$_2$ and 60.0 mg (1.08×10^{-4} mol) of BPPM were dissolved in 8 mL of benzene under an argon atmosphere and stirred for 15 min. Similarly, the (−)-DIOP–rhodium catalyst was prepared from 24.4 mg (4.95×10^{-5} mol) of [Rh(cycloocta-1,5-diene)Cl]$_2$ and 53.8 mg (1.08×10^{-4} mol) of (−)-DIOP in 8 mL of benzene.

Asymmetric Hydrogenation of Ketopantoyl Lactone. In a typical run, 1.28 g (10.0 mmol) of ketopantoyl lactone was added to 8 mL of a degassed benzene solution of BPPM–rhodium complex (1.08×10^{-2} mmol, 1.08 mol%) in a autoclave under argon. After the argon atmosphere was displaced by hydrogen, the hydrogenation was carried out under an initial hydrogen pressure of 50 atm at 30 °C for 48 h with stirring. The GLC analysis of the reaction mixture revealed that the conversion of the reaction was 100%. The solvent was evaporated, and the residue was distilled under reduced pressure to afford 1.21 g (93%) of pantoyl lactone: bp 92 °C (4 mmHg); $[\alpha]^{25}_D$ −44.0° (c 2.010, H_2O). An NMR (100 MHz) measurement using Eu(facam)$_3$ showed that the purity of the enantiomer thus obtained was 86% enantiomeric excess.

The pantoyl lactone (1.21 g) thus obtained was recrystallized from *n*-hexane–benzene (3:1) to afford 854 mg (70.6%) of pure D(−)-pantoyl lactone, $[\alpha]^{25}_D$ −50.8 ± 0.1° (c 2.055, H_2O).

When the conversion of the reaction was lower than 99%, the reaction mixture was submitted to column chromatography on silica. Then, pantoyl lactone was separated from unreacted ketopantoyl lactone and used for the measurement of optical rotation.

Synthesis of Ethyl D(+)-Pantothenate. Ethyl D(+)-pantothenate was synthesized by a modified method of Güssner et al.[13] Pure

D(−)-pantoyl lactone (2.60 g, 20 mmol), obtained in the above reaction, was mixed with freshly distilled β-alanine ethyl ester (2.80 g, 24 mmol) in 20 mL of benzene and heated under reflux for 6 h. After the solvent was evaporated, the residue was submitted to column chromatography on silica. The unreacted pantoyl lactone was recovered (0.52 g, 20%) from the *n*-hexane–benzene eluate, and ethyl D(+)-pantothenate (3.80 g, 77%) was obtained from the ether eluate. Ethyl D(+)-pantothenate: colorless liquid; $[\alpha]^{18}_D$ +42.20° (*c* 2.18, absolute EtOH). Anal. Calcd for $C_{11}H_{21}O_5N$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.39; H, 8.69; N, 5.47.

The previously reported maximum rotation of this compound by Güssner et al. was $[\alpha]^{18}_D$ +36.8° (*c* 4.68, absolute EtOH). This lower value could be due to a partial racemization during distillation at high temperature.

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Registry No.—Ethyl D(+)-pantothenate, 10527-68-1; BPPM, 61478-28-2; $[Rh(cycloocta-1,5-diene)Cl]_2$, 12092-47-6; ketopantoyl lactone, 13031-04-4; D(−)-pantoyl lactone, 599-04-2; BPPM–rhodium(I) complex, 66787-44-8; ethyl β-alaninate, 924-73-2.

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Synthesis of Pomiferin, Auriculasin, and Related Compounds

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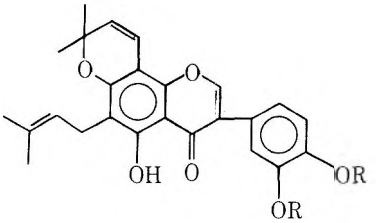
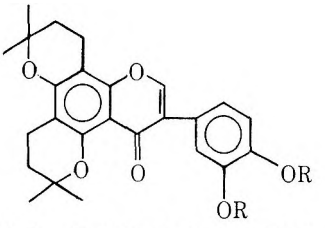
Nuclear prenylation of 3′,4′-di-*O*-methylorobol (**4**) with prenyl bromide under alkaline conditions has yielded its 7-*O*-prenyl (**8**), 6-*C*-prenyl (**12**), and 6,8-di-*C*,*C*-prenyl (**9**) derivatives. Acetylation, partial methylation, and cyclization with formic acid of **12** and **9** separately and their NMR spectra established their structures. Cyclodehydrogenation of **9** with DDQ gave di-*O*-methyl derivatives (**6** and **18**) of pomiferin and auriculasin, respectively. Pomiferin (**1**) and auriculasin (**5**) themselves were synthesized by nuclear prenylation of orobol (**19**), giving the 6-*C*-prenyl (**21**) and the 6,8-di-*C*,*C*-prenyl (**20**) derivatives. Cyclodehydrogenation of 6,8-di-*C*,*C*-prenylorobol (**20**) afforded both the isomers (**1** and **5**). Cyclodehydrogenations of **21** and **12** yielded 6″,6″-dimethylpyrano[2″,3″:7,6]orobol (**22**) and its dimethyl ether (**16**), respectively.

Pomiferin was isolated from the fruit of the osaje orange tree, *Maclura pomifera* Raf., along with osajin (Dr. D. Dreyer, Western Regional Research Laboratory, Berkeley, states that both osajin and pomiferin are present in almost equal amounts in the fruit), and assigned the structure of 5,3′4′-trihydroxy-6-*C*-prenyl-6″,6″-dimethylpyrano[2″,3″:7,8]isoflavone (**1**) by Wolfrom et al.[1,2] using mostly the chemical

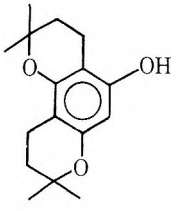


1, R = H (pomiferin)
6, R = Me

methods of degradation and color reactions. The only synthetic evidence given so far has been the synthesis of its derivative, dihydroisopomiferin (**2**), formed in two stages. Wolfrom et al.[2] synthesized dihydroisopomiferin (**2**) from bis(dihydropyrano)phloroglucinol (**3**) by Hoesch reaction with 3,4-dimethoxybenzyl cyanide, followed successively by isoflavone condensation with ethyl formate in the presence of sodium and demethylation with HI, whereas Raizada et al.[3]

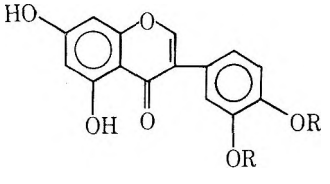


2, R = H (dihydroisopomiferin)
11, R = Me



3

synthesized **2** from 3′,4′-di-*O*-methylorobol (**4**) by reacting it with prenyl bromide in the presence of zinc chloride and benzene. Auriculasin recently isolated from *Milletia auriculata* (Leguminosae) has been assigned the isomeric structure **5** by Minhaj et al.[4] on the basis of its special data and those on its trimethyl ether and triacetate. We now report the synthesis



4, R = Me
19, R = H

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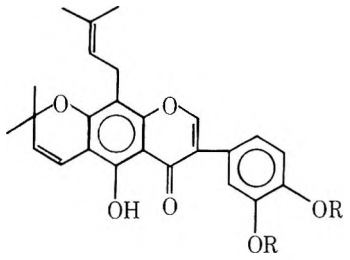
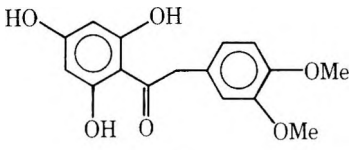


5, R = H (auriculasin)
18, R = Me

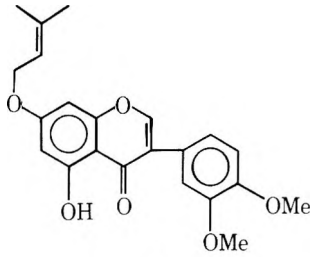
of both the natural compounds **1** and **5** and their 3′,4′-dimethyl ethers **6** and **18**, respectively.

The synthesis of 3′,4′-dimethyl ethers (**6** and **18**) starts with the preparation of orobol 3′,4′-dimethyl ether (**4**) which has been accomplished by Bass's general method of isoflavone synthesis.[5] It involves heating 2,4,6-trihydroxyphenyl 3,4-dimethoxybenzyl ketone (**7**) with methanesulfonyl chloride



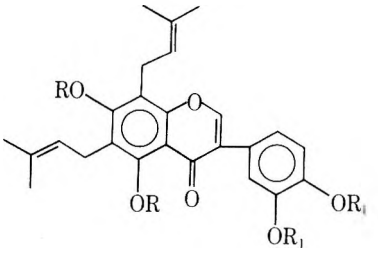
7

in the presence of boron trifluoride etherate and DMF. Orobol 3′,4′-dimethyl ether (**4**), when refluxed with prenyl bromide in the presence of K_2CO_3 and acetone, yielded its 7-prenyl ether (**8**) as shown by its NMR spectrum.[6] Thus, it showed



8

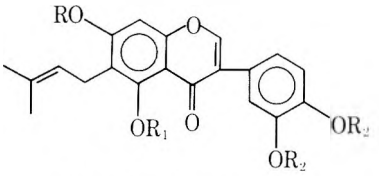
besides the signals of the starting compound, a doublet of OCH_2 at 4.53, two singlets of an olefinic *gem*-dimethyl group at 1.75 and 1.82, and a triplet of one methine hydrogen at 5.42 ppm. On the other hand, when orobol dimethyl ether (**4**) was reacted with prenyl bromide in the presence of methanolic sodium methoxide, a mixture of three compounds was isolated. The product formed in the largest yield was identified as the 6,8-di-*C*,*C*-prenyl derivative (**9**). Thus, it formed a diacetate (**10**) (NMR 2.23, 2.41 ppm (2 s)). Further, both the hydroxy compound (**9**) and its diacetate (**10**) showed no signal



9, R = H; R_1 = Me
10, R = Ac; R_1 = Me
20, R = R_1 = H

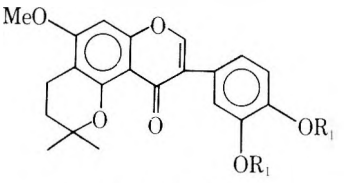
for aromatic protons of the condensed benzene ring but instead showed signals of two *C*-prenyl groups. The structure of di-*C*,*C*-prenylisoflavone (**9**) was finally supported by treatment with HCOOH when dihydroisopomiferin dimethyl ether (**11**) was obtained in agreement with the earlier description.[2,3] Further NMR spectra showed the expected two triplets of four protons each at 2.58 and 2.78 ppm.

The second product of the above prenylation reaction was identified as the 6-*C*-prenyl derivative (**12**) on the basis of formation of its diacetate (**13**) (NMR 2.33, 2.40 ppm (2 s)) and a monomethyl ether (**14**) (NMR 3.87, 3.89 ppm (2 s, three methoxy groups)). Further the NMR spectra of all these



12, R = R_1 = H; R_2 = Me
13, R = R_1 = Ac; R_2 = Me
14, R = R_2 = Me; R_1 = H
21, R = R_1 = R_2 = H

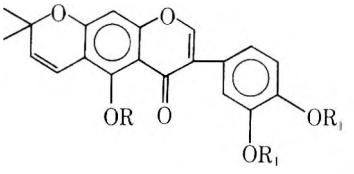
compounds, viz. **12**, **13** and **14**, showed the presence of only one *C*-prenyl unit and one aromatic proton of the ring A (NMR 6.49, 6.87, and 6.36 ppm (s), respectively). The orientation of the *C*-prenyl unit in the 6 position was established by acid cyclization of **14** to give the dihydropyrano derivative (**15**)



15, R_1 = Me

which showed a negative ferric reaction and two triplets at 1.81 and 2.67 ppm in its NMR spectrum. Had this been the 8-*C*-prenyl isomer, it would not have yielded the 2,2-dimethyl dihydropyrano derivative. The third minor product of the above C-prenylation reaction was identified as 7-prenyloxy-3′,4′-dimethoxy-5-hydroxyisoflavone (**8**).

The above *C*-prenyl derivatives **9** and **12** were separately cyclodehydrogenated with DDQ. The latter (**12**) gave 2,2-dimethylpyrano derivative having the structure 5-hydroxy-3′,4′-dimethoxy-6″,6″-dimethylpyrano[2″,3″:7,6]isoflavone (**16**). In accordance with this structure, it formed a monoacetate (**17**: NMR 2.30 ppm (1 s, 3 H)) and both compounds (**16** and **17**) showed two characteristic doublets at about 5.5



16, R = H; R_1 = Me
17, R = Ac; R_1 = Me
22, R = R_1 = H
23, R = R_1 = Ac

and 6.6 ppm of the pyran ring and a deshielded aromatic hydrogen as a singlet at 6.26 ppm. But 6,8-di-*C*,*C*-prenyl-3′,4′-di-*O*-methylorobol (**9**) on cyclodehydrogenation with DDQ gave two products. The major product was found identical with pomiferin dimethyl ether (**6**). The angular pyrano structure was proved by its mass spectrum which showed a mass ion peak at 392 having the *m/e* value of $(M - 56)^+$ characteristic of an *o*-prenylphenol.[7] The minor product was identified as a linear pyrano isomer, viz., auriculasin dimethyl ether (**18**), by its mass spectrum showing the mass ion peak at 393 having an *m/e* value of $(M - 55)^+$.

In order to synthesise pomiferin (**1**) and auriculasin (**5**) themselves, orobol (**19**) prepared from di-*O*-methylorobol (**4**) by heating with HI was subjected to nuclear prenylation as

in an earlier case. Here, a mixture of two products was obtained. The major product was identified as 6,8-di-*C*,*C*-prenylorobol (**20**) by its NMR spectrum. The second product was characterized as 6-*C*-prenylorobol (**21**) because it gave a trimethyl ether (**14**) identical with the one described above.

Cyclodehydrogenation of **21** with DDQ provided 5,3′,4′-trihydroxy-6″,6″-dimethylpyrano[2″,3″:7,6]isoflavone (**22**). Its structure was supported by the formation of its triacetate (**23**) and NMR spectra of both **22** and **23**.

When 6,8-di-*C*,*C*-prenylorobol (**20**) was refluxed with DDQ in benzene, a mixture of two 2,2-dimethylpyrano derivatives (**1** and **5**) was obtained. The structures of both of these derivatives were established by preparing their dimethyl ethers with 2 mol of dimethyl sulfate. The dimethyl ether of the major chromene (**1**) was found identical with **6** and that of the minor chromene identical with **18**. Further, the compound **1** was found identical in all respects with the natural sample of pomiferin,[1] and the compound **5** with auriculasin. Hence the constitutions of pomiferin and auriculasin are established by their total syntheses.

Experimental Section

General. All melting points are uncorrected. Unless stated otherwise, UV data were taken in MeOH; figures before parentheses represent λ_{max} in nanometers and those written in parentheses log ϵ values; IR spectra were recorded in Nujol mull; NMR spectra were run on a 80 MHz machine in $CDCl_3$ with Me_4Si as an internal standard; chemical shifts are expressed in parts per million (ppm) downfield from Me_4Si; R_f values refer to TLC carried out on plates coated with silica gel "G", and these plates were either developed with 10% aqueous sulfuric acid or with 3% alcoholic ferric chloride; column chromatography was done on silica gel; one of the following solvent systems was used for TLC: (A) benzene, (B) benzene–ethyl acetate (9:1), (C) benzene–ethyl acetate (17:3), and (D) toluene–ethyl formate–formic acid (5:4:1).

3′,4′-Di-*o*-methylorobol (4). To a well-stirred and ice-cooled solution of 2,4,6-trihydroxyphenyl 3,4-dimethyloxybenzyl ketone (**7**) (4 g) in DMF (35 mL) was added boron trifluoride etherate (7 mL) dropwise during the course of 30 min. The temperature was raised to 60 °C and then methanesulfonyl chloride (4.5 mL) in DMF (10 mL) was added in one lot. The resulting mixture was heated for 90 min on a water bath, cooled, and then added to ice-cold water (500 mL). The solid was collected and crystallized from a pyridine–water mixture when **4** separated as colorless crystals (3.6 g): mp 253–254 °C; R_f 0.46 (solvent B); intense green ferric reaction; IR 3380, 1640 cm^{-1}; UV 262 (3.97).

Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.9; H, 5.0. Found: C, 65.0; H, 5.1.

5-Hydroxy-7-prenyloxy-3′,4′-dimethoxyisoflavone (8). A solution of the isoflavone **4** (100 mg) in acetone (20 mL) was refluxed with prenyl bromide (0.05 mL) and K_2CO_3 (1 g) for 3 h. Acetone was distilled off and water added to the residue. The solid thus obtained crystallized from MeOH yielding **8** as colorless needles (90 mg): mp 127–128 °C; R_f 0.55 (solvent A); green ferric reaction; IR 3450 and 1650 cm^{-1}; UV λ_{max} 255 (4.14); NMR 1.75, 1.82 (6 H, 2 s, $(CH_3)_2C$=), 3.90 (6 H, s, $2CH_3O$), 4.53 (2 H, d, J = 7 Hz, OCH_2), 5.42 (1 H, t, J = 6.5 Hz, $ArCH_2CH$=), 6.35, 6.98 (2 H, 2 d, J = 3 Hz, **H**-6 and -8, respectively), 6.82–7.02 (3 H, m, H-2′, -5′, and -6′), and 7.80 (1 H, s, H-2).

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.1; H, 5.9. Found: C, 68.9; H, 6.0.

Nuclear Prenylation of 3′,4′-Di-*O*-methylorobol (4). To a solution of **4** (4 g) in anhydrous MeOH (150 mL) was added a methanolic solution of sodium methoxide (5 g of Na/60 mL of MeOH). The mixture was cooled, treated with prenyl bromide (6 mL) in one lot, and refluxed for 4 h. After removal of the solvent, the mixture was treated with ice and acidified in cold dilute HCl. The solid product was examined by TLC using the solvent system B which showed the presence of four main compounds. It was therefore subjected to column chromatography and the column eluted successively with (1) benzene–light petroleum (1:9), (2) benzene–light petroleum (1:4), (3) benzene–light petroleum (1:1), and (4) benzene–ethyl acetate (9:1) when four fractions, A–D, were obtained.

Fraction A crystallized from a benzene–light petroleum mixture to yield **6,8-di-*C*,*C*-prenyl-3′,4′-dimethoxy-5,7-dihydroxyisoflavone (9)** as colorless crystals (0.73 g): mp 124–125 °C; R_f 0.65 (solvent B); green ferric reaction; IR 3340, 1630, 1680 cm^{-1}; UV λ_{max} 210, 240 (3.80 and 4.10, respectively); 90 MHz NMR 1.77, 1.85 (12 H, 2 s, $2(CH_3)_2C$=), 3.48 (4 H, d, J = 7 Hz, $2ArCH_2CH$=), 3.90 (6 H, s, $2CH_3O$), 5.10–5.40 (2 H, m, $2ArCH_2CH$=), 6.90–7.30 (3 H, m, H-2′, -5′, and -6′), and 7.92 (1 H, s, H-2).

Anal. Calcd for $C_{27}H_{30}O_6$: C, 72.0; H, 6.7. Found: C, 72.0; H, 7.1.

The diacetate (**10**) prepared from **9** by the acetic anhydride–pyridine method crystallized from a benzene–light petroleum mixture as colorless flakes: mp 114–115 °C; R_f 0.35 (solvent B); IR 1750 and 1640 cm^{-1}; UV λ_{max} 206 and 254 (4.02 and 4.32, respectively); NMR 1.72, 1.84 (12 H, 2 s, $2(CH_3)_2C$=), 2.23, 2.41 (6 H, 2 s, $2CH_3CO_2$), 3.28, 3.47 (4 H, 2 d, J = 7 Hz, $2ArCH_2$), 3.87, 3.94 (6 H, 2 s, CH_3O), 4.80–5.20 (2 H, m, 2XC**H**=), 6.80–7.12 (3 H, m, H-2′, -5′, and -6′), and 7.87 (1 H, s, H-2).

Anal. Calcd for $C_{31}H_{34}O_8$: C, 69.7; H, 6.4. Found: C, 70.0; H, 6.8.

Fraction B was crystallized from MeOH when **5-hydroxy-7-prenyloxy-3′,4′-dimethoxyisoflavone (8)** formed colorless crystals (0.15 g); mp and mmp with the sample prepared above 127–128 °C.

Fraction C was crystallized from ethyl acetate–light petroleum mixture to give 6-***C*-prenyl-3′,4′-dimethoxy-5,7-dihydroxyisoflavone (**12**) as colorless crystals (0.25 g): mp 209–210 °C; R_f 0.58 (solvent A); IR 1620 and 3300 cm^{-1}; UV λ_{max} 218 and 254 (4.18 and 4.09, respectively); NMR 1.65, 1.78 (6 H, 2 s, $(CH_3)_2C$=), 3.40 (2 H, d, J = 7 Hz, $ArCH_2CH$=), 3.69 (6 H, s, $2CH_3O$), 5.06–5.32 (1 H, m, C**H**=), 6.49 (1 H, s, H-8), 6.85–7.26 (3 H, m, H-2′, -5′, and -6′), and 7.97 (1 H, s, H-2).

Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.1; H, 5.8. Found: C, 69.2; H, 6.1.

The diacetate (**13**) prepared from **12** by the acetic anhydride–pyridine method crystallized from benzene as colorless needles: mp 184–185 °C; R_f 0.45 (solvent C); IR 1630 and 1745 cm^{-1}; NMR 1.64, 1.80 (6 H, 2 s, $(CH_3)_2C$=), 2.33, 2.40 (6 H, 2 s, $2CH_3CO_2$), 3.25 (2 H, d, J = 7 Hz, $ArCH_2$), 3.88 (6 H, s, $2CH_3O$), 4.82–5.12 (1 H, m, ArC**H**=), 6.87 (1 H, s, H-8), 6.90–7.20 (3 H, m, H-2′, -5′, and -6′), and 7.82 (1 H, s, H-2).

Anal. Calcd for $C_{26}H_{26}O_8$: C, 66.9; H, 5.6. Found: C, 66.8; H, 5.9.

Fraction D on crystallization from an acetone–MeOH mixture afforded the starting material **4**, 2.3 g.

Dihydroisopomiferin 3′,4′-Dimethyl Ether (11). The isoflavone **9** (200 mg) was heated with formic acid (25 mL) on a boiling water bath for 2 h and then left overnight at room temperature. The product was poured into ice-cold water (250 mL) and the solid was collected and subjected to column chromatography. Elution with a benzene–light petroleum mixture (1:4) gave **11** which crystallized from MeOH–acetone mixture as colorless needles: mp 213–214 °C (lit.[2] mp 207.5–209 °C); R_f 0.50 (solvent B); IR 1635 cm^{-1}; NMR 1.34, 1.37 (12 H, 2 s, $(CH_3)_2C$<), 1.78, 1.87 (4 H, 2 t, J = 6 Hz, $2ArCH_2CH_2$), 2.58, 2.78 (4 H, 2 t, J = 6 Hz, $2ArCH_2$), 3.81, 3.84 (6 H, 2 s, $2CH_3O$), 6.80–7.20 (3 H, m, H-2′, -5′, and -6′), and 7.72 (1 H, s, H-2).

Anal. Calcd for $C_{27}H_{30}O_6$: C, 72.0; H, 6.7. Found: C, 72.0; H, 6.9.

6-*C*-Prenyl-5-hydroxy-7,3′,4′-trimethoxyisoflavone (14). An acetone solution of the isoflavone **12** (200 mg) was refluxed with dimethyl sulfate (0.14 mL) in the presence of ignited K_2CO_3 (1 g) for 3 h. The solvent was removed and the residue treated with water (100 mL). The solid was collected and crystallized from MeOH when **14** separated as colorless plates (160 mg): mp 134–135 °C; R_f 0.60 (solvent B); green ferric reaction; IR 3250 and 1620 cm^{-1}; UV 216 and 280 (3.83 and 4.05, respectively); NMR 1.65, 1.78 (6 H, 2 s, $(CH_3)_2C$=), 3.35 (2 H, d, J = 7 Hz, $ArCH_2CH$=), 3.87, 3.89 (9 H, 2 s, $3CH_3O$), 5.19 (1 H, t, J = 6.5 Hz, $ArCH_2CH$=), 6.36 (1 H, s, H-8), 6.88–7.01 (3 H, m, H-2′, -5′, and -6′), and 7.81 (1 H, s, H-2).

Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.7; H, 6.1. Found: C, 70.0; H, 5.9.

6″,6″-Dimethyl-7,3′,4′-trimethoxy-4″,5″-dihydropyrano[2″,3″:5,6]isoflavone (15). The isoflavone **14** (100 mg) was heated with formic acid (10 mL) for 3 h. The product crystallized from a benzene–light petroleum mixture to afford **15** as colorless crystals (60 mg): mp 185–86 °C; R_f 0.36 (solvent B); IR 1575 and 1640 cm^{-1}; NMR 1.40 (6 H, s, $(CH_3)_2C$<), 1.81, 2.65 (4 H, 2 t, J = 7 Hz, $ArCH_2CH_2$), 3.88 (9 H, s, $3CH_3O$), 6.37 (1 H, s, H-8), 6.65–7.27 (3 H, m, H-2′, -5′, and -6′), and 7.72 (1 H, s, H-2).

Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.7; H, 6.1. Found: C, 70.0; H, 5.8.

6″,6″-Dimethyl-5-hydroxy-3′,4′-dimethoxypyrano[2″,3″:7,6]isoflavone (16). To a solution of the isoflavone **12** (150 mg) in freshly distilled dry benzene (30 mL) was added DDQ (90 mg) and the resulting mixture refluxed for 2 h on a boiling water bath when colorless hydroquinone separated out. It was filtered while hot and the filtrate evaporated to dryness. The residue on column chromatography and elution with benzene–light petroleum mixture (1:3) yielded **16** (80 mg) as light yellow needles: mp 136 °C; light green ferric reaction; R_f 0.55 (solvent B); IR 1620 cm^{-1}; UV 208 and 276 (4.03 and 4.07, respectively); 60 MHz NMR 1.42, 1.66 (6 H, 2 s, $(CH_3)_2C$<), 3.86 (6 H, s, $2CH_3O$), 5.53, 6.63 (2 H, 2 d, J = 10 Hz, ArCH=C**H**), 6.36 (1 H, s, **H**-8), 6.92–7.22 (3 H, m, H-2′, -5′, and -6′), and 7.84 (1 H, s, **H**-2).

Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.4; H, 5.3. Found: C, 69.6; H, 5.4.

The monoacetate of **17** prepared from **16** by the acetic anhydride–sodium acetate method crystallized from MeOH as white flakes: mp 185–186 °C; R_f 0.45 (solvent B); 220 MHz NMR 1.40, 1.45 (6 H, 2 s, $(CH_3)_2C<$), 2.30 (3 H, s, CH_3CO_2), 3.80 (6 H, s, $2CH_3O$), 5.55, 6.76 (2 H, 2 d, J = 10 Hz, ArCH=CH), 6.40 (1 H, s, H-8), 6.76–7.00 (3 H, m, H-2′, -5′, and -6′), and 7.74 (1 H, s, H-2).

Anal. Calcd for $C_{24}H_{22}O_7$: C, 68.2; H, 5.3. Found: C, 68.2; H, 5.2.

Pomiferin 3′,4′-Dimethyl Ether (6) and Auriculasin 3′,4′-Dimethyl Ether (18). A solution of the isoflavone **9** (300 mg) and DDQ (150 mg) in benzene (25 mL) was refluxed for 30 min. The product on column chromatography and elution with benzene–light petroleum mixture (1:4) gave a solid which again proved to be a mixture by TLC. This on fractional crystallization from ethyl acetate–light petroleum mixture gave a solid (mother liquor A) which recrystallized from MeOH to afford **6** as light yellow neeldes (120 mg): mp 130–131 °C (lit.[2] mp 132 °C); R_f 0.70 (solvent B); green ferric reaction; IR 3360, 1630 cm^{-1}; UV 224 and 278 (4.18 and 4.28, respectively); NMR 1.50 (6 H, s, $(CH_3)_2C<$), 1.70, 1.82 (6 H, 2 s, $(CH_3)_2C=$), 3.38 (2 H, d, J = 8 Hz, $ArCH_2CH=$), 3.90 (6 H, s, $2CH_3O$), 5.23 (1 H, t, J = 7 Hz, $ArCH_2CH=$), 5.53, 6.66 (2 H, 2 d, J = 10 Hz, ArCH=CH), 6.87–7.15 (3 H, m, H-2′, -5′, and -6′), and 7.82 (1 H, s, H-2); MS 448 (M^+), 433 395, 392 $(M - 56)^+$, 377, 215, 181, 152, 97.

Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.3; H, 6.3. Found: C, 72.0; H, 6.6.

The mother liquor A after evaporation yielded a viscous mass which after crystallization twice from MeOH gave **18** as shining yellow needles (40 mg): mp 98–99 °C; R_f 0.62 (solvent B); green ferric reaction; IR 1645 cm^{-1}, UV 218 and 274 (4.25 and 4.34, respectively); 100 MHz NMR 1.44, 1.48 (6 H, 2 s, $(CH_3)_2C<$), 1.68, 1.80 (6 H, 2 s, $(CH_3)_2C=$), 3.36 (2 H, d, J = 7.5 Hz, $ArCH_2CH=$), 3.90 (6 H, s, $2CH_3O$), 5.16–5.32 (1 H, m, $ArCH_2CH=$), 5.56, 6.70 (2 H, 2 d, J = 10 Hz, ArCH=CH), 6.83–7.18 (3 H, m, H-2′, -5′, and -6′), and 7.84 (1 H, s, H-2); MS 448 (M^+), 433, 405, 393 $(M - 55)^+$, 377, 365, 351, 338, 215, 181, 162, 118, 91.

Anal. Calcd for $C_{27}H_{28}O_6$: C, 72.3; H, 6.3. Found: C, 72.0; H, 6.1.

Orobol (19) was prepared by demethylation of **4** with HI and identified by converting it into its acetate which crystallized from MeOH as white flakes: mp 160–161 °C (lit.[8] mp 163 °C); R_f 0.54 (solvent B); NMR 2.26, 2.30, and 2.38 (12 H, 3 s, $4CH_3CO_2$), 6.87 (1 H, d, J = 3 Hz, H-6), 7.14 (1 H, d, J = 3 Hz, H-8), 7.18–7.38 (3 H, m, H-2′, -5′, and -6′), and 7.92 (1 H, s, H-2).

Nuclear Prenylation of Orobol (19). To a solution of orobol **19** (2 g) in anhydrous MeOH (100 mL) was added a methanolic solution of sodium methoxide (2.1 g of Na/25 mL of MeOH). This mixture was cooled and treated with prenyl bromide (2.6 mL) in one lot and then refluxed for 2 h. The product on column chromatography and successive elution with (1) benzene–light petroleum (1:4), (2) benzene alone, and (3) ethyl acetate–benzene (1:9) gave three fractions A to C.

Fraction A crystallized from a benzene–light petroleum mixture to yield **5,7,3′,4′-tetrahydroxy-6,8-di-*C*,*C*-prenylisoflavone (20)** as colorless crystals (120 mg): mp 156–157 °C; R_f 0.46 (solvent D); green ferric reaction; NMR 1.48, 1.75, 1.82 (12 H, 3 s, $2(CH_3)_2C=$), 3.25–3.50 (4 H, m, $2ArCH_2CH=$), 5.00–5.37 (2 H, m, $2ArCH_2CH=$), 6.58–7.06 (3 H, m, H-2′, -5′, and -6′), and 8.01 (1 H, s, H-2).

Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.1; H, 6.2. Found: C, 70.8; H, 6.0.

Fraction B on crystallization from benzene–light petroleum mixture afforded **6-*C*-prenylorobol (21)** as white flakes (90 mg): mp 243–244 °C; R_f 0.30 (solvent D); IR 1655, 1620 cm^{-1}; NMR (CD_3COCD_3) 1.65, 1.78 (6 H, 2 s, $(CH_3)_2C=$), 3.42 (2 H, d, J = 7 Hz, $ArCH_2CH=$), 5.08–5.32 (1 H, m, $ArCH_2CH=$), 6.33 (1 H, s, H-8), 6.75–7.21 (3 H, m, H-2′, -5′, and -6′), and 7.95 (1 H, s, H-2).

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.8; H, 5.2. Found: C, 67.5; H, 5.3.

An acetone solution of **21** (60 mg) was treated with dimethyl sulfate (0.035 mL) and anhydrous K_2CO_3 (1 g) for 4 h. The product crystallized from MeOH yielding **14** as colorless needles (40 mg); mp and mmp with the synthetic sample prepared above 134–135 °C.

Fraction C proved to be the starting compound.

6″,6″,6‴,6‴-Tetramethyl-4″,5″,4‴,5‴-tetrahydro-3′,4′-dihydroxybis(pyrano[2″,3″:7,8::2‴,3‴:5,6]isoflavone[dihydroisopomiferin]) (2). The isoflavone **20** (100 mg) was heated with formic acid (15 mL) for 2 h. The product crystallized from benzene–light petroleum mixture yielding **2** as colorless crystals (50 mg): mp 262–263 °C (lit.[2] mp 264.5–265 °C); R_f 0.61 (solvent C); NMR 1.25, 1.35 (12 H, 2 s, $2(CH_3)_2C<$), 1.62–1.85 (4 H, m, $2ArCH_2CH_2$), 2.58–2.86 (4 H, m, $2ArCH_2CH$), 6.81–7.20 (3 H, m, H-2′, -5′, and -6′), and 7.82 (1 H, s, H-2).

Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.1; H, 6.2. Found: C, 70.9; H, 6.0.

6″,6″-Dimethyl-5,3′,4′-trihydroxypyrano[2″,3″:7,6]isoflavone (22). To a solution of **21** (100 mg) in benzene (30 mL) was added DDQ (50 mg) and the resulting solution refluxed for 30 min. The product on column chromatography and elution with benzene–light petroleum (1:1) yielded **22** as light yellow needles (20 mg): mp 166–167 °C; R_f 0.66 (solvent C); light brown ferric reaction; NMR 1.48 (6 H, s, $(CH_3)_2C<$), 5.58, 6.61 (2 H, 2d, J = 10 Hz, ArCH=CH), 6.25 (1 H, s, H-8), 7.25–7.53 (3 H, m, H-2′, -5′, and -6′), and 7.81 (1 H, s, H-2).

Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.2; H, 4.5. Found: C, 68.1; H, 4.6.

The triacetate (**23**) prepared from **22** by the acetic anhydride–pyridine method crystallized from MeOH as colorless crystals: mp 151–152 °C; R_f 0.40 (solvent D); NMR 1.47 (6 H, s, $(CH_3)_2C<$), 2.42 (9 H, s, $3CH_3CO_2$), 5.59, 6.68 (2 H, 2 d, J = 10 Hz, ArCH=CH), 6.27 (1 H, s, H-8), 6.85–7.21 (3 H, m, H-2′, -5′, and -6′), and 7.67 (1 H, s, H-2).

Anal. Calcd for $C_{26}H_{22}O_9$: C, 61.9; H, 4.6. Found: C, 61.4; H, 4.8.

Pomiferin (1) and Auriculasin (5). A solution of **20** (150 mg) and DDQ (70 mg) in dry benzene (30 mL) was refluxed for 10 min. The product on column chromatogrphy and elution with benzene–light petroleum mixture (1:9) gave a solid which again proved to be a mixture on TLC. This on fractional crystallization from ethyl acetate–light petroleum mixture yielded a solid (mother liquor A) which when crystallized from MeOH afforded pomiferin (**1**) as pale yellow crystals (50 mg): mp and mmp with the natural sample 198–199 °C (lit.[2] mp 200.5 °C); R_f 0.58 (solvent A); green ferric reaction; UV 280 and 310 (4.40 and 4.51, respectively); NMR 1.50 (6 H, s, $(CH_3)_2C$), 1.70, 1.83 (6 H, 2 s, $(CH_3)_2C=$), 3.38 (2 H, d, J = 8 Hz, $ArCH_2CH=$), 5.25 (1 H, t, J = 6.5 Hz, $ArCH_2CH=$), 5.62, 6.72 (2 H, 2 d, J = 10 Hz, ArCH=CH), 6.93–7.26 (3 H, m, H-2′, -5′, and -6′), and 7.90 (1 H, s, H-2). The IR spectrum was superimposable on that of natural sample.

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.4; H, 5.7. Found: C, 71.3; H, 5.5.

The identity of the synthetic pomiferin was further established by converting it (50 mg) into its dimethyl ether (**6**) by refluxing with dimethyl sulfate (0.025 mL), dry K_2CO_3 (1 g), and acetone (30 mL) for 2 h; mp and mmp with the sample described above were 132 °C.

The mother liquor A on evaporation yielded a semisolid mass which crystallized from benzene yielding auriculasin (**5**) as pale yellow needles (20 mg): mp 174–176 °C; green ferric reaction; R_f 0.55 (solvent A); UV λ_{max} 240, 310 (4.40 and 4.52); NMR (with 90 MHz machine) 1.86 (6 H, s, $(CH_3)_2C<$), 1.90 (6 H, s, $(CH_3)_2C=$), 3.52 (2 H, d, J = 7 Hz, $ArCH_2CH=$), 5.20–5.31 (1 H, m, $ArCH_2CH=$), 5.45, 6.41 (2 H, 2 d, J = 10 Hz, ArCH=CH), 6.99–7.37 (3 H, m, H-2′, -5′, -6′), and 7.96 (1 H, s, H-2). These properties agree closely with those described for natural compound.[4]

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.4; H, 5.7. Found: C, 71.3; H, 5.4.

Its identity was established by converting it (50 mg) into its dimethyl ether (**18**) by refluxing with dimethyl sulfate (0.025 mL), K_2CO_3 (1 g), and acetone (10 ml) for 2 h; mp and mmp with the sample prepared above were 98–99 °C.

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Registry No.—**1**, 572-03-2; **2**, 66777-58-0; **4**, 53084-11-0; **5**, 60297-37-2; **6**, 5456-71-3; **7**, 53084-06-3; **8**, 66777-59-1; **9**, 66777-60-4; **10**, 66777-61-5; **11**, 66777-62-6; **12**, 66777-63-7; **13**, 66777-64-8; **14**, 66777-65-9; **15**, 66777-66-0; **16**, 66777-67-1; **17**, 66777-68-2; **18**, 66777-69-3; **19**, 480-23-9; **20**, 66777-70-6; **21**, 66777-71-7; **22**, 66777-72-8; **23**, 66777-73-9; methanesulfonyl chloride, 124-63-0; prenyl bromide, 870-63-3.

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Prostaglandins and Congeners. 19.[1] Vinylstannanes: Useful Organometallic Reagents for the Synthesis of Prostaglandins and Prostaglandin Intermediates

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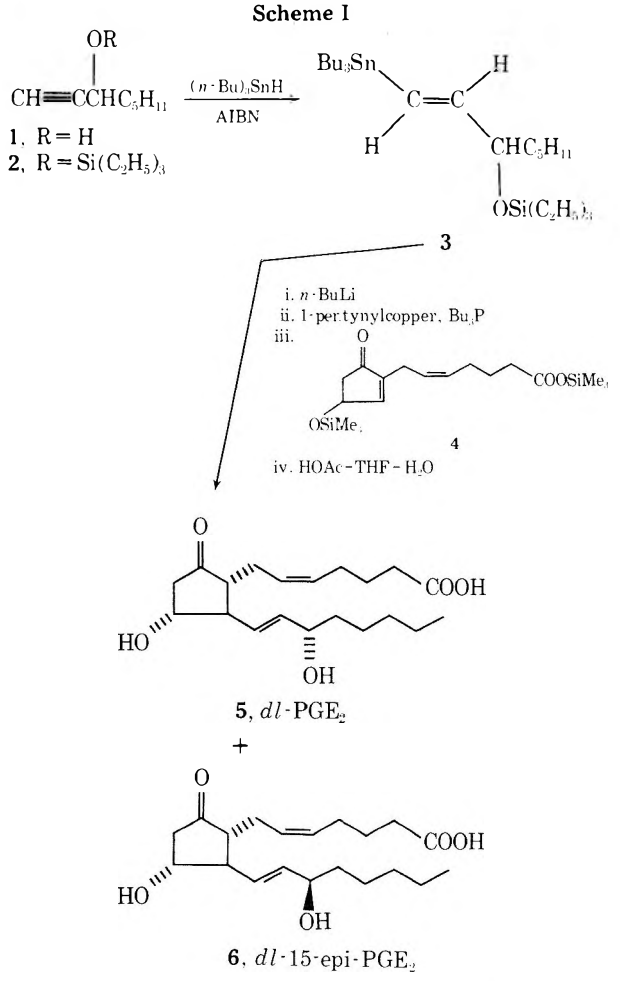
dl-PGE_2 and certain 15-deoxy-16-hydroxyprostaglandins were prepared by the conjugate addition to cyclopentenones of the mixed cuprate derived from the appropriately functionalized 1-alkenylstannanes. The preparation, *E*/*Z* ratio, and isomerization of (*E*)- and (*Z*)-1-(tri-*n*-butylstannyl)-1-alkenes from the corresponding 1-alkynes are discussed. In addition, the usefulness of (*E*)-1-alkenylstannyl reagent in providing a facile preparation of the corresponding (*E*)-1-iodo- or (*E*)-1-bromo-1-alkene is described.

Recent reports from these laboratories[2] and elsewhere[3] have described useful procedures for the synthesis of prostaglandins based upon the conjugate addition to cyclopentenones of (*E*)-1-alkenyl ligands of lithiocuprate derived from (*E*)-1-iodo-1-alkenes. We now report our efforts in utilizing the facile vinylstannyl cleavage[4,5] of readily available vinylstannane derivatives to generate the appropriately functionalized (*E*)-1-lithio-1-alkenyl reagents necessary for prostaglandin synthesis.

Treatment of 1-octyn-3-ol (**1**) with chlorotriethylsilane and imidazole in DMF[6] provided the silyl ether **2**, which upon treatment[7] with tri-*n*-butylstannane (TBS-H) in the presence of azobis(isobutyronitrile) (AIBN) was converted to (*E*)-1-(tri-*n*-butylstannyl)-3-(triethylsilyloxy)-1-octene (**3**) in 87% yield after distillation (Scheme I). None of the corresponding *Z* isomer of vinylstannane **3** was detectable in the ^{13}C NMR spectrum. We find it noteworthy that in situations wherein a trityloxy group is present in the molecule, no addition of TBS-H to an acetylene is noted.

Scheme I



1, R = H
2, R = $Si(C_2H_5)_3$

Lithiation of vinylstannane **3** with 1 equiv of *n*-BuLi at −50 °C for 1 h, followed by addition of 1-pentynylcopper solubilized in tri-*n*-butylphosphine[8] and treatment of the resulting asymmetric cuprate with the trimethylsilyloxy protected cyclopentenone **4**[9] provided, after deblocking and dry-column chromatography, a 42% yield of *dl*-PGE_2 (**5**) and *dl*-15-epi-PGE_2 (**6**) in a ratio of ca. 40:60.[10,11]

This facile preparation of vinylstannanes was also extended to the β-chain precursors for 15-deoxy-16-hydroxyprostaglandins[2d,12,13] as illustrated in Scheme II. Hydrostannation of 4-methyl-4-(trimethylsilyloxy)-1-octyne[14] (**7**) with 1 equiv of TBS-H yielded (90%) 1-(tri-*n*-butylstannyl)-4-methyl-4-(trimethylsilyloxy)-1-octene (**8**) as an *E*/*Z* (**8a**/**8b**) mixture in the ratio of 10:1. The presence of the *Z* isomer **8b** was clear from the ^{13}C NMR spectrum; the signals due to carbons 1, 2, 3, and 1′ had minor side peaks shifted ±0.5–1.5 ppm attributable to the *Z* isomer. We have observed very similar ^{13}C NMR patterns in other functionalized vinylstannanes, although no separation was observed by TLC or GLC.

Vinylstannane **8** was lithiated with 1 equiv of *n*-BuLi at −35 °C for 2 h and converted to the mixed cuprate, which was conjugatively added to the bis(trimethylsilyloxy)cyclopentenone **9**[15] in the manner described above to furnish all racemic 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 (**10**) and all racemic 13-*cis*-15-deoxy-16-hydroxy-16-methylprostaglandin E_1 (**11**) in an overall 60% yield. The ratio of **10**/**11** was 12:1, approximately reflecting the original *E*/*Z* ratio of starting vinylstannane (**8a**/**8b**). The less polar 13-*cis* congener **11** was identified by comparison of the ^{13}C NMR spectrum of **11** with the spectrum of authentic 13-*cis*-15-deoxy-16-hydroxy-16-methylprostaglandin E_2.[16] The two 16-epimers of both **10** and **11** were not separable by TLC and HPLC, although the ^{13}C NMR spectrum clearly indicated the presence of two epimers in each instance.

Lithium–tin exchange of vinylstannane **8** was a slower process than that for the allylic counterpart **3**; under the conditions adequate for lithiation of **3** (1 equiv of *n*-BuLi, −50 °C, 1 h), **8** was only partially lithiated. We now routinely accomplish the lithium–tin exchange with 1 equiv of *n*-BuLi at −35 °C for 2 h in THF. We wish to point out that at this temperature, vinyl–tin cleavage is extremely slow in ether.[17]

In an effort to prepare the β-chain precursor **13b** for the synthesis of a 16,16-dimethylprostaglandin, trimethylsilyloxyoctyne[18] **12** was treated with TBS-H and AIBN. The product obtained gave a complex ^1H NMR spectrum, which upon careful inspection implied a 3:2 mixture of (*Z*)- and

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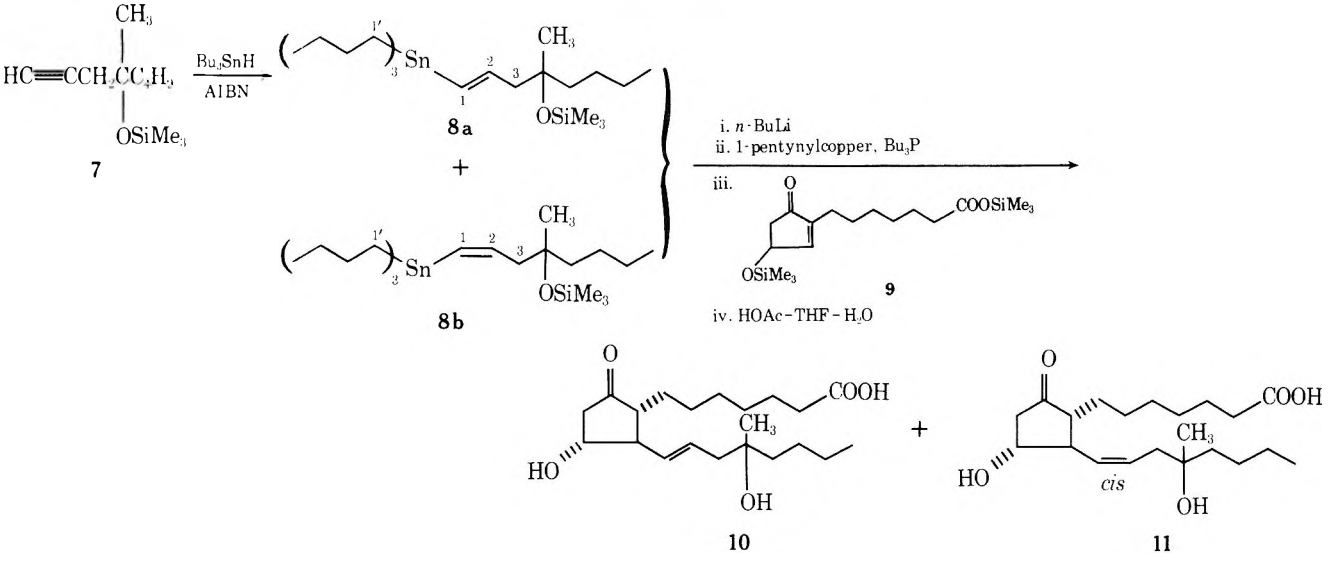
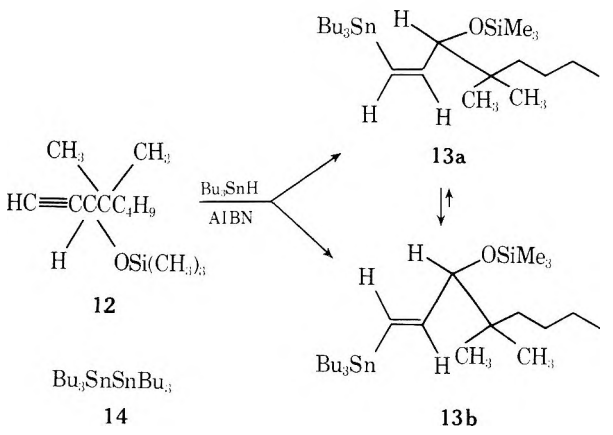
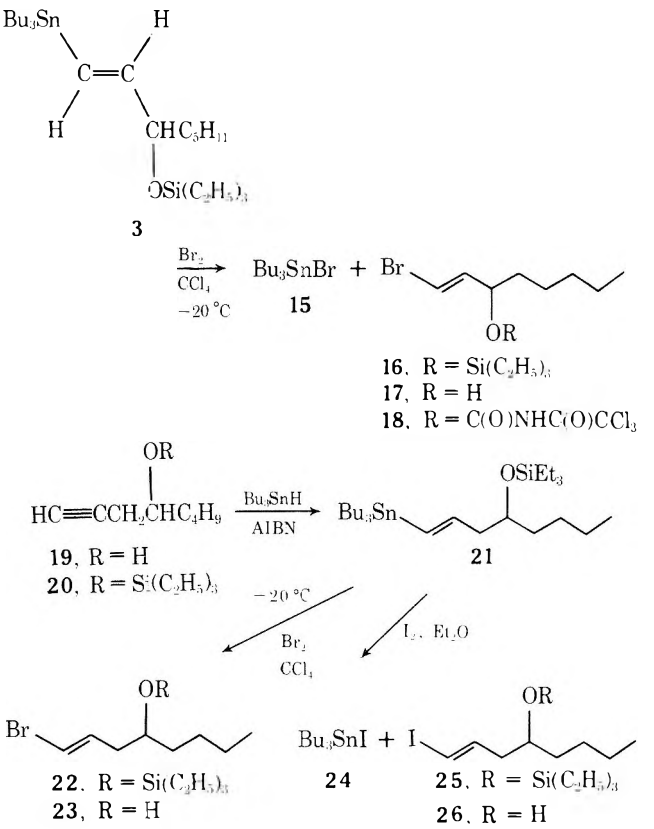
Scheme II



Scheme III



Scheme IV



(*E*)-vinylstannanes **13a** and **13b,** respectively (Scheme III). Lithiation of this mixture under the usual conditions (−50 °C, THF, 2 h) indicated that the *Z* isomer is considerably less reactive than the corresponding *E* isomer. Intrigued by this anomaly in the *E* vs. *Z* ratio, we investigated the conditions[19] necessary to isomerize **13a** to **13b.**

A sample of octyne 12 was treated with 0.9 equiv of TBS-H and a catalytic amount (0.2%) of AIBN (135 °C, 2 h). GLC (5% SE-30) and ^{1}H NMR spectrum indicated that the *Z* isomer **13a** was predominantly present (10:1 ratio). Further heating (2 h) produced no change on this ratio, nor did further heating after an additional 0.2 equiv of TBS-H was added; when fresh AIBN was added to the same reaction mixture, again no change was observed. However, when a second additional charge of TBS-H and AIBN was added to this reaction mixture, followed by heating, a *Z*/*E* ratio of 2:3 was observed. Further heating did not affect this ratio; but when a third charge of TBS-H and AIBN was added, a ratio of 1:9 (*Z*/*E*) was achieved.[20] A new peak appeared on GLC which had the identical retention time as hexa-*n*-butylditin (**14**). Apparently the destruction of excess TBS-H (bubbles were evident) becomes a competitive reaction when the rate of isomerization is decreased as in the case of the hindered 4,4-dimethyloctyne (**12**).

We have observed this unusual *Z*/*E* vinylstannane ratio with other propargylic ethers wherein there are substitutions adjacent to the silyloxy function. In such cases, we recommend the use of excess TBS-H in order to achieve a high *E*/*Z* ratio. It is apparent that the *E*/*Z* ratio cannot be assumed and must be determined in each instance.

Vinylstannanes represent useful precursors for various functionalized vinyl halides as illustrated in Scheme IV. When treated with 1 equiv of bromine in carbon tetrachloride[21] at −20 °C, the (*E*)-1-vinylstannane **3** was converted to bromotri-*n*-butylstannane (**15**) and (*E*)-1-vinyl bromide **16.** The stannane **15** can be easily removed by passing the reaction mixture through a short pad of silica gel with hexane. The triethylsilyl protecting group of the product **16** was unexpectedly cleaved to give **17,** which can then be reprotected. Inspection of the ^{1}H NMR spectrum of **17** did not enable us to characterize the double bond configuration. However, the exclusive trans nature of the vinyl bromide was confirmed from the ^{1}H NMR spectrum of the trichlorourethane derivative **18,** prepared in situ in a NMR tube with a few drops of trichloroacetyl isocyanate[22] ($J_{1,2}$ = 13.5 Hz), which was identical with the urethane prepared from an authentic

sample.[23] Vinyl bromide **17** has been used as a β-chain precursor for prostaglandin synthesis via Grignard conjugate addition.[23]

Similarly, vinylstannane **21**, prepared by treating 4-hydroxy-1-octyne[2d] (**19**) with chlorotriethylsilane to give **20** followed by addition of TBS-H and AIBN, was converted into the corresponding vinyl bromide **22** which, upon silica gel chromatography, provided the alcohol **23.**

Utilizing the stereospecific vinyl–tin cleavage reaction,[24] we have also investigated the transformation of vinylstannanes to the corresponding vinyl iodides,[3d] which undergo facile lithiation at −78 °C with *t*-BuLi and are used widely in prostaglandin synthesis.[2,3] Treatment of vinylstannane **21** with 1 equiv of iodine in ether furnished iodotri-*n*-butylstannane (**24**) and vinyl iodide **25.** The silyl protecting group of **25** was cleaved to provide **26** during purification (filtration with hexane through a short pad of silica gel to remove **24**).[25] Iodination of various functionalized vinylstannanes indicates that this transformation is both stereospecific and quantitative.[26]

Experimental Section

All reactions were performed under an atmosphere of argon or nitrogen. Solvents were removed under reduced pressure using a Büchi rotavapor followed by vacuum pumping. Boiling points are uncorrected. Dry-column chromatography was carried out with Woelm silica gel (equilibrated with 10% of the eluting solvent for several hours).

Infrared (IR) spectra were recorded with neat samples on a Perkin-Elmer Model 21 spectrophotometer or Nicolet 7199 FT-IR instrument. Proton magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ solutions on HA-100D spectrometer. Carbon-13 magnetic resonance (^{13}C NMR) spectra were taken in $CDCl_3$ solutions on Varian XL-100FT NMR spectrometer (25.2 MHz). Chemical shifts of ^{1}H and ^{13}C NMR are given in parts per million downfield from an internal tetramethylsilane standard. Mass spectra (MS) were recorded on an AEI MS-9 instrument at 70 eV.

3-(Triethylsilyloxy)-1-octyne (2). To a stirred solution of 50 g (0.4 mol) of 1-octyn-3-ol and 83 g (1.22 mol) of imidazole in 500 mL of dry DMF, cooled in an ice bath to 5 °C under an atmosphere of nitrogen, was slowly added 90 g (0.6 mol) of triethylchlorosilane. After 15 min, the reaction mixture was warmed to room temperature and stirred overnight. It was then cautiously poured into a mixture of 500 g of ice and 750 mL of hexane with stirring. The aqueous phase was separated and extracted with hexane. The combined hexane extract was washed with water and brine and dried (anhydrous sodium sulfate). The solvent was removed under reduced pressure to give an oil which was vacuum distilled to afford 83.5 g (yield 87%) of colorless liquid: bp 70–72 °C (0.3 mm); ^{1}H NMR δ 2.35 (d, J = 2 Hz, C-1 H), 4.36 (td, J = 6 and 2 Hz, C-3 H); MS m/e 240 (M^+, calcd for $C_{14}H_{28}OSi$, 240.1904; found, 240.1901), 169 ($M - C_5H_{11}$).

(*E*)-1-(Tri-*n*-butylstannyl)-3-(triethylsilyloxy)-1-octene (3). To a stirred mixture of 20 g (78.6 mmol) of 3-(triethylsilyloxy)-1-octyne (**2**) and 150 mg of azobis(isobutyronitrile) was added 30 mL (113 mmol) of tri-*n*-butylstannane with a syringe under a nitrogen atmosphere. The mixture was heated at 130 °C and stirred for 2 h, then cooled to room temperature. The excess tri-*n*-butylstannane was removed by distillation at 70 °C (0.05 mm). The product was vacuum distilled at 165 °C (0.05 mm) to give 36.5 g (yield 87%) of colorless liquid: ^{1}H NMR δ 4.05 (br m, 1 H, C-3 H), 6.0 (m, 2 H, olefin); ^{13}C NMR δ 152.2 (C-2), 126.6 (C-1), 77.0 (C-3), 38.2 (C-4), 32.0, 29.3, 27.4, 25.1, 22.8, 14.1, 13.7, 9.6, 6.9, 5.1. Anal. Calcd for $C_{26}H_{56}OSiSn$: C, 58.76; H, 10.62. Found: C, 58.99; H, 10.69.

***dl*-Prostaglandin E_2 (5) and *dl*-15-Epiprostaglandin E_2 (6).** To a stirred solution of 3.2 g (6.0 mmol) of (*E*)-1-(tri-*n*-butylstannyl)-3-(triethylsilyloxy)-1-octene (**3**) in 2.5 mL of freshly distilled THF, cooled in a dry ice–acetone bath under an atmosphere of nitrogen, was added 2.6 mL (6.2 mmol) of *n*-BuLi (2.4 M in hexane) during 15 min. The resulting solution was stirred at the same temperature for 20 min, then at −50 °C for 1 h. To this resulting vinyllithium solution was added, at −78 °C, a solution of 0.79 g (7.02 mmol) of 1-pentynylcopper[27] and 2.43 g (12 mmol) of tri-*n*-butylphosphine in 4 mL of ether during 10 min. After stirring at −78 °C for 2 h, the mixed cuprate (yellow solution) was formed and a solution of 1.62 g (4.39 mmol) of 4-(trimethylsilyloxy)-2-(6′-carbotrimethylsilyloxy-2′-(*Z*)-hexenyl)cyclopent-2-en-1-one (**4**) in 3 mL of ether was added during 15 min. The mixture was allowed to stir at −78 °C for 10 min, then at −35 °C for 1.5 h, recooled to −70 °C and quenched by pouring into 100 mL of cold saturated NH_4Cl and 100 mL of ether. The aqueous layer was separated and extracted with ethyl acetate. The combined organic extract was washed with dilute HCl, water, and brine, and the solvent was evaporated to dryness to give a pale brown oil. The oil was treated with 30 mL of acetic acid, 15 mL of THF, and 7.5 mL of water and stirred at room temperature for 1 h, then diluted with toluene and concentrated in vacuo to dryness. The residual oil was applied to 15 g of silica gel (Silic ARCC-7) and washed with 80 mL of hexane followed by 100 mL of ethyl acetate; the ethyl acetate eluate was concentrated in vacuo to afford 2.4 g of yellow oil. This liquid was subjected to silica gel dry column chromatography, eluting with hexane–EtOAc–HOAc (20:80:1). From the column segments was isolated 395 mg of the less polar (R_f 0.5) *dl*-15-epi-PGE_2 (**6**): IR ν 3400 (OH), 1710 (C=O), 970 (*trans*-C=C); ^{1}H NMR δ 0.87 (br t, 20-CH_3), 2.75 (dd, J = 17 and 9 Hz, one of 10-CH_2), 4.06 (m, 11β-H and 15-H), 5.40 (m, Δ^5-H), 5.66 (m, Δ^{13}-H); ^{13}C NMR δ 214.8 (C-9), 177.7 (C-1), 136.6 (C-14), 130.8 (C-5), 130.1 (C-13), 126.9 (C-6), 72.4 (C-15), 72.1 (C-11), 54.9 (C-12), 51.1 (C-8), 46.4 (C-10), 37.1 (C-16), 33.2 (C-2), 31.8 (C-18), 26.4 (C-4), 25.2 (C-7), 25.0 (C-17), 24.6 (C-3), 22.6 (C-19), 14.0 (C-20); MS m/e 334 ($M - H_2O$, calcd for $C_{20}H_{30}O_4$, 334.2144; found, 334.2136), 316, 298, 190. The more polar (R_f 0.35) product (265 mg) was identified as *dl*-PGE_2 (**5**); IR ν 3400 (OH), 1710 (C=O), 970 (*trans*-C=C); ^{1}H NMR δ 0.87 (br t, 20-CH_3), 2.75 (dd, J = 17 and 7 Hz, one of 10-CH_2), 4.06 (m, 11β-H and 15-H), 5.36 (m, Δ^5-H), 5.60 (m, Δ^{13}-H); ^{13}C NMR δ 214.6 (C-9), 177.9 (C-1), 136.6 (C-14), 131.6 (C-13), 130.8 (C-5), 126.7 (C-6), 73.3 (C-15), 72.1 (C-11), 54.5 (C-12), 53.6 (C-8), 46.2 (C-10), 36.9 (C-16), 33.3 (C-2), 31.8 (C-18), 26.4 (C-4), 25.2 (C-7 and C-17), 24.5 (C-3), 22.6 (C-19), 14.0 (C-20); MS m/e 334 ($M - H_2O$, calcd for $C_{20}H_{30}O_4$, 334,2144; found, 334.2153), 316, 298, 190.

(*E*)-1-(Tri-*n*-butylstannyl)-4-methyl-4-(trimethylsilyloxy)-1-octene (8a). This material was prepared from the hydrostannation of **7** by the procedure described for the preparation of **3**: bp 150–155 °C (0.06 mm); IR ν 1600 (olefin); ^{1}H NMR δ 0.08 (s, Me_3Si), 1.20 (s, 4-CH_3), 2.30 (br s, 2H, C-3 H), 6.0 (m, 2 H, olefin); ^{13}C NMR (the numbers in parentheses denoted * indicate the chemical shifts due to the corresponding *Z* isomer **8b**) δ 146.1 (145.6*) (C-2), 130.5 (129.8*) (C-1), 76.0 (C-4), 51.2 (49.7*) (C-3), 42.2 (42.6*) (C-5), 29.2 (C-2′), 27.5 (4-CH_3), 27.3 (C-3′), 26.2 (C-6), 23.3 (C-7), 14.2 (C-8), 13.7 (C-4′), 9.52 (10.3*) (C-1′), 2.69 (Me_3Si). Anal. Calcd for $C_{24}H_{52}OSiSn$: C, 57.25; H, 10.41. Found: C, 57.12; H, 10.69.

All Racemic 15-Deoxy-16-hydroxy-16-methylprostaglandin E_1 (10) and All Racemic 13-*cis*-15-Deoxy-16-hydroxy-16-methylprostaglandin E_1 (11). To a stirred solution of 6.03 g (11.9 mmol) of (*E*)-1-(tri-*n*-butylstannyl)-4-methyl-4-(trimethylsilyloxy)-1-octene (**8a**) in 5 mL of THF, cooled in a dry ice–acetone bath under an atmosphere of nitrogen, was added 5.5 mL (12.0 mmol) of *n*-BuLi (2.2 M in hexane) during 15 min. The resulting solution was stirred at the same temperature for 10 min, then at −35 °C for 2 h. The following experiments (mixed cuprate formation, conjugate addition, deblocking, and dry-column chromatography) were performed in the manner described for the preparations of **5** and **6.** From the dry-column segments was isolated 2.1 g of all racemic 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 (**10**) [^{1}H NMR δ 1.12 (s, 16-CH_3), 4.08 (q, J = 8 Hz, 11β-H), 5.45 (dd, J = 15 and 7 Hz, C-13 H), 5.72 (dt, J = 15 and 7 Hz, C-14 H); ^{13}C NMR[28] δ 215.5 (C-9), 133.8 (C-13), 129.5 (129.4) (C-14), 73.0 (72.9) (C-16), 71.9 (C-11), 54.6 (C-8 and C-12), 46.3 (C-10), 44.8 (C-17), 42.2 (41.1) C-15), 34.1 (C-2), 29.3, 28.8, 27.5, 26.4, 26.2, 26.1, 24.6, 23.3 (C-19), 14.1 (C-20); MS m/e 350 ($M - H_2O$, calcd for $C_{21}H_{34}O_4$, 350.2457; found, 350.2470), 335. 332, 317, 293, 275, 250, 232, 204] and 170 mg of all racemic 13-*cis*-15-deoxy-16-hydroxy-16-methyprostaglandin E_1 (**11**); ^{1}H NMR δ 1.46 (s, 16-CH_3), 4.00 (br q, J = 8 Hz, 11β-H), 5.48 (t, J = 9 Hz, C-13 H), 5.76 (m, C-14 H); ^{13}C NMR[28] δ 215.6 (C-9), 177.8 (C-1), 133,6 (C-13), 128.4 (128.2 (C-14), 73.3 (73.0) (C-16), 72.1 (C-11), 55.4 (C-8), 49.0 (C-12), 46.5 (C-10), 43.9 (40.4) (C-15), 39.2 (C-17), 34.2 (C-2), 29.3, 28.9, 27.1, 26.6, 26.0, 24.8, 24.5, 23.2 (C-19), 14.1 (C-20). MS m/e 350 ($M - H_2O$, calcd for $C_{21}H_{34}O_4$, 350.2457; found, 350.2477), 332, 275, 250, 232.

Preparation and Isomerization of (*Z*)- and (*E*)-1-(Tri-*n*-butylstannyl)-3-(trimethylsilyloxy)-4,4-dimethyl-1-octene (13a and 13b). A solution of 2 g (8.8 mmol) of 3-(trimethylsilyloxy)-4,4-dimethyl-1-octyne[18] (**12**), 2.6 mL (9.7 mmol, 1.1 equiv) of tri-*n*-butylstannane and 100 mg of azobis(isobutyronitrile) was stirred in an oil bath under an argon atmosphere and the temperature was raised gradually to 135 °C. After 2 h, an aliquot was analyzed by GLC (6 ft, 5% SE-30, oven temperature 230 °C), two peaks were observed at retention times of 4.7 and 5.1 min in a ratio of ~55:45, the former being assigned to (*E*)-1-(tri-*n*-butylstannyl)-3-(trimethylsilyloxy)-4,4-dimethyl-1-octene (**13b**) [^{1}H NMR δ 3.66 (m, C-3 H), 5.92 (m, olefin)] and the latter to the corresponding *Z* isomer **13a** [^{1}H NMR

δ 3.52 (d, J = 10 Hz, C-3 H), 5.91 (d, J = 14, C-1 H), 6.46 (dd, J = 14 and 10 Hz, C-2 H)].

This reaction mixture was distilled under vacuum to afford, after a forerun, the desired **13a/13b** product mixture; bp 140–142 °C (0.02 mm); MS m/e 457 (M − C_4H_9, calcd for $C_{21}H_{45}OSi^{116}Sn$, 457.2257; found, 457.2255), 367.

After three successive treatments of the above reaction mixture with additional TBS-H (0.6 mL each) and AIBN (10 mg each) at 135 °C for 2 h, the product E/Z ratio of approximately 9:1 was obtained. A peak of hexa-n-butylditin (Alfred Bader Co.) at a retention time of 7.2 min on GLC was also observed.

When the above experiment was repeated using 0.9 equiv (7.9 mmol) of tri-n-butylstannane, the initial product E/Z ratio (**13b/13a**) was 1:9 as evidenced by GLC and the ^{1}H NMR spectrum. After two successive treatments of the reaction mixture with additional TBS-H and AIBN as described above, this ratio was converted to 7:3.

(*E*)-1-Bromo-3-hydroxy-1-octene (17). To a stirred solution of 5.85 g (11.0 mmol) of (*E*)-1-(tri-n-butylstannyl)-3-(triethylsilyloxy)-1-octene (**3**) in 6 mL of CCl_4, cooled at −20 °C under an atmosphere of nitrogen, was added very slowly a solution of 1.759 g (11.0 mmol) of bromine in 6 mL of CCl_4 during a period of 1 h. After addition, the dropping funnel was rinsed with 0.5 mL of CCl_4 and the solution was added to the reaction mixture dropwise until a faint yellow color persisted. The solution was allowed to warm to room temperature and concentrated in vacuo to give a mixture of bromotri-n-butylstannane (**15**) and (*E*)-1-bromo-3-(triethylsilyloxy)-1-octene (**16**) as a colorless liquid; IR, no OH; ^{1}H NMR δ 4.10 (m, C-3 H), 6.21 (m, olefin). The liquid was applied to 60 g of silica gel (SilicAR CC-7) and washed with 300 mL of hexane followed by 300 mL of ethyl acetate. The hexane solution was concentrated in vacuo to give 4.6 g of bromotri-n-butylstannane (**15**); MS m/e 366 (M^+, calcd for $C_{12}H_{27}{}^{116}SnBr$, 366.0311; found, 366.0312), 309 (M − C_4H_9), 287. The ethyl acetate solution was concentrated in vacuo to give 3.1 g of (*E*)-1-bromo-3-hydroxy-1-octene (**17**): IR ν 3400 (OH), 1630 (C=C); ^{1}H NMR δ 4.10 (q, J = 6.5 Hz, C-3 H), 6.23 (dd, J = 13.5 and 6.5 Hz, C-2 H), 6.32 (d, J = 13.5 Hz, C-1 H); MS m/e 135 (M − C_5H_{11}, calcd for C_3H_4BrO, 134.9446; found, 134.9447), 127 (M − Br). A few drops of trichloroacetyl isocyanate was added to the ^{1}H NMR sample tube of **17** to provide the trichlorourethane derivative **18** and the ^{1}H NMR spectrum was recorded: δ 5.27 (q, J = 7.5 Hz, C-3 H), 6.19 (dd, J = 13.5 and 7.5 Hz, C-2 H), 6.55 (d, J = 13.5 Hz, C-1 H), 8.54 (br s, NH).

4-(Triethylsilyloxy)-1-octyne (20). This material was prepared from the silylation of **19** by the procedure described for the preparation of **2**: bp 54–54.5 °C (0.2 mm); ^{1}H NMR 1.97 (t, J = 3 Hz, C-1 H), 2.35 (dd, J = 6 and 3 Hz, C-3 H), 3.87 (br quintet, J = 6 Hz, C-4 H). Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 69.42; H, 11.89.

(*E*)-1-(Tri-*n*-butylstannyl)-4-(triethylsilyloxy)-1-octene (21). This material was prepared from the hydrostannation of **20** according to the procedure described for the preparation of **3**: ^{1}H NMR δ 2.30 (m, C-3 H), 3.68 (m, C-4 H), 5.92 (m, olefin); ^{13}C NMR δ 146.2 (C-2), 130.2 (C-1), 72.4 (C-4), 46.4 (C-3), 36.9 (C-5), 29.3, 27.7, 27.4, 23.0, 14.1, 13.7, 9.5, 7.0, 5.3.

Anal. Calcd for $C_{26}H_{56}OSiSn$: C, 58.75; H, 10.62. Found: C, 58.68; H, 11.06.

(*E*)-1-Bromo-4-hydroxy-1-octene (23). This material was prepared from **21** according to the procedure described for the preparation of **17**: IR ν 3400 (OH), 1630 (C=C); ^{1}H NMR δ 2.2 (t, J = 6 Hz, C-3 H), 3.66 (quintet, J = 6 Hz, C-4 H), 6.20 (m, 2 H, olefin); MS m/e 149 (151) (M − C_4H_9), 119 (212) (M − $C_5H_{11}O$).

(*E*)-1-Iodo-4-hydroxy-1-octene (26). To a stirred solution of 1.063 g (2 mmol) of (*E*)-1-(tri-n-butylstannyl)-4-(triethylsilyloxy)-1-octene (**21**) in 15 mL of ether was added 507 mg (2 mmol) of iodine portionwise. The solution was allowed to stir at room temperature for 2 h and a pale reddish color persisted in the reaction mixture. The solvent was evaporated in vacuo to dryness to give a mixture of iodotri-n-butylstannane (**24**) and (*E*)-1-iodo-4-(triethylsilyloxy)-1-octene (**25**) as a yellow liquid: IR ν 1605 (C=C), no OH; ^{1}H NMR δ 2.18 (t, J, 7 Hz, C-3 H), 3.68 (quintet, J = 7 Hz, C-4 H), 6.0 (d, J = 15 Hz, C-1 H), 6.52 (dt, J = 15 and 7.5 Hz, C-2 H); MS m/e 339 (M − C_2H_5), 311 (M − C_4H_9), 201 (M − C_3H_4I), 167 (C_3H_4I). This mixture was applied to 20 g of silica gel (SilicAR CC-4) and washed with 200 mL of hexane followed by 200 mL of ether. The hexane solution was concentrated in vacuo to give 0.75 g of iodotri-n-butylstannane (**24**). Anal. Calcd for $C_{12}H_{27}ISn$: C, 34.58; H 6.52. Found: C, 35.22; H, 6.62. The ether solution was concentrated in vacuo to give 0.57 g of (*E*)-1-iodo-4-hydroxy-5-octene (**26**); IR ν 3400 (OH), 1630 (C=C); ^{1}H NMR δ 2.14 (m, C-3 H), 3.64 (m, C-4 H), 6.10 (d, J = 15 Hz, C-1 H), 6.56 (dt, J = 15 and 7.5 Hz, C-2 H); MS m/e 254 (M^+, calcd for $C_8H_{15}IO$, 254.0169; found. 254.0171), 197 (M − C_4H_9), 167 (M − $C_5H_{11}O$).

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Registry No.—**1**, 37911-28-7; **2**, 66792-26-5; **3**, 66792-27-6; **4**, 59013-08-0; **5**, 22230-04-2; **6**, 31660-13-6; **7**, 66792-28-7; **8a**, 66792-29-8; **8b**, 66792-30-1; **9**, 63178-00-7; **10**, 66792-31-2; **11**, 66792-32-3; **12**, 64270-00-4; **13a**, 66792-33-4; **13b**, 66792-34-5; **15**, 1461-23-0; **16**, 66792-35-6; **17**, 52418-90-3; **18**, 66792-36-7; **19**, 52517-92-7; **20**, 66792-37-8; (*E*)-**21**, 66792-38-9; (*Z*)**21**, 66792-39-0; **22**, 66792-40-3; **23**, 66792-41-4; **24**, 7342-47-4; (*E*)-**25**, 66792-42-5; (*Z*)-**25**, 66792-43-6; (*E*)-**26**, 65989-29-9; (*Z*)-**26**, 66792-44-7; TBS-H, 688-73-3; triethylchlorosilane, 994-30-9.

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(15) Compound **9** was prepared from the unprotected cyclopentenone [G. Piancatelli and A. Scettri, *Tetrahedron Lett.*, 1131 (1977), and references cited therein] using hexamethyldisilazane–trimethylchlorosilane in pyridine; see also ref 9.
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and **26** obtained were contaminated with 20% of the corresponding (*Z*)-1-vinyl iodide as evidenced by the ^1H and ^{13}C NMR spectra.

(26) A vinyl iodide incorporating the triethylsilyloxy functionality such as **25** has been utilized successfully in the synthesis of prostaglandin congeners in this laboratory.

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Plakortin, an Antibiotic from *Plakortis halichondrioides*

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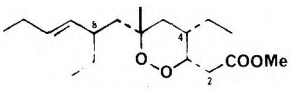
The Caribbean sponge *Plakortis halichondrioides* contains a lipid-soluble antibiotic, plakortin. The structure of plakortin (**1**) was deduced from spectroscopic data and by chemical degradation. Plakortin (**1**) was shown to be a cyclic peroxide. A related ketone (**12**) was isolated and the structure deduced from spectroscopic data.

Although there have been several large compilations of data recording in the in vitro antimicrobial activity of marine sponges,[2] relatively few of the metabolites responsible for antimicrobial activity have been isolated and identified.[3] Antimicrobial screening of crude extracts of some Caribbean sponges revealed that the crude ethanol extract of *Plakortis halichondrioides* (Wilson) inhibited the growth of *Staphylococcus aureus* and *Escherichia coli*. The antimicrobial activity was associated with the major metabolite of the sponge, which was named plakortin. In this paper, we wish to describe the structural elucidation of plakortin (**1**).



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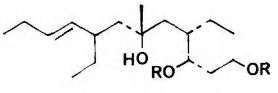


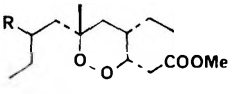
2 R = H
3 R = Ac

Plakortis halichondrioides (Wilson) was collected using SCUBA (−10 m) at Hookers Reef, Panama. The ether-soluble portion of an ethanol extract of the sponge was chromatographed on Florisil to obtain plakortin (**1**) (5.7% dry weight). Plakortin (**1**) had the molecular formula $C_{18}H_{32}O_4$. The infrared spectrum of plakortin (**1**) indicated the presence of an ester group (1735 cm^{-1}) and the absence of other carbonyl or hydroxyl groups. The ^{13}C NMR spectrum contained a carbonyl signal at δ 171.9 (s), a methoxyl signal at 51.5 (q), two signals for carbon atoms bearing oxygen at 81.0 (s) and 78.8 (d), and two signals at 134.4 (d) and 131.5 (d) due to a disubstituted olefin. The ^1H NMR spectrum confirmed the presence of a trans-disubstituted olefin [δ 5.38 (dt, 1 H, J = 15, 6, 6 Hz) and 5.10 (dd, 1 H, J = 15, 9 Hz)] and a methyl ester [δ 3.70 (s, 3 H)]. We therefore concluded that plakortin (**1**) was the methyl ester of a carboxylic acid containing a cyclic peroxide and a trans-disubstituted olefin.

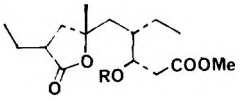
The ^1H spectrum also contained four additional methyl signals at δ 1.37 (s, 3 H), 0.97 (t, 3 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz), and 0.80 (t, 3 H, J = 7 Hz) and a signal assigned to the proton at C-3 at 4.49 (m, 1 H, J = 9.5, 6, 3.5 Hz) which was coupled to two mutually coupled signals at 3.05 (dd, 1 H, J = 15.5, 9.5 Hz) and 2.35 (dd, 1 H, J = 15.5, 3.5 Hz) and a third signal at 2.18 (m, 1 H). Since each of the triplet methyl signals must be adjacent to a methylene group, the structure of plakortin (**1**) could be solved by determining the position of the olefinic bond in the chain, its relationship to the peroxide ring, and the size of the peroxide ring.

The presence of the peroxide ring was confirmed by reduction of plakortin (**1**) with lithium aluminum hydride in dry ether at 0 °C to obtain the triol **2**. On acetylation with acetic anhydride in pyridine, the triol gave a diacetate **3**. By comparison of the ^1H NMR spectra of the triol **2** and the diacetate **3**, we deduced that the triol contained a primary alcohol, derived from reduction of the methyl ester, together with secondary and tertiary alcohols resulting from reduction of the cyclic peroxide ring.

Ozonolysis of plakortin (**1**), followed by addition of dimethyl sulfide to the ozonide, gave a mixture of an acid **5** and an aldehyde **4** which rapidly autoxidized to the acid **5**. The acid **5**, $C_{15}H_{26}O_6$, had lost a three-carbon fragment and contained only two methyl triplets at δ 0.97 and 0.92 in the ^1H NMR spectrum. Esterification of the acid **5** with diazomethane, followed by hydrogenation of the corresponding diester **6** over 10% palladium on charcoal, resulted in the formation on the γ-lactone **7** (IR 1765 cm^{-1}). The secondary alcohol function-

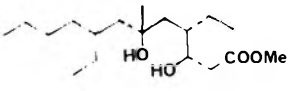


4 R = CHO
5 R = COOH
6 R = COOMe



7 R = H
8 R = Ac

ality of the lactone **7** was acetylated with acetic anhydride in pyridine to obtain the corresponding acetate **8**. Hydrogenation of plakortin (**1**) under identical conditions resulted in the formation of a dihydroxy ester (**9**) which did not cyclize to a lactone, indicating that the ester which had resulted from cleavage of the olefin was involved in γ-lactone formation with the oxygen on the fully substituted carbon atom. Since the olefinic proton at δ 5.10 in plakortin (**1**) was coupled to only one nonolefinic proton, there must be an alkyl group at C-8.



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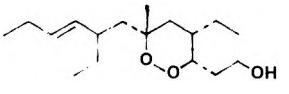

10

Reduction of plakortin (**1**) with lithium tri-*tert*-butoxyaluminum hydride in refluxing ether resulted in reduction of the ester group, but not the peroxide bond, to obtain a primary alcohol **10**. The mutually coupled signals at δ 2.35 and 3.05 in the ^1H NMR spectrum of plakortin (**1**) were absent from the ^1H NMR spectrum of the alcohol **10**, suggesting that these signals were due to a methylene group situated between the

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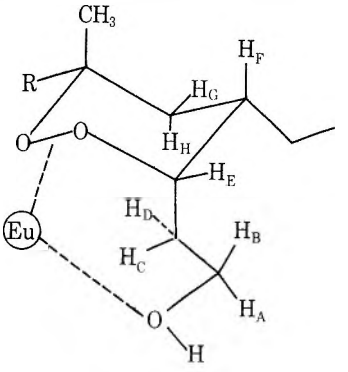
Table I. Chemical Shifts (δ), Eu(fod)$_3$-Induced Chemical Shifts (Δδ), and Calculated and Measured (Using Dreiding Model) Eu–hydrogen Distances for Selected Hydrogen Atoms in the ^{1}H NMR Spectrum of Alcohol 10



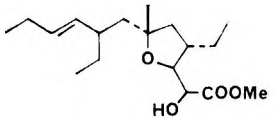
	δ, ppm	Δδ, ppm	r_{calcd}, Å	r_{meas}, Å
H_A	3.84	*a*		
H_B	3.84	*a*		
H_C	~2.3	7.66	5.5	5.4
H_D	~1.8	4.83	6.4	6.2
H_E	4.11	5.77	6.0	6.0
H_F	2.2	3.13	7.4	7.8
H_G	~1.5	2.28	8.2	8.4
H_H	~1.5	3.71	7.0	7.3
CH_3-ax	1.39	2.28	8.2	7.8
CH_3-eq				6.6

[a] Variation of chemical shift with concentration of Eu(fod)$_3$ added was not linear.

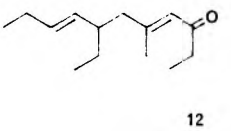
carboxylic ester and the carbon bearing the peroxide functionality. Since the proton signal at δ 4.49 in **1** was coupled to three other protons, there must be a side chain at C-4. A lanthanide-induced shift (LIS) study on the alcohol **10** (see below) clearly showed the presence of a six-membered peroxide ring. Thus both alkyl side chains at C-4 and C-8 must be ethyl groups, allowing the structure **1** to be drawn.

Some stereochemical information could be obtained from interpretation of the LIS data. The protons at C-5 could be resolved into two signals with coupling constants of 13 and 12 Hz and 13 and 4 Hz, respectively. These coupling constants are typical of methylene protons in a six-membered ring which are coupled to a single axial proton. The coupling between the protons at C-3 and C-4 (6 Hz) was best observed in the spectrum of plakortin (**1**) and indicated an equatorial proton at C-3. A semiquantitative analysis of the LIS data (Table I) allowed an assignment of a europium ion position and confirmed these stereochemical assignments. The relative stereochemistry at C-8 has not been determined.

On treatment with sodium methoxide in methanol, plakortin (**1**) underwent an interesting rearrangement to an isomeric ether **11**. The ether **11** contained a hydroxyl group



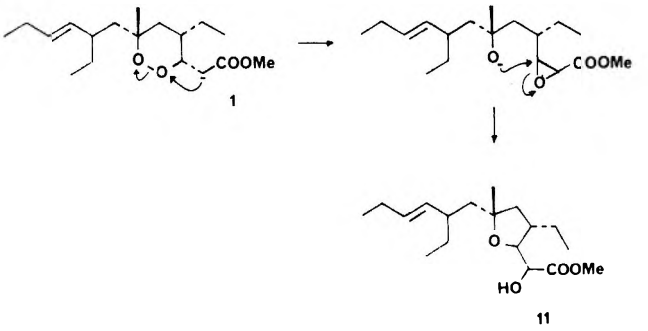
11



12

(IR 3550 cm^{-1}) which was shown to be at C-2. The ^{1}H NMR spectrum of **11** contained a signal at δ 4.34 (d, 1 H, J = 2.5 Hz) which was shifted to δ 5.10 on acetylation; this signal was assigned to the C-2 proton of an α-hydroxy ester. A spin-decoupling study on the ether **11** revealed that the α-hydroxy proton at C-2 was coupled to a proton at δ 3.80, which was in turn coupled to a single proton at δ 2.32 by a 10-Hz coupling constant. The proton at 2.32 ppm was in turn coupled to two

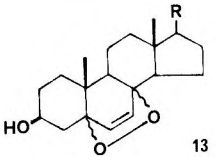
Scheme I. A Mechanism for the Rearrangement of Plakortin (1) to Alcohol 11



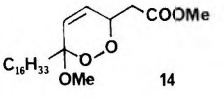
mutually coupled methylene protons at 1.91 and 1.36 ppm. A mechanism for the rearrangement is suggested in Scheme I.

The sponge contained a ketone **12** as a minor metabolite. The structure of ketone **12**, $C_{14}H_{24}O$, was assigned on the basis of its spectral data. The ultraviolet [λ_{max} (MeOH) 237 nm (ε 18 900)] and infrared (1690 cm^{-1}) spectra indicated the presence of an α,β-unsaturated ketone. The ^{1}H NMR spectrum contained four methyl signals at δ 2.10 (s, 3 H), 1.07 (t, 3 H, J = 7 Hz), 0.95 (t, 3 H, J = 7 Hz), and 0.85 (t, 3 H, J = 7 Hz), a methylene quartet at 2.44, and three olefinic protons at 6.00 (s, 1 H), 5.39 (dt, 1 H, J = 15, 6, 6 Hz), and 5.07 (dd, 1 H, J = 15, 9 Hz). The methyl triplet at δ 1.07 and the methylene quartet at δ 2.44 suggest the presence of an ethyl ketone, while the singlets at δ 6.00 and 2.10 are due to a proton at C-4 and a methyl group at C-5 which lie cis to the carbonyl group. All other features of the ^{1}H NMR spectrum and the ^{13}C NMR spectrum are consistent with the remaining portion of the ketone **12** being identical with the eight-carbon side chain in plakortin (**1**).

Cyclic peroxides of steroids having the general structure **13** have been found in many sponges.[4] Since the steroidal peroxides were found as mixtures of α and β peroxide isomers in



13



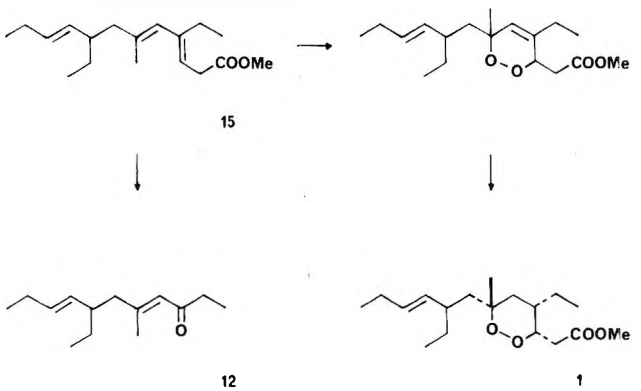
14

the same 85:15 ratio that was obtained by photooxidation of ergosterol,[5] it has been suggested that the cyclic peroxides were autoxidation products of steroidal 5,7-dienes. The cyclic peroxide chondrillin (**14**) was shown to be optically active and must therefore be formed by an enzyme-mediated addition of oxygen to the corresponding diene.[6] Since plakortin (**1**) was also optically active and was not a mixture of diastereoisomers, it must be assumed that plakortin (**1**) was formed by enzyme-mediated reactions. The isolation of the ketone **12** as a minor product has led to the suggestion that both the ketone **12** and plakortin (**1**) might be derived from a common 1,3-diene intermediate **15** (Scheme II). The carbon skeleton of plakortin (**1**) has not previously been described.

Experimental Section

Melting points were measured on a Fisher-Johns apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian HR-220 and CFT-20 instruments, respectively. Infrared and ultraviolet spectra were recorded on Perkin-Elmer Model 136 and 124 spectrophotometers, respectively. Optical rotations were measured on a Perkin-Elmer 141 polarimeter, using a 10-cm cell thermostated at 20 °C. Low-resolution mass spectra were recorded on a Hewlett-Packard 5930-A mass spectrometer. High-resolution mass measurements were obtained from the Analytical Facility at California Institute of Technology. All solvents used were either spectral grade or redistilled from glass prior to use.

Scheme II. Both Plakortin (1) and the Ketone 12 Can Be Derived from a Common Intermediate (15)



Extraction and Chromatography. *Plakortis halichondrioides* (Wilson) was collected by hand, using SCUBA (−10 m), at Hookers Reef, San Blas, Panama (9° 33′ 35″ N, 79° 41′ W) and stored in ethanol for ~1 yr. The sponge (49 g dry weight) was homogenized in ethanol and filtered. The solid was exhaustively extracted with ethanol in a Soxhlet extractor, and the combined ethanol extracts were evaporated to a gum. The organic material was partitioned between water and ether to obtain a crude ether extract (6.9 g). The ether extract (5.1 g) was chromatographed on a Florisil column using a sequence of solvents of increasing polarity from hexane through ether and ethyl acetate to methanol. A fraction eluted with ether was further purified by LC on μ-Porasil using 4% ether in hexane to obtain the ketone **12** (90 mg, 0.25% dry weight). Fractions eluted with 5–20% ethyl acetate in ether gave plakortin (**1**; 2.08 g, 5.2% dry weight), which was essentially pure but which could be further purified by LC on μ-Porasil using 7% ether in hexane.

Plakortin (Methyl 4,8-diethyl-6-methyl-3,6-peroxy-9-dodecenoate, 1): $[\alpha]_D^{20}$ +189° (c 2.9, $CHCl_3$); IR (CCl_4) 1735, 1470, 1450, 1390, 1000, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz), 1.37 (s, 3 H), 1.55 (dd, 1 H, J = 13, 4 Hz), 2.05 (m, 3 H), 2.18 (m, 1 H), 2.35 (dd, 1 H, J = 15.5, 3.5 Hz), 3.05 (dd, 1 H, J = 15.5, 9.5 Hz), 3.70 (s, 3 H), 4.49 (m, 1 H, J = 9.5, 6, 3.5 Hz), 5.10 (dd, 1 H, J = 15, 9 Hz), 5.38 (dt, 1 H, J = 15, 6, 6 Hz); ^{13}C NMR ($CDCl_3$) δ 11.0 (q), 11.5 (q), 13.9 (q), 21.3 (q), 25.2 (t), 29.5 (t), 29.9 (t), 31.4 (t), 34.9 (d), 36.0 (t), 40.2 (d), 46.5 (t), 51.5 (q), 78.8 (d), 81.0 (s), 131.5 (d), 134.4 (d), 171.9 (s); high-resolution mass measurement 312.228, $C_{18}H_{32}O_4$ requires 312.230.

7-Ethyl-5-methyl-4,8-undecadien-3-one (12): $[\alpha]_D^{20}$ +17° (c 1.4, $CHCl_3$); UV (MeOH) 237 nm (ε 18 900); IR (CCl_4) 1690, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 7 Hz), 0.95 (t, 3 H, J = 7 Hz), 1.07 (t, 3 H, J = 7 Hz), 2.10 (s, 3 H), 2.44 (q, 2 H, J = 7 Hz), 5.07 (dd, 1 H, J = 15, 9 Hz), 5.39 (dt, 1 H, J = 15, 6, 6 Hz), 6.00 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 8.2 (q), 11.6 (q), 14.1 (q), 19.6 (q), 25.6 (t), 28.0 (t), 37.5 (t), 42.6 (d), 47.4 (t), 124.4 (d), 132.1 (d), 132.7 (d), 156.9 (s), 201.6 (s); high-resolution mass measurement 208.181, $C_{14}H_{24}O$ requires 208.183.

Reduction of Plakortin (1) with Lithium Aluminum Hydride. Lithium aluminum hydride (20 mg, 0.53 mmol) was added to a stirred solution of plakortin (**1**; 30 mg, 0.096 mmol) in dry ether at 0 °C. After stirring for 15 min, the excess reagent was destroyed with ethyl acetate and the product was partitioned between ether and dilute hydrochloric acid. The ether extract was dried over anhydrous sodium sulfate and the solvent evaporated to yield a crude alcohol mixture (23 mg). The mixture of alcohols was separated on a silica gel plate to obtain the triol **2** (15 mg, 55% theoretical) and the alcohol **10** (2 mg). The triol **2** gave the following spectral data: IR (CCl_4) 3225, 1470, 1390, 975, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H, J = 7 Hz), 0.91 (t, 3 H, J = 7 Hz), 0.98 (t, 3 H, J = 7 Hz), 1.19 (s, 3 H), 3.85 (m, 3 H), 5.22 (dd, 1 H, J = 15, 9 Hz), 5.55 (dt, 1 H, J = 15, 6, 6 Hz).

A portion of the triol (10 mg, 0.035 mmol) was dissolved in a mixture of acetic anhydride (1 mL) and pyridine (2 mL) and the solution was allowed to stand overnight at room temperature. Evaporation of the reagents in vacuo gave a residue which was partitioned between ether and water. The ether extract was dried over sodium sulfate and the solvent evaporated to give a residue (11 mg) which was purified by LC on μ-Porasil using 40% ether in hexane as eluent to obtain the diacetate **3** (9 mg, 70% theoretical): IR (CCl_4) 3450, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 7 Hz), 0.93 (t, 3 H, J = 7 Hz), 0.98 (t, 3 H, J = 7 Hz), 1.11 (s, 3 H), 2.00 (s, 3 H), 2.04 (s, 3 H), 4.09 (m, 2 H), 5.23 (m, 2 H), 5.50 (dt, 1 H, J = 15, 6, 6 Hz); high-resolution mass measurement 370.273, $C_{21}H_{38}O_5$ requires 370.272.

Ozonolysis of Plakortin (1). A stream of ozone in oxygen was bubbled into a solution of plakortin (**1**; 20 mg, 0.064 mmol) in dichloromethane (5 mL) at −78 °C until a blue-colored solution was obtained. Excess ozone was removed in a stream of dry nitrogen. Dimethyl sulfide (0.2 mL) was added, and the solution was allowed to warm to room temperature. After 30 min, the solvents were removed in vacuo to obtain a yellow oil. Chromatography of the product on a silica gel plate using 1:1 hexane–ether gave the aldehyde **4** (9 mg, 46% theoretical) and the acid **5** (7 mg, 36% theoretical). On standing overnight, the aldehyde **4** oxidized to the acid **5**. A solution of diazomethane solution in ether was added to a solution of the acid **5** in ether until the solution remained yellow. Evaporation of the solvent in vacuo gave the methyl ester **6**. In a subsequent experiment, plakortin (**1**; 120 mg, 0.38 mmol) was converted into the ester **6** (115 mg, 0.37 mmol) in 96% yield.

Acid 5: IR (CCl_4) 2665 (br), 1740, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz), 1.39 (s, 3 H), 2.04 (dd, 1 H, J = 15, 10 Hz), 2.23 (m, 1 H), 2.42 (dd, 1 H, J = 15.5, 3.5 Hz), 2.50 (m, 1 H), 3.02 (dd, 1 H, J = 15.5, 9.5 Hz), 3.40 (s, 3 H), 4.52 (m, 1 H, J = 9.5, 6, 3.5 Hz).

Ester 6: ^1H NMR ($CDCl_3$) 0.86 (t, 3 H, J = 7 Hz), 0.91 (t, 3 H, J = 7 Hz), 1.30 (s, 3 H), 2.01 (dd, 1 H, J = 15, 10 Hz), 2.18 (m, 1 H), 2.37 (dd, 1 H, J = 15, 3 Hz), 2.50 (m, 1 H), 3.03 (dd, J = 15, 9 Hz), 3.67 (s, 3 H), 3.70 (s, 3 H), 4.50 (m, 1 H).

Hydrogenation of Ester 6. Palladium on charcoal catalyst (10%, 10 mg) was added to a solution of the ester **6** (115 mg, 0.37 mmol), and the solution was stirred under an atmosphere of hydrogen overnight. The catalyst was removed by filtration and the solvent evaporated to obtain the lactone **7** as a pale yellow oil (115 mg): IR (CCl_4) 3200, 1765, 1730 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 11.7 (q), 12.0 (q), 23.5 (t), 24.3 (t), 27.6 (q), 37.8 (t), 39.9 (t), 40.3 (t), 40.6 (d), 42.2 (d), 51.8 (q), 69.1 (d), 84.6 (s), 173.5 (s), 178.6 (s). A portion of the lactone **7** (12 mg) was dissolved in a mixture of acetic anhydride (0.5 mL) and pyridine (1.0 mL), and the solution was allowed to stand overnight. The solvents were removed in vacuo, and the residue was partitioned between ether and water. The organic material was purified by LC on μ-Porasil, using 40% ether in hexane as eluant, to obtain the lactone acetate **8** (7 mg, 56% theoretical): IR (CCl_4) 1765, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (t, 6 H, J = 7 Hz), 1.41 (s, 3 H), 2.02 (s, 3 H), 2.26 (dd, 1 H, J = 13, 10 Hz), 2.54 (m, 2 H), 2.67 (m, 1 H), 3.67 (s, 3H), 5.41 (m, 1H); high-resolution mass measurement 328.186, $C_{17}H_{28}O_6$ requires 328.188.

Reduction of Plakortin (1) with Lithium Tri-*tert*-butoxyaluminum Hydride. Lithium tri-*tert*-butoxyaluminum hydride (100 mg, 0.39 mmol) was added to a solution of plakortin (**1**; 50 mg, 0.06 mmol) in ether (10 mL), and the solution was boiled under reflux for 2 h. The excess reagent was destroyed by addition of water, and the reaction product was partitioned between ether and dilute hydrochloric acid. The ether extract was dried over anhydrous sodium sulfate and the solvent evaporated to give a colorless oil (48 mg). The oil was purified by LC on μ-Porasil, using 40% ether in hexane as eluant, to obtain the alcohol **10** (38 mg, 85% theoretical): IR (CCl_4) 3310, 1470, 1388, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (t, 3 H, J = 7 Hz), 0.87 (t, 3 H, J = 7 Hz), 0.98 (t, 3 H, J = 7 Hz), 1.39 (s, 3 H), 1.45 (t, 1 H, J = 14 Hz), 1.52 (dd, 1 H, J = 14, 5 Hz), 2.04 (m, 5 H), 2.20 (m, 1 H), 3.84 (t, 2 H, J = 6 Hz), 4.11 (m, 1 H), 5.09 (dd, 1 H, J = 15, 9 Hz), 5.36 (dt, 1 H, J = 15, 6, 6 Hz).

Lanthanide-Induced Shift Experiment. A solution of the alcohol **10** (7 mg) in deuteriochloroform (500 μL) was prepared. NMR spectra (220 MHz) were recorded after each addition (5 μL) of a solution of $Eu(fod)_3$ (27 mg) in deuteriochloroform (58 μL). The induced shifts (Δδ) were deduced by plotting the chemical shift of each proton signal against the quantity of reagent added. The induced shifts are summarized in Table I.

Treatment of Plakortin (1) with Sodium Methoxide. Plakortin (**1**; 25 mg, 0.08 mmol) was added to a 1 N solution of sodium methoxide in methanol (10 mL), and the solution was allowed to stand at room temperature for 3 h. The base was neutralized by addition of dry ice and the solvent evaporated. The ether-soluble material (22 mg) was essentially one compound which was purified by LC to obtain the alcohol **11** (14 mg, 56% theoretical): IR (CCl_4) 3550, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 7 Hz), 0.86 (t, 3 H, J = 7 Hz), 0.98 (t, 3 H, J = 7 Hz), 1.14 (s, 3 H), 1.36 (m, 1 H), 1.68 (m, 1 H), 1.91 (m, 1 H), 2.02 (m, 3 H), 2.32 (m, 1 H), 3.77 (s, 3 H), 3.80 (dd, 1 H, J = 10, 2.5 Hz), 4.34 (d, 1 H, J = 2.5 Hz), 5.14 (dd, 1 H, J = 15, 9 Hz), 5.34 (dt, 1 H, J = 15, 6, 6 Hz); ^{13}C NMR ($CDCl_3$) 12.6, 13.6, 13.9, 25.2, 25.6, 27.4, 29.7, 40.8, 41.6, 44.7, 47.9, 52.1, 71.9, 83.3, 84.8, 131.3, 134.3, 172.7.

Acetylation of Alcohol 11. A solution of the alcohol **11** (8 mg) in acetic anhydride (0.2 mL) and pyridine (0.3 mL) was allowed to stand at room temperature for 18 h. The solvent was removed in vacuo to obtain the corresponding acetate: ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 7 Hz), 0.92 (t, 3 H, J = 7 Hz), 0.97 (t, 3 H, J = 7 Hz), 1.10 (s, 3 H),

2.15 (s, 3 H), 3.71 (s, 3 H), 3.81 (dd, 1 H, J = 10, 2.5 Mz) 5.10 (d, 1 H, J = 2.5 Hz), 5.15 (m, 1 H), 5.35 (m, 1 H).

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Registry No.—1, 66940-35-0; 2, 66940-36-1; 3, 66940-37-2; 4, 66940-38-3; 5, 66940-39-4; 6, 66940-40-7; 7, 66940-41-8; 8, 66940-42-9; 10, 66940-43-0; 11, 66940-44-1; 11 acetate, 66940-45-2; 12, 66984-56-3.

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Biosynthesis of the Anthracycline Antibiotics Nogalamycin and Steffimycin B

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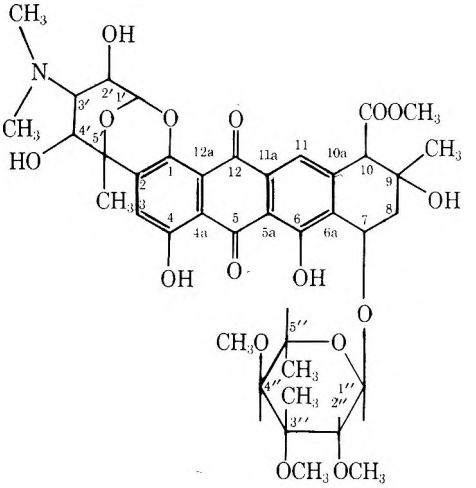
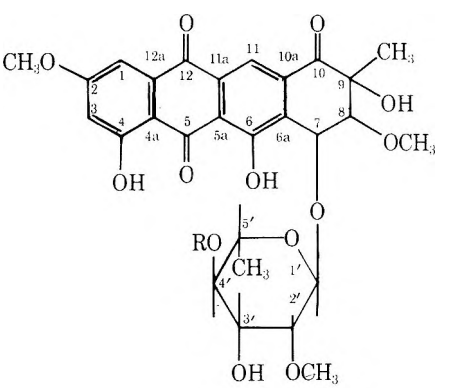
It has been shown that the aglycones of nogalamycin (1) and steffimycin B (3) arise from ten acetate units starting with the methyl groups at C-9. The neutral sugars are derived from glucose, while CH_3O and CH_3N methyl groups come from methionine.

The antibiotic nogalamycin (1) has been of interest as an antitumor agent for a number of years.[1] Some of its conversion products are even more active in this respect, and their antitumor properties are being extensively investigated.[2] Furthermore, 1 is a member of the anthracycline antibiotic family of which one member, adriamycin, is widely used in cancer chemotherapy.[3] Steffimycin (2) and steffimycin B (3) are also anthracycline antibiotics although they are only very modestly active as antitumor agents. However, the steffimycins are members of a subgroup of three anthracyclines whose structures differ markedly from the other anthracyclines. For these reasons it was felt that it would be worthwhile to investigate the biosynthesis of 1, 2, and 3 and compare their biosynthesis with those of daunomycin[4] and ϵ-pyrromycinone[5] which have already been reported. In the case of daunomycin only biosynthesis of the aglycone was established, but in the present work the biosynthesis of the sugars was also studied.

The procedure utilized to study the biosynthetic pathways of 1 and 3 was addition of ^{13}C-labeled compounds which might logically be expected to act as antibiotic precursors to fermentations of *Streptomyces nogalater*, UC-2783, and *Streptomyces elgreteus*, UC-5453, grown on minimal media. The ^{13}C-enriched 1 and 3 formed by *S. nogalater* and *S. elgreteus*, respectively, was isolated, and the positions of the ^{13}C-enriched carbon atoms established by ^{13}C NMR spectra. As a result of previous work[4,5] and current concepts of biosynthesis, it seemed very probable that both aglycones would be built completely from acetate units. For example, it has been shown[4] that the aglycone of daunomycin arises through a polyketide intermediate derived from acetate and one unit of propionate with loss of the terminal carboxyl group. Ollis and co-workers[5] have proposed a similar biosynthetic pathway for ϵ-pyrromycinone, the aglycone of rutilantin. A common biosynthetic pathway for formation of hydroxyanthraquinones by fungi is the condensation of ten acetate units.[6] Accordingly, *S. nogalater* and *S. elgreteus* fermentations in appropriate carbon-poor media were enriched with $CH_3{}^{13}COONa$ and $^{13}CH_3COONa$ to give 1 and 3 labeled with



1



2, R = H
3, R = CH_3

^{13}C. Isolation of the products was carried out, and ^{13}C NMR spectra were obtained to establish the positions of the carbon atoms enriched with ^{13}C. Similar procedures were used, but

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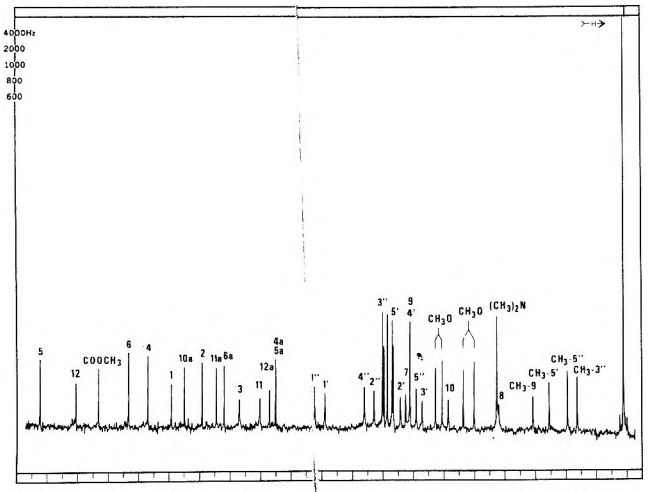

Figure 1. ^{13}C NMR spectrum ($CDCl_3$) of nogalamycin at natural abundance ^{13}C concentration.

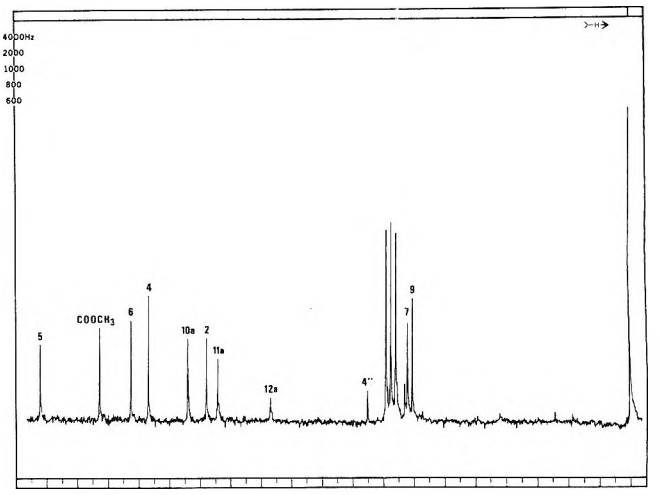

Figure 3. ^{13}C NMR spectrum ($CDCl_3$) of nogalamycin from cultures supplemented with $CH_3{}^{13}COONa$.

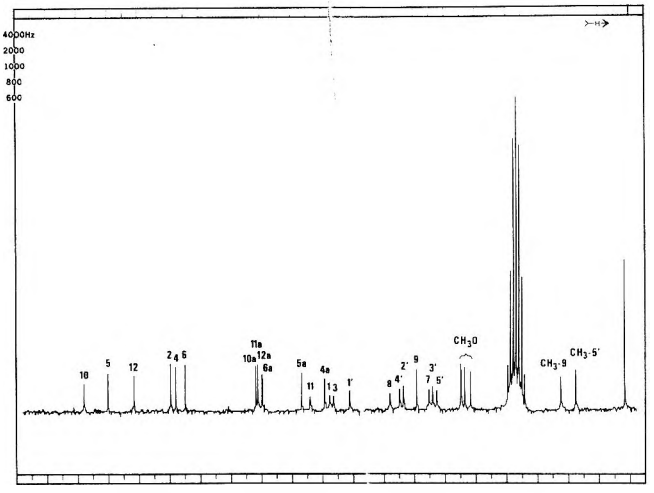

Figure 2. ^{13}C NMR spectrum (Me_2SO-d_6) of steffimycin B at natural abundance ^{13}C concentration.

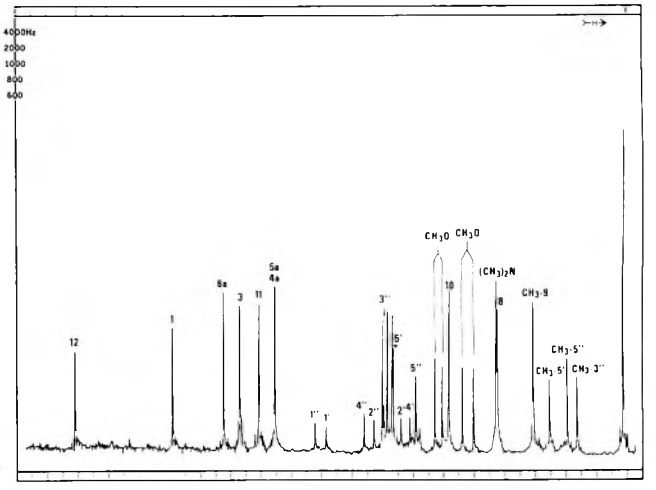

Figure 4. ^{13}C NMR spectrum ($CDCl_3$) of nogalamycin from cultures supplemented with $^{13}CH_3COONa$.

adding $^{13}CH_3$-labeled methionine and uniformly ^{13}C-labeled glucose, to study incorporation of one-carbon units and sugar biosynthesis.

Before discussing biosynthesis, it is necessary to reassign some of the ^{13}C chemical shifts previously published for **1**.[7] The ^{13}C NMR spectrum of **1** was originally taken in $CDCl_3$ and C-7 and C-4′ were assigned chemical shifts of δ 69.7 and 71.1, respectively. The spectra of several of the analogues were taken in DMF-d_7, and in the spectrum of the analogue which has nogalose replaced by methoxy, the chemical shift assigned to C-7 was δ 72.5. This discrepancy was somewhat surprising. A ^{13}C NMR spectrum of **1** has now been taken in DMF-d_7, and the resulting differences in chemical shifts of some of the carbon atoms makes it necessary to reverse the C-7 and C-4′ assignments. In the DMF-d_7 spectrum, the peaks for C-2′, C-3′, and C-5′ have moved downfield by δ 0.6 while the peak originally assigned to C-4′ has moved downfield by δ 2.2. The peak movements are much more consistent if the chemical shift originally assigned to C-7 is assigned as C-4′ which would then have moved downfield by δ 0.6 in DMF-d_7. Also, the new value agrees much better with that for C-7 in the analogue mentioned above. In the DMF-d_7 spectrum, the peaks for C-8, C-9, and C-10 have undergone very substantial changes from the values obtained for them in $CDCl_3$ with C-8 and C-9 peaks moving upfield by δ 1.3 and 1.1, respectively, while the C-10 peak moved downfield by δ 1.2. The change of δ 2.2 downfield for the reassigned value of C-7 would fit in with these reasonably large changes which probably are a result of conformation differences in the two solvents perhaps arising from DMF-d_7 binding of the C-9 hydroxyl group. In order to investigate the chemical shifts assigned to C-4a and C-12a, about which there was some doubt, a gated decoupling spectrum was run in DMF-d_7. In such a spectrum, C-4a should show coupling with the proton at C-3, but C-12a should be a singlet as no protons are in appropriate positions for coupling. The spectrum showed a well-defined singlet at δ 116.9 establishing that this value should be assigned to C-12a as the δ 116.1 peak in the $CDCl_3$ spectrum moved to δ 116.9 in DMF-d_7. The peaks at δ 115.0 and 114.7 showed so much splitting that the exact coupling was not established. However, these results make necessary the assignment of peaks at δ 116.1 and 114.1 in the $CDCl_3$ spectrum of **1** to C-12a and C-4a, respectively.

The chemical shifts in the ^{13}C NMR spectrum of **1** have thus been completely assigned,[7] and the spectrum is shown in Figure 1. The spectra derived from **1** enriched with ^{13}C by addition of $CH_3{}^{13}COONa$ and $^{13}CH_3COONa$ are shown in Figures 3 and 4, respectively. In both cases a polyketide intermediate derived totally from acetate should give ten strong peaks assignable to alternate carbon atoms in the aglycone. The addition of $CH_3{}^{13}COONa$ should have enriched carbons starting at C-9, and $^{13}CH_3COONa$ should enrich the carbon atoms starting with CH_3 at C-9. The spectrum (Figure 3) derived from **1** enriched with $CH_3{}^{13}COONa$ has chemical shifts of δ 191.2 (C-5), 171.9 ($COOCH_3$), 161.7 (C-6), 155.9 (C-4), 143.2 (C-10a), 137.2 (C-2), and 133.4 (C-11a) which are so strong relative to the signals for adjacent carbon atoms that

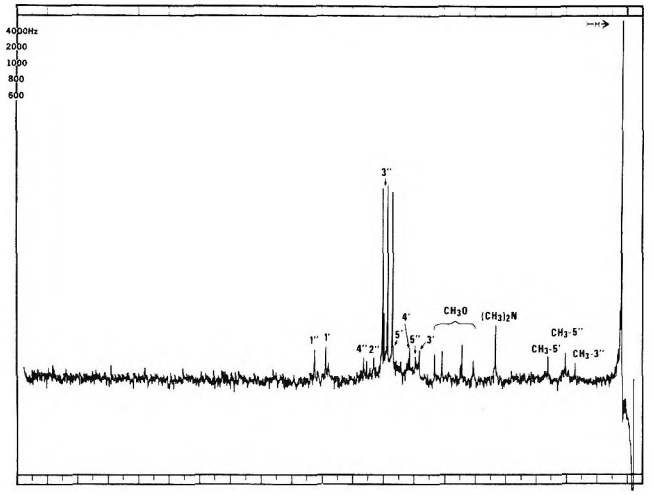

Figure 5. ^{13}C NMR spectrum ($CDCl_3$) of nogalamycin from cultures supplemented with uniformly ^{13}C-labeled D-glucose.

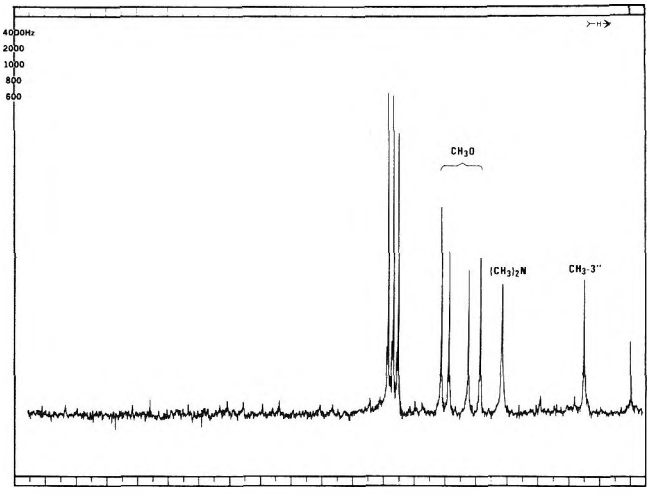

Figure 6. ^{13}C NMR spectrum ($CDCl_3$) of nogalamycin from cultures supplemented with $^{13}CH_3$-labeled methionine.

it is quite clear that these carbon atoms are enriched in ^{13}C as expected if the aglycone were derived from ten acetate units. The strong peaks at δ 69.9 and 71.5 must arise from C-9 and C-7, respectively. The expected tenth peak, which after the above reassignment would be at δ 116.1, would arise from C-12a if the polyacetate biogenesis view is correct. There is a peak at this position albeit one not nearly so strong as the others. However, in view of the absence of other aromatic carbon peaks in this area, it must arise from an enriched C-12a carbon atom. In such case, the labeled carbon atoms would be exactly as expected for polyacetate biosynthesis of the aglycone portion of **1**. In addition, weakly enriched peaks arising from some of the carbon atoms in the two sugars can be observed, but this would have no bearing on the biosynthesis of aglycone. The spectrum (Figure 4) of material derived from $^{13}CH_3COONa$ enrichment is somewhat more complex. Only six peaks in the carbonyl and aromatic region are quite obviously strongly enriched in ^{13}C with respect to other aromatic and carbonyl peaks, and polyketide biosynthesis would require seven. The peak with a chemical shift of δ 114.1 is slightly higher than other enriched carbon atom peaks so it seems probable that it represents C-4a and C-5a after reassignment of C-4a. Such a situation would be that expected from polyacetate biosynthesis. The methyl carbon at C-9 would be expected to be enriched, and this is the case as is obvious from comparing methyl peak heights in Figure 1 with those in Figure 4. In the spectrum of **1** the ratio of the height of the C-9 CH_3 peak to the height of the C-5′ CH_3 peak is 0.66 while in the spectrum in Figure 4 it is 2.13 showing quite clearly that the CH_3 carbon at C-9 is enriched. The same argument applied to the peaks arising from C-8 and C-10 established that they have been substantially enriched. Thus, the expected ten-carbon atoms have been shown to arise from C-2 of acetate, and the consistency of $CH_3{}^{13}COONa$ and $^{13}CH_3COONa$ is perfect with the reassignment of C-4a, C-12a, C-7, and C-4′. However, a number of peaks arising from sugar carbon atoms and various methyl groups are high enough to indicate ^{13}C enrichment of these carbon atoms. Such incorporations are known to occur.

Addition of uniformly ^{13}C-labeled glucose to an *S. nogalater* fermentation was for the purpose of determining whether or not the two sugars of **1** were derived from glucose. It is known that the amino sugar has the glucose configuration,[7] although not whether it is D or L, suggesting a strong possibility of direct origin from glucose. Nogalose, the neutral sugar, has the L-rhamnose configuration, and it has been shown that many microorganisms can convert D-glucose to L-rhamnose.[8] The ^{13}C NMR spectrum in Figure 5 is that obtained from material enriched in ^{13}C by inclusion of uniformly labeled glucose in the fermentation. Carbon atoms in methyl groups and in C-1 to C-6 of nogalose were substantially enriched although not nearly at the level obtained in the aglycone arising from labeled acetate. A comparison of Figures 1 and 5 with respect to peak heights of peaks from aliphatic carbon atoms relative to those of aromatic carbons shows that peaks at δ 100.8 (C-1″), 84.3 (C-4″), 81.3 (C-2″), 78.7 (C-3″), 67.7 (C-5″), and 18.3 (CH_3 at C-5″) arise from enriched carbon atoms establishing that glucose is directly converted to nogalose. The results were not as clear with respect to the amino sugar. Peaks at δ 97.0 (C-1′), 75.1 (C-5′), 69.6 (C-4′), 66.4 (C-3′), and 24.0 (CH_3 at C-5′) have heights comparable to those from nogalose and must also arise from enriched carbon atoms, strongly suggesting that the amino sugar is derived from glucose. However, no enriched peak for C-2′ was seen. All of the methyl groups show evidence of ^{13}C enrichment indicating degradation of glucose to one-carbon fragments which were ultimately used for methylation.

The addition of $^{13}CH_3$-labeled methionine to *S. nogalater* fermentations gave **1** whose ^{13}C NMR spectrum (Figure 6) showed substantial enrichment in the four CH_3O groups (δ 61.4, 58.9, 52.6, and 48.8), in the methyl groups attached to nitrogen (δ 41.6), and in one CH_3C group, the one at C-3″ in nogalose. Relative peak heights in Figures 1 and 6 quite clearly establish the enriched carbon atoms. These results confirm that methyl groups on heteroatoms arise from methionine, and that at some stage in the conversion of D-glucose to nogalose a transfer of methyl from methionine to C-3″ of nogalose occurs. Figure 11 shows the origin of the various carbon atoms.

Investigation of the biosynthesis of **3** was carried out in the same fashion except using the organism *S. elgreteus*. Because of the nearly identical structures of **2** and **3** it was assumed that results obtained for **3** would hold for **2**. Since yields of **3** were better than those of **2**, the formation of **3** was studied. Incorporation of $CH_3{}^{13}COONa$ into **3** gave material whose ^{13}C NMR spectrum (Figure 7) indicated substantial enrichment of nine-carbon atoms with ^{13}C while there was slight enrichment of CH_3O groups and sugar carbon atoms. The enrichment of the nine most enriched carbon atoms calculated on the basis of relative peak heights was at least 20-fold. These highly enriched carbon atoms were C-5, C-2, C-4, C-6, C-10a, C-11a, C-12a, C-9, and C-7. The latter carbon atom was apparently misassigned at δ 70.2[9] originally and it should have been δ 71.6 with C-3′ at δ 70.2 (Figure 2). This pattern of enrichment would be appropriate for formation of steffimycinone (the aglycone of **2** and **3**) from ten acetate units with the

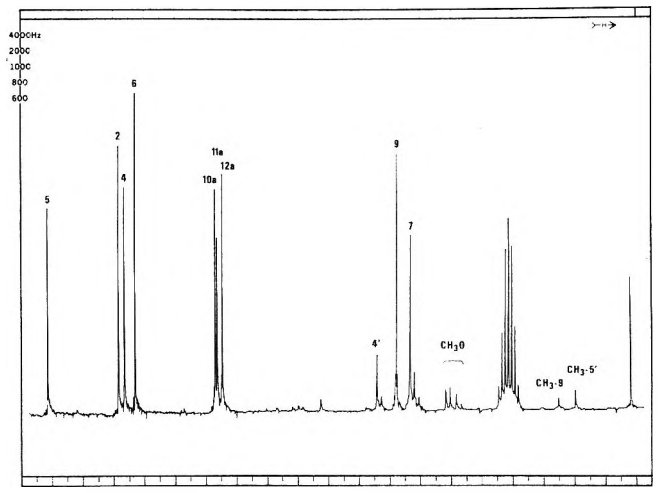

Figure 7. ^{13}C NMR spectrum (Me_2SO-d_6) of steffimycin B from cultures supplemented with $CH_3{}^{13}COONa$.

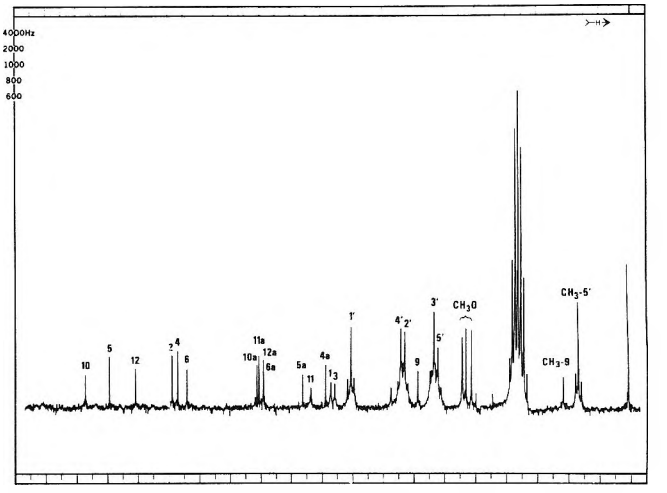

Figure 9. ^{13}C NMR spectrum (Me_2SO-d_6) of steffimycin B from cultures supplemented with uniformly ^{13}C-labeled D-glucose.

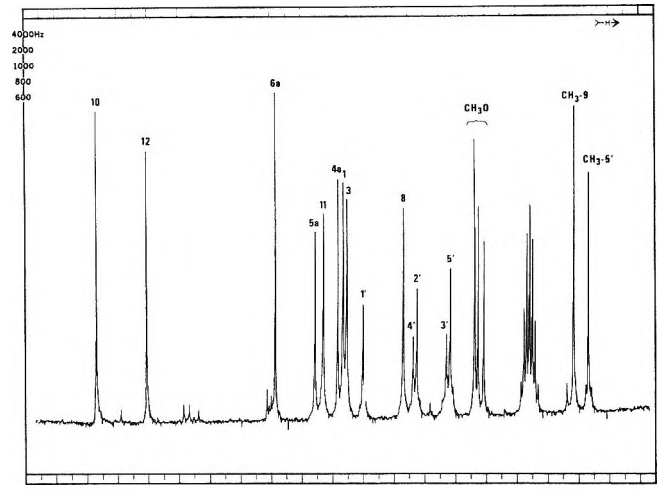

Figure 8. ^{13}C NMR spectrum (Me_2SO-d_6) of steffimycin B from cultures supplemented with $^{13}CH_3COONa$.

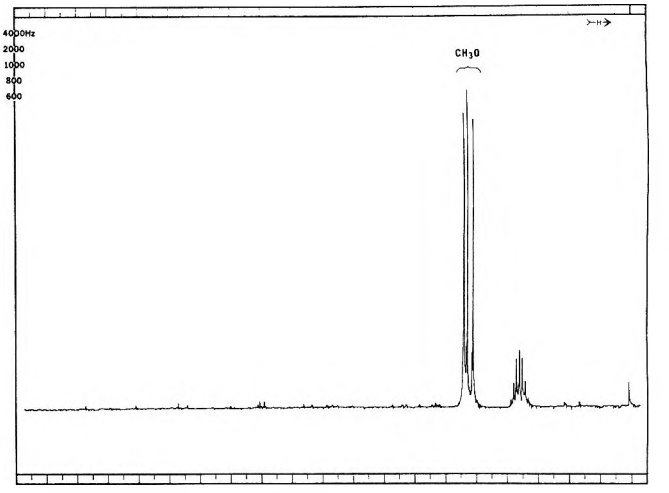

Figure 10. ^{13}C NMR spectrum (Me_2SO-d_6) of steffimycin B from cultures supplemented with $^{13}CH_3$-labeled methionine.

initial acetate giving C-9 and its attached CH_3, and an eventual loss of the carboxyl carbon in the terminal acetate unit as in daunomycin. If such were the case, enrichment with $^{13}CH_3COONa$ should lead to ten highly enriched carbon atoms in steffimycinone, and this is what happens. In the spectrum (Figure 8) obtained from material isolated from an *S. elgreteus* fermentation to which $^{13}CH_3COONa$ had been added, eight aromatic and carbonyl carbon atoms gave peaks which were five- to ten-fold larger than the peaks for the other aromatic carbon atoms. Furthermore, these were the peaks expected from polyacetate synthesis being those arising from C-10, C-12, C-6a, C-5a, C-11, C-4a, C-1, and C-3. However, it appeared that the acetate methyl group had also been incorporated into the sugar and CH_3O carbon atoms making it somewhat more difficult to clearly establish that carbon at C-8 and CH_3 at C-9 were, as would be expected from acetate biosynthesis, greatly enriched with ^{13}C. The height of the C-8 peak is about the same as that of the clearly enriched carbon atoms and about 1.8 times as high as the C-2′ peak whereas in the spectrum of **3** (Figure 2) the height of the C-8 peak is lower than the C-2′ peak height. This change in relative height strongly suggests ^{13}C enrichment at C-8. The C-9 CH_3 group also gives a very strong peak, but it is not in an absolute sense a great deal stronger than is the one for methyl at C-5′. In the spectrum of **3**, the C-9 CH_3 peak is the weaker one whereas in the enriched material it is stronger, and it is obviously many-fold higher than peaks due to C-7 or C-9. Furthermore, such a carbon atom would not be expected to arise from a conversion of ^{13}C methyl or acetate to a one-carbon fragment as could carbon atoms in the sugar. Thus, the patterns seen in the spectra reproduced in Figures 7 and 8 are consistent with the view that steffimycinone arises from ten acetate units starting at the C-9 CH_3 with loss of the terminal carboxyl.

A fermentation of *S. elgreteus* to which ^{13}C uniformly labeled D-glucose had been added gave a sample of **3** whose ^{13}C NMR spectrum is shown in Figure 9. The height of peaks derived from the six C-1′ to C-6′ carbon atoms of the sugar relative to the aromatic carbon peak heights in Figure 9 and in the spectrum of **3** (Figure 2) are such that they demonstrate ^{13}C enrichment of these carbon atoms two- to fivefold. In this case, the glucose must be incorporated intact into the 2,4-di-*O*-methyl-L-rhamnose moiety. The only other carbon atoms enriched were those of the CH_3O groups again suggesting breakdown of glucose to one-carbon units which are used for methylation.

The results of addition of $^{13}CH_3$-labeled methionine to an *S. elgreteus* fermentation were quite clear cut. Figure 10 shows the spectrum of **3** derived from such a fermentation. The carbon atoms of the CH_3O groups were so highly enriched that the peaks arising from them are virtually the only ones visible, and it is clearly shown that methylation on oxygen occurs by direct transfer of methyl groups from methionine with no other methylation by methionine.

Figure 12 shows the origin of the various carbon atoms.

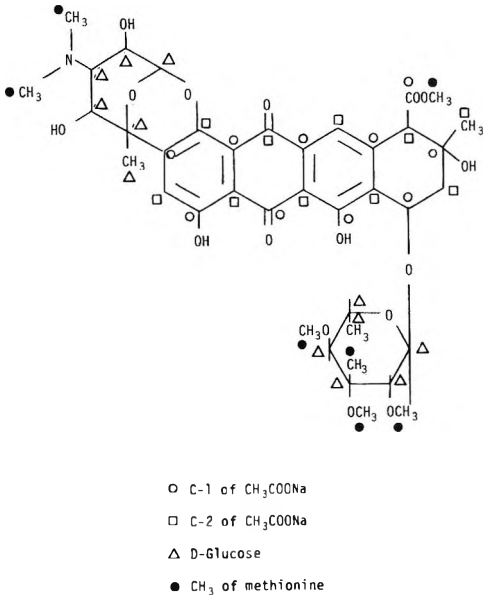

Figure 11. Origin of various carbon atoms in nogalamycin.

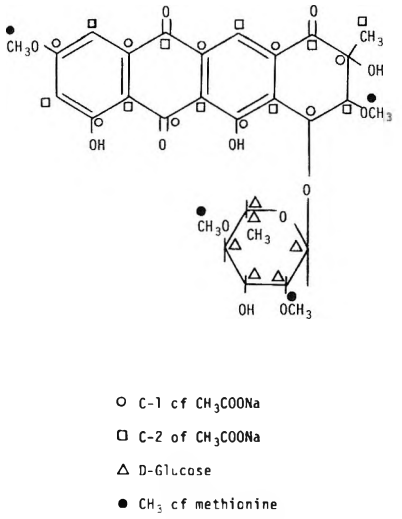

Figure 12. Origin of various carbon atoms in steffimycin B.

Experimental Section

Fermentation. *S. nogalater and S. elgreteus* were stored and maintained on sterile soils in the culture collection of The Upjohn Company and were cultured in seed media as described by Arcamone and co-workers.[10] Following 48 h of aerobic incubation of the seed stage at 28 °C, the cultures were used as inocula (5%) for an inorganic salts medium termed P.A.S.[11] enriched with 0.1% yeast extract and the indicated carbon source. Individual fermentations were carried out in 100-mL volumes in 500-mL wide-mouthed Erlenmeyer flasks shaken at 250 rpm. In all cases, the ^{13}C-enriched carbon sources were either incorporated into P.A.S. before inoculation or were added to cultures 36 h after inoculation. When $CH_3{}^{13}COONa$ or $^{13}CH_3COONa$ (90%, Stohler Isotope Chemicals) was used as a ^{13}C source, they were incorporated into sterile media at a concentration of 1 g/L of P.A.S. In these experiments the P.A.S. medium was additionally supplemented with 0.1% yeast extract and 0.5% unenriched CH_3COONa. Under these conditions, *S. nogalater* and *S. elgreteus* were cultured aerobically at 28 °C for 72–96 h. In the experiments using ^{13}C-labeled D-glucose (>50% uniformly labeled, Merck Sharp & Dohme) and $^{13}CH_3$-labeled methionine (90%, Merck Sharp & Dohme), the ^{13}C-labeled material was injected at 36 h postinoculation as a sterile aqueous solution. In both cases the ^{13}C-carbon sources were added to final concentrations of 60 mg/L of P.A.S. medium enriched with 0.1% yeast extract and 0.5% unenriched CH_3COONa. All fermentations were incubated aerobically at 28 °C for 72 h following isotope addition.

Isolation. (a) Nogalamycin (1). The isolation of 1 was carried out by a previously unpublished procedure developed by Meyer and Hofstetter.[12] A 4- to 4.5-L fermentation was adjusted to pH 2 with concentrated HCl and filtered using filter aid. The filter cake was washed with 1/10 v/v of water, and the filtrate was extracted with three 1/4 v/v of *n*-BuOH. The combined extracts were evaporated to dryness under reduced pressure, and the residue was dissolved in 100 mL of H_2O. The aqueous solution was adjusted to pH 7 with 1 N NaOH and extracted with three 40-mL portions of CH_2Cl_2. The combined extracts were evaporated to dryness under reduced pressure, and the residue was chromatographed on 20 g of silica gel using CH_2Cl_2–CH_3OH (9:1). The fractions containing pure 1 were combined on the basis of TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2) and evaporated to give 30–60 mg of pure 1.

(b) Steffimycin B (3). This was isolated by the procedure of Brodasky and Reusser[13] except for the chromatographic purification. This was done by a combination of preparative TLC ($CHCl_3$–CH_3OH; 95:5) and silica gel chromatography (CH_2Cl_2–CH_3OH; 99:1). The yield from 3- to 3.5-L fermentations was 90–140 mg identified by TLC using $CHCl_3$–CH_3OH (95:5).

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Registry No.—1, 1404-15-5; 3, 54526-94-2.

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Synthesis of the Non-K-region and K-Region *trans*-Dihydrodiols of Benzo[*e*]pyrene

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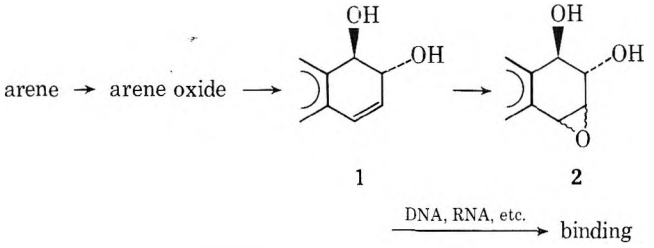
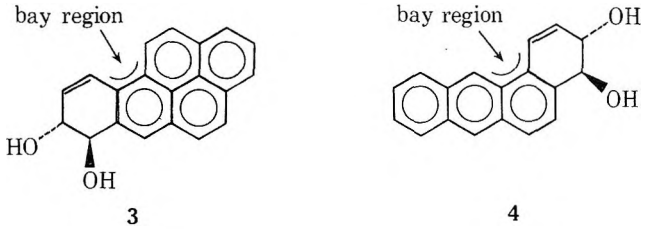
Syntheses of *trans*-9,10-dihydroxy-9,10-dihydrobenzo[*e*]pyrene (**14b**) and of *trans*-4,5-dihydroxy-4,5-dihydrobenzo[*e*]pyrene (**17a**) are described. The preparation of the non-K-region *trans*-dihydrodiol **14b** proceeded via standard procedures from 9-oxo-9,10,11,12-tetrahydrobenzo[*e*]pyrene (**7**), the synthesis of which is described. Intramolecular cyclization of methyl 4-pyrenylbutyrate (**6**) in HF produced primarily the undesired seven-membered ring ketone **8**, but cyclization in hot polyphosphoric acid gave the desired ketone **7** in good yield. Evidence is presented that **8** is the kinetic product of cyclization and that **7** is the more stable isomer which is produced under conditions of thermodynamic control. The NMR spectrum of the non-K-region dihydrodiol **14b** in acetone-d_6 indicates that the hydroxyl groups adopt a predominantly quasi-diaxial conformation. The trans-K-region dihydrodiol **17a** was prepared from benzo[*e*]pyrene [B(e)P] by a multistep procedure involving conversion of B(e)P to the *cis*-diol, oxidation to the quinone, and reduction of the quinone with KBH_4. The *trans*-diol **17a** easily oxidizes in the presence of air.

Recent studies of benzo[*a*]pyrene [B(a)P][1] and benz[*a*]anthracene (BA)[2] have provided strong evidence for the importance of the metabolic route: arene → arene oxide → dihydrodiol → diol epoxide in the activation of those polycyclic aromatic hydrocarbons to ultimate mutagenic and carcinogenic forms. Moreover, these studies have demonstrated that isomeric dihydrodiols (**1**) and diol epoxides (**2**)



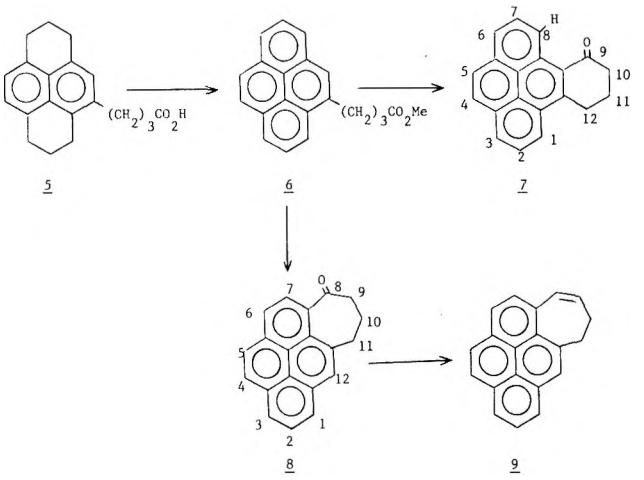
differ considerably in their properties, with dihydrodiols that can form "bay region"[3] diol epoxides being metabolically activated to a considerably greater extent than isomeric dihydrodiols that do not have a double bond that forms part of a bay region. Specifically, for B(a)P and BA, the derivatives **3** and **4** form highly mutagenic and tumorigenic diol epoxides.

We have described a theoretical approach[4] that rationalizes the high reactivity of the diol epoxides derived from **3** and **4**



based upon their calculated relative ease of conversion to carbonium ions.[5] As part of our program to further test the predictive value of the calculations, we have synthesized the K- and non-K-region dihydrodiols of benzo[*E*]pyrene [B(e)P]. Although the tumorigenicity of B(e)P has been questioned, a recent report indicates that B(e)P has significant activity as a tumor initiator.[6] The non-K-region dihydrodiol derived from B(e)P, **14b** (Scheme II), has a double bond in a bay region, and its diol epoxide is calculated to be fairly reactive,

Scheme I



although less reactive than those derived from **3** and **4** ($\Delta E_{deloc}/\beta$ values for **14b**, **3**, and **4** are 0.713, 0.794, and 0.766, respectively). However, if metabolic activation of **14b** to a diol epoxide is important in the carcinogenesis of B(e)P, it may be anticipated that **14b** would be substantially more carcinogenic than B(e)P. Also, unlike other dihydrodiols of PAH thus far prepared, **14b** is unique in having *both* the benzylic hydroxyl group and the double bond form parts of bay regions.

Results and Discussion

Synthesis of 9-Oxo-9,10,11,12-tetrahydrobenzo[*e*]pyrene (7). A general synthetic approach to the preparation of non-K-region dihydrodiols of PAH utilizes as starting material an appropriate tetrahydrobenzo ring ketone.[7] The required ketone (**7**, Scheme I) for the synthesis of **14b** has not been previously described in the literature. The ester, **6**, was prepared in 90% overall yield from γ-1,2,3,6,7,8-hexahydro-4-pyrenylbutyric acid (**5**)[8] by esterification followed by dehydrogenation. Cyclization of **6** in HF afforded two light yellow aromatic ketones, **7** and **8** (**7**/**8** = 1:7). The seven-membered ring ketone **8** was also the major product when the acid chloride derived from **6** was cyclized in $AlCl_3$/benzene.

The nuclear magnetic resonance (NMR) spectrum of **7** allowed its assignment as the desired six-membered ring ketone. Thus, the chemical shift of the proton at C_8 in **7** (δ 9.64) is significantly downfield from the other aromatic protons (δ

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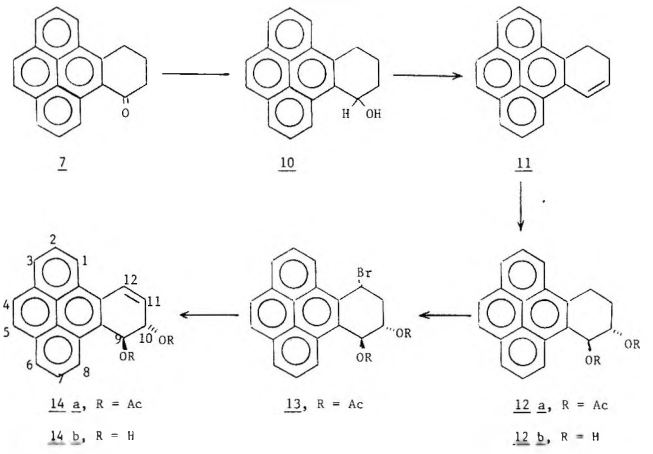
Scheme II



7.95–8.45), as expected for a hydrogen that is in a "bay region" and also in the plane of a carbonyl group. Similarly, H_5 in 4-oxo-1,2,3,4-tetrahydrophenanthrene is shifted downfield (δ 9.45) relative to the other aromatic proton absorptions (δ 7.25–7.95).[7] In contrast, the seven-membered ring ketone, **8**, has all aromatic proton absorptions in the range δ 7.9–8.3. As shown in Scheme II, reduction of **7** with $LiAlH_4$/THF gave alcohol **10** (94%), which was dehydrated in HOAc/HCl to alkene **11** (84%). Dehydrogenation of **11** over Pd/C at 220 °C gave B(e)P, which was identified by its UV spectrum and mixture melting point with an authentic sample. The structure of the seven-membered ring ketone, **8**, was assigned on the basis of consistency with spectral evidence (see Experimental Section) and the source of its production.

Good yields (86%) of the desired six-membered ring ketone, **7**, were obtained upon cyclization of **6** in polyphosphoric acid at 90–100 °C. In polyphosphoric acid at 100 °C, 8 is rapidly isomerized to **7**. Thus, it is likely that 8 is the kinetic product of cyclization, but that under the more forcing conditions in PPA, it is converted to **7**. The formation of seven-membered rather than six-membered rings in intramolecular acylation reactions is unusual. To our knowledge, only two other examples of this type have been reported,[9,10] and in one of those cases the position attacked was activated by a methoxyl group.[9] The kinetically controlled formation of the seven-membered ring ketone from **6** is understandable, in this case, as an intramolecular manifestation of the well-documented much greater reactivity of the C_1 position of pyrene toward Friedel–Crafts acylation relative to the other positions in pyrene.[11]

Attempts to convert the seven-membered ring ketone, **8**, to the unknown hydrocarbon, cyclohepta[*cd*]pyrene, have thus far been unsuccessful. The ketone can be converted to the dihydro compound, **9** (Scheme I), in good yield (86% overall), but both dehydrogenation with DDQ or Pd/C and bromination (NBS)/dehydrobromination (DBN) failed to yield isolable amounts of cyclohepta[*cd*]pyrene.

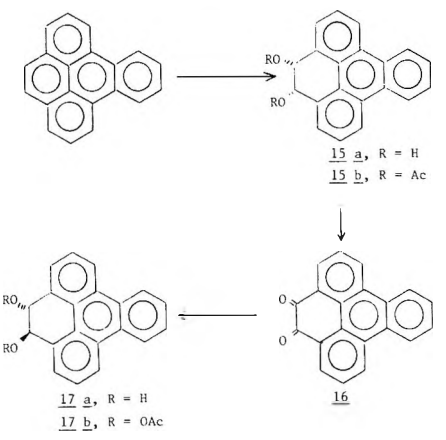
Synthesis of *trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*e*]pyrene, 14b. Ketone **7** was converted to alkene **11** in good yield, as described in the previous section. Conversion of **11** to *trans*-tetrahydrodiacetate **12a** was effected with $AgOAc/I_2$ in 63% yield. Although initial formation of the iodoacetate derivative of **11** was very rapid, prolonged heating at benzene reflux in the presence of excess AgOAc was required to effect formation of **12a**. The major identifiable byproduct of the reaction was B(e)P. The tetrahydrodiacetate, **12a**, was brominated with NBS in CCl_4 to give a high yield (91%) of a mixture of stereoisomeric bromodiacetates (**13**), which was directly dehydrobrominated with DBN in dry THF. Yields of the dihydrodiol diester, **14a**, were variable, ranging from virtually quantitative to very low. Good yields of **14a** seem to require avoidance of extended reaction periods and of high temperatures (an optimum yield was reached at 2.5 h and 0 °C) and careful handling of the crude product, which is very sensitive to acid. On several occasions, handling of a sample of **14a**, known to be pure by NMR, resulted in the formation of additional products, believed to be phenolic acetates based upon the chemical shift of the acetate protons (δ 2.45 and 2.53). Since virtually quantitative yields of **14a** were produced several times from the diastereomeric mixture (roughly 1:1), both stereoisomers evidently suffer dehydrobromination under these conditions.

Conversion of **14a** to dihydrodiol **14b** was effected in ammoniacal MeOH. The crude product was purified by column chromatography on Florisil, followed by crystallization from CH_2Cl_2. Although dihydrodiol **14b** was also sensitive to acid, it proved easier to purify than its precursor, **14a**. Consequently, in relatively large-scale preparations of **14b**, **12a** was converted to **14b** with only minimal purification at intermediate stages. When this approach was used, overall yields of 50–60% were typically achieved in the three-step sequence. Attempts to convert **12a** directly to **14a** with DDQ, by a recently described procedure,[12] were unsuccessful. The structure of dihydrodiol **14b** was firmly established by its spectral properties, most revealing of which was the NMR spectrum (see Experimental Section).

The coupling constant, $J_{9,10}$, between the carbinol hydrogens is not clearly visible in acetone-d_6 and is evidently <1.5 Hz. In Me_2SO-d_6, however, $J_{9,10}$ is measurable as ~0.8 Hz. These values indicate that the hydroxyl groups reside in a predominantly quasi-diaxial conformation, as has been observed for other dihydrodiols in which the benzylic hydroxyl group is in a "bay region".[7,13] In dihydrodiol diacetate **14a**, the immediate synthetic precursor of **14b**, $J_{9,10}$ = 2.2 Hz, again indicative of a predominant quasi-diaxial relationship of the acetoxyl groups. Previous attempts to prepare diol epoxides by direct epoxidation of benz[*a*]anthracene 1,2-dihydrodiol[14] and benzo[*a*]pyrene 9,10-dihydrodiol[15] proved exceedingly difficult because mixtures of products were formed. Like **14b**, these bay region dihydrodiols have hydroxyl groups that reside predominantly in the quasi-diaxial conformation, and they are not stereoselectively attacked on the face of the ring that bears the allylic hydroxyl group.[16] Although dihydrobenzo[*e*]pyrene, **11**, is smoothly epoxidized with *m*-chloroperoxybenzoic acid, dihydrodiol **14b** was converted to several products by a tenfold excess of *m*-chloroperoxybenzoic acid in THF at 0 °C.

Synthesis of *trans*-4,5-Dihydroxy-4,5-dihydrobenzo[*e*]pyrene (17a). The K-region *trans*-dihydrodiol of benzo[*e*]pyrene, **17a**, was prepared in three steps from benzo[*e*]-pyrene, as shown in Scheme III. Oxidation of B(e)P with OsO_4 gave the *cis*-diol **15a**, which was purified by conversion to the diacetate with Ac_2O/pyridine (50% overall yield), followed by conversion back to **15a** (97% yield) in ammoniacal MeOH.

Scheme III



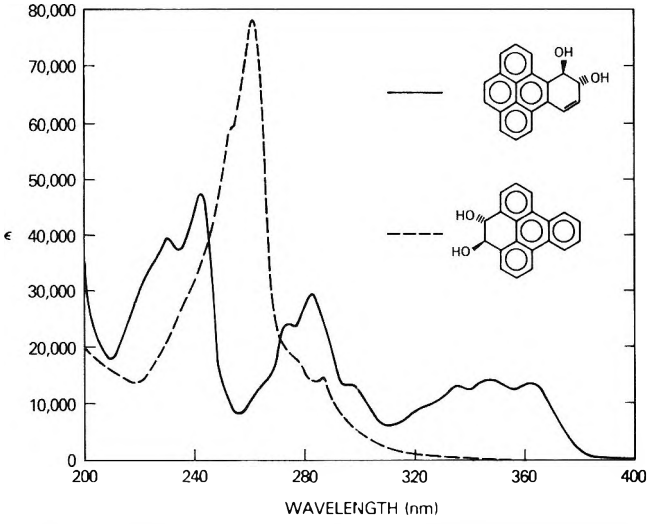


Figure 1. Ultraviolet spectra of *trans*-9,10-dihydroxy-9,10-dihydrobenzo[*e*]pyrene (in EtOH) and *trans*-4,5-dihydroxy-4,5-dihydrobenzo[*e*]pyrene (in 85:15 = MeOH/H_2O).

Oxidation of the *cis*-diol **15a** to the quinone **16** was effected quantitatively with DDQ in dioxane. An attempt to prepare quinone **16** directly from B(e)P by oxidation with $Na_2Cr_2O_7$ in acetic acid was unsuccessful. Reduction of the quinone with KBH_4 gave the crude *trans*-diol **17a**, which was directly converted to the more easily purified *trans*-diacetate **17b**. Ammoniacal MeOH, under N_2, converted **17b** to the air-sensitive *trans*-diol **17a** in quantitative yield. The ultraviolet spectra of the K-region *trans*-dihydrodiol **17a**, and of the non-K-region *trans*-dihydrodiol **14b**, are presented in Figure 1.

Biological Activity. Metabolic activation of isomeric dihydrodiols from BA,[17] 7-methylbenz[*a*]anthracene,[18] chrysene,[19] dibenzo[*a,h*]anthracene,[20] and B(a)P[21] has resulted in the highest mutagenic response for those benzo-ring dihydrodiols which have bay region double bonds, presumably through metabolism to bay region diol epoxides. A major interest in benzo[*e*]pyrene dihydrodiol stems from the fact that it may not be metabolized to a diol epoxide. Benzo[*a*]pyrene 9,10-dihydrodiol, which also has quasi-axial hydroxyl groups, is metabolized almost entirely by hydroxylation of the aromatic nucleus.[15]

Experimental Section

Proton magnetic resonance spectra were recorded on Varian T-60, XL-100, and 220 MHz spectrometers. Unless otherwise noted, $CDCl_3$ was used as solvent. Coupling constants, *J*, are recorded in hertz and chemical shifts in parts per million (δ) with tetramethylsilane as internal standard. UV spectra were recorded on a Cary 16 spectrophotometer. Melting points are uncorrected. The designations α and β are used to indicate relative stereochemistry. Benzo[*e*]pyrene was obtained from Aldrich Chemical Co., Milwaukee, Wisc.

Methyl 4-Pyrenylbutyrate (6). γ-1,2,3,6,7,8-Hexahydro-4-pyrenylbutyric acid (**5**; 2.5 g)[8] was dissolved in MeOH (400 mL) and concentrated HCl (12 drops) was added. After 5 h at room temperature, the reaction was worked up in the usual manner, giving methyl γ-1,2,3,6,7,8-hexahydro-4-pyrenylbutyrate as a light yellow solid (2.62 g, 99%): mp 50–54 °C; ^1H NMR (60 MHz) δ 6.9–7.1 (3 H, m), 3.66 (3 H, s), 1.6–3.3 (12 H, m); M^+ 308. Methyl γ-1,2,3,6,7,8-hexahydro-4-pyrenylbutyrate (2.57 g) and 10% Pd/C (0.25 g) were mixed and heated at 220 °C under N_2 for 3 h. The residue was taken up in EtOAc and filtered through Celite. The EtOAc was removed, leaving a yellow oil which was crystallized from EtOAc/hexane to give **6** as a white solid (2.29 g, 91%): mp 48–50 °C; ^1H NMR (60 MHz) δ 7.8–8.4 (9 H, m), 3.66 (3 H, s), 3.1–3.5 (2 H, m), 2.2–2.6 (4 H, m); M^+ 302.

8-Oxo-8,9,10,11-tetrahydrocyclohepta[*cd*]pyrene (8). Liquid HF (20 mL) was added to ester **6** (1.0 g) in a polystyrene container at 0 °C. The mixture was stirred at room temperature for ~10 h, then H_2O (20 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and H_2O (20 mL). The usual workup left a yellow solid (0.86 g, 96%) of mp 172–174 °C after recrystallization from EtOAc/*i*-PrOH: ^1H NMR (220 MHz) δ 7.9–8.3 (8 H, m), 3.25 (2 H, t), 2.95 (2 H, t), 2.38 (2 H, quintet); M^+ 270. Anal. Calcd for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.77; H, 5.26.

9-Oxo-9,10,11,12-tetrahydrobenzo[*e*]pyrene (7). A solution of ester **6** (6.06 g) in polyphosphoric acid (250 mL, Victor Chemical Co.) was stirred under N_2 for 2 h at 100 °C. The solution was cooled, H_2O (400 mL) was added, and the mixture was extracted with EtOAc (2 × 200 mL). The usual workup yielded a solid residue, which upon recrystallization from benzene/cyclohexane gave **7** as a yellow solid (4.65 g, 86%): mp 133–134 °C; ^1H NMR (220 MHz) δ 9.64 (H_8, dd), 7.95–8.45 (7 H, m), 3.52 (2 H, t), 2.90 (2 H, t), 2.35 (2 H, quintet), $J_{7,8}$ = 7.8, $J_{6,8}$ = 2.0 Hz. Anal. Calcd for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.61; H, 5.35.

10,11-Dihydrocyclohepta[*cd*]pyrene (9). Ketone **8** (300 mg) was added, under N_2, to a mixture of $LiAlH_4$ (40 mg) in freshly distilled THF (10 mL). The mixture was stirred for 5 min, then aqueous NH_4Cl (1 mL) was carefully added dropwise and the mixture was treated with CH_2Cl_2 (75 mL) and H_2O (10 mL) and was filtered. The usual workup gave 8-hydroxy-8,9,10,11-tetrahydrocyclohepta[*cd*]pyrene as a white solid (282 mg, 93%) which was used without further purification. The above alcohol (165 mg) was added, under N_2, to a mixture of glacial HOAc (50 mL) and concentrated HCl (2 drops) at 85 °C and the solution was stirred for 30 min. The reaction mixture was cooled and then poured onto ice (150 g). The white precipitate that formed was collected by filtration, washed extensively with saturated aqueous $NaHCO_3$ and H_2O, and dried to give **9** (143 mg, 93%): mp 113–114 °C; ^1H NMR (60 MHz) δ 7.6–8.2 (8 H, m), 6.85 (H_8, d), 6.26 (H_9, m), 3.2–3.6 (2 H, m), $J_{8,9}$ = 11.5, $J_{7,8}$ = 6.0 Hz. Anal. Calcd for $C_{20}H_{14}$: C, 94.45; H, 5.55. Found: C, 94.17; H, 5.66. Conversion of **9** to the epoxide via the bromohydrin Amberlite route[16] as usual, except that 0 °C workup of the bromohydrin was required to avoid decomposition, afforded 8,9-epoxy-8,9,10,11-tetrahydrocyclohepta[*c,d*]pyrene as a light yellow solid: mp 149–151 °C (dec); ^1H NMR (100 MHz) δ 2.1–4.0 (5 H, m), 4.33 (H_8, d), 7.8–8.3 (8 H, m), $J_{8,9}$ = 4.5 Hz; M^+ 270 (base peak).

9-Hydroxy-9,10,11,12-tetrahydrobenzo[e]pyrene (10). Ketone **7** (3 g) was dissolved in dry THF (30 mL) and added dropwise, under N_2, to a suspension of $LiAlH_4$ (0.153 g) in dry THF (30 mL). The mixture was stirred for 10 min, then aqueous NH_4Cl was added and the mixture was filtered. The collected solids were extensively washed with EtOAc and the solvents were removed under reduced pressure, leaving a yellow solid, which was dissolved in EtOAc (200 mL). The usual workup gave **10** as a yellow solid (2.84 g, 94%) which was used without further purification: ^1H NMR (60 MHz) δ 7.7–8.5 (8 H, m), 5.40 (H_9, m), 2.8–3.3 (2 H, m), 1.7–2.3 (2 H, m).

9,10-Dihydrobenzo[e]pyrene (11). Alcohol **10** (2.84 g) was dissolved, under N_2, in a mixture of glacial HOAc (150 mL) and concentrated HCl (4 drops) at 85 °C and the solution was stirred for 2 h. Ice was added to the mixture and **11** precipitated. The alkene was collected by filtration, washed extensively with saturated aqueous $NaHCO_3$ and H_2O, and dried to give **11** as a yellow solid (2.22 g, 84%), which melted at 120–122 °C after one crystallization from cyclohexane: ^1H NMR (60 MHz) δ 7.9–8.6 (8 H, m), 7.45 (H_{12}, m), 6.40 (H_{11}, m), 3.2–3.6 (2 H, m), 2.3–2.7 (2 H, m), $J_{11,12}$ = 10, $J_{10,12}$ = ~1, $J_{10,11}$ = 5 Hz. The reaction of **11** (80 mg) with *m*-chloroperoxybenzoic acid (550 mg) in anhydrous THF (15 mL) under N_2 for 1.5 h gave, after conventional workup, 9,10-epoxy-9,10,11,12-tetrahydrobenzo[e]pyrene: mp 156–157 °C; ^1H NMR (100 MHz) δ 4.88 (H_9, d), 3.93 (H_{10}, m), $J_{9,10}$ = 4.5 Hz. Attempts to prepare the epoxide via the bromohydrin route were unsuccessful because of competitive formation of small amounts of ring-brominated tetrahydroepoxide, which could not be removed by fractional crystallization.

***trans*-9,10-Diacetoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (12a).** Iodine (1.71 g) was added to a suspension of AgOAc (2.29 g) in dry benzene (150 mL), under N_2. The mixture was stirred for 1 h, then alkene **11** (1.62 g) was added and the mixture was stirred at room temperature for 1 h and then was refluxed for 14 h. The reaction mixture was filtered hot and the solids were washed with hot benzene. The filtrate was concentrated to give a solid which upon recrystallization from CH_2Cl_2/EtOAc gave **12a** as a white solid (1.0 g) of mp 200–202 °C. Additional **12a** (0.5 g) was obtained by concentrating the mother liquor and chromatographing the residue on Florisil, with CH_2Cl_2 as solvent: total yield 1.5 g (63%); ^1H NMR (100 MHz) δ 7.7–8.4 (8 H, m), 6.68 (H_9, d), 5.42 (H_{10}, q), 3.2–3.6 (2 H, m), 2.2–2.6 (2 H, m), 2.10 (3 H, s), 1.96 (3 H, s), $J_{9,10}$ = $J_{10,11}$ = 3.0 Hz; M^+ 372. Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.35; H, 5.36.

12-Bromo-9α,10β-diacetoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (13). A mixture of CCl_4 (50 mL), *N*-bromosuccinimide (50

mg), **12a** (94 mg), and α,α'-azoisobutyrodinitrile (5 mg) was maintained at 65 °C with a heat lamp while a stream of N_2 was passed through the solution. Typical reaction times were 30 min, although the time of initiation varied from 10 min to 1 h, and was noted by the dissolving of the NBS. Workup in the usual manner gave the crude product (86 mg, 91%) as a roughly 1:1 mixture of diastereomeric bromodiacetates. Recrystallization from CCl_4 yielded one isomer: ^1H NMR (60 MHz) δ 8.0–8.8 (8 H, m), 6.87–6.96 (H_9, m), 6.1–6.3 (H_{12}, dd), 5.4–5.6 (H_{10}, m), 2.9–3.3 (2 H, m), 2.08 (3 H, s), 2.05 (3 H, s). Recrystallization of the mother liquors from ether gave the second isomer: ^1H NMR (60 MHz) δ 8.0–8.6 (8 H, m), 7.06 (H_9, d), 6.0–6.4 (2 H, m), 2.6–3.6 (2 H, m), 2.16 (3 H, s), 2.08 (3 H, s). Both isomers were slightly cross-contaminated, and were not purified further.

***trans*-9,10-Diacetoxy-9,10-dihydrobenzo[*e*]pyrene (14a).** To a solution of **13** (250 mg, isomeric mixture) in freshly distilled THF (15 mL) at 0 °C, under N_2, was added 1,5-diazabicyclo[4.3.0]non-5-ene (70 drops). The mixture was stirred at 0 °C for 2.5 h. EtOAc (50 mL) was added and the organic phase was extracted with H_2O (2 × 40 mL), 0.1 N HCl (2 × 40 mL), saturated aqueous $NaHCO_3$ (40 mL), and H_2O (40 mL), dried, filtered, and concentrated to give **14a** as an off-white solid (192 mg, 94%) that was pure by NMR. Recrystallization of **14a** from EtOAc gave material of mp 146–147 °C; ^1H NMR (100 MHz) δ 7.9–8.6 (8 H, m), 7.81 (H_{12}, d), 7.05 (H_9, br s), 6.57 (H_{11}, m), 5.47 (H_{10}, dd), 2.05 (3 H, s), 1.97 (3 H, s), $J_{10,11}$ = 5.6, $J_{11,12}$ = 10.5, $J_{9,10}$ = 2.2 Hz; M^+ 370.

***trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*e*]pyrene (14b).** Diacetate **14a** (106 mg) was dissolved in THF (30 mL) and MeOH (30 mL) and NH_3 was bubbled through the cooled (0 °C) solution for 15 min. The solution was stirred for 28 h at room temperature, then concentrated, and the residue was chromatographed on Florisil with CH_2Cl_2 as the first solvent, which removed minor, highly colored impurities, then with EtOAc/CH_2Cl_2 = 1:1, which eluted **14b** (75 mg, 91%). Although TLC (silica gel, 1:1 = EtOAc/hexane) showed only one spot, **14b** was further purified by recrystallization from CH_2Cl_2, which gave **14b** as an off-white solid: mp 185–186 °C dec; ^1H NMR (100 MHz, acetone-d_6 after exchange with MeOH-d_4) δ 8.6–8.8 (2 H, m), 8.0–8.4 (6 H, m), 7.72 (H_{12}, d), 6.58 (H_{11}, dd), 5.64 (H_9 br s), 4.54 (H_{10}, m), $J_{11,12}$ = 10.0, $J_{10,11}$ = 5.4, $J_{9,11}$ = 1.1 Hz; UV (EtOH) λ_{max} (ϵ) 230 (39 600), 242 (47 300), 275 (24 200), 283 (29 700), 295 (sh, 13 500), 337 (13 200), 347 (14 600), 361 (13 600). The fluorescence spectrum (MeOH, excitation at 242 or 280 nm) exhibited a broad emission, with maxima at 397 and 406 nm, and a shallow minimum at 402 nm. Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.83; H, 5.13.

***trans*-9,10-Dihydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (12b).** Tetrahydrodiacetate **12a** (182 mg) was dissolved in THF (30 mL) and MeOH (60 mL) and NH_3 was bubbled through the cooled (0 °C) solution for 15 min. The solution was stirred for 24 h at 25 °C and concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL). The usual workup gave a residue from which **12b** (110 mg, 78%) was obtained by crystallization from CH_2Cl_2 as an off-white solid: ^1H NMR (100 MHz, acetone-d_6, after exchange with MeOH-d_4) δ 7.9–8.8 (8 H, m), 5.40 (H_9, br s), 4.42 (H_{10}, m), 3.3–3.6 (2 H, m), 2.1–2.8 (2 H, m).

***cis*-4,5-Dihydroxy-4,5-dihydrobenzo[*e*]pyrene (15a).** To benzo[*e*]pyrene (1 g) in pyridine (12 mL) was added a solution of OsO_4 (1 g) in pyridine (2 mL). The solution was stored at room temperature for 6 weeks in the dark. The desired osmate ester, which had separated as a dark precipitate, was decomposed with $NaHSO_3$ in aqueous pyridine[22] followed by extraction of the dihydrodiol into EtOAc. Conventional workup gave the crude product, which was acetylated with Ac_2O/pyridine at room temperature for 16 h. The *cis*-diacetate **15b** (730 mg, 50%) was isolated by preparative layer chromatography on silica gel, using $CHCl_3/CH_3OH$ = 90:5 as solvent, as a solid: mp 192–194 °C; M^+ 370; ^1H NMR (100 MHz) δ 8.4–8.7 (4 H, m), 7.5–7.7 (6 H, m), 6.50 (2 H, s), 2.06 (6 H, s). Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.82; H, 4.89. Found: C, 77.71; H, 5.05. The *cis*-diacetate (600 mg) was dissolved in THF (10 mL) and MeOH (70 mL) and the solution was saturated with NH_3. The reaction was worked up after 24 h at room temperature to give the crude product, which upon recrystallization from EtOAc gave **15a** (450 mg, 97%) as a solid: mp 208–214 °C dec; M^+ 286.

Benzo[*e*]pyrene-4,5-dione (16). A solution of *cis*-dihydrodiol **15a** (50 mg) and DDQ (300 mg) in dioxane (25 mL) was stirred at room temperature overnight. The solvent was removed and the residue was dissolved in $CHCl_3$. The organic phase was washed with saturated Na_2CO_3, dried, and concentrated to give **16** (47 mg, 95%), which upon recrystallization from $CHCl_3$ had mp >320 °C. Anal. Calcd for $C_{20}H_{10}O_2$: C, 85.09; H, 3.57. Found: C, 84.83; H, 3.32.

***trans*-4,5-Dihydroxy-4,5-dihydrobenzo[*e*]pyrene (17a).** A mixture of quinone **16** (149 mg) and KBH_4 (120 mg) in freshly distilled THF (100 mL) and *i*-PrOH (30 mL) was refluxed for 3 days. The reaction was worked up to give the crude *trans*-dihydrodiol, which was converted to the *trans*-diacetate in pyridine (2 mL) and Ac_2O (3 mL) at room temperature for 16 h. The reaction mixture was concentrated to dryness and the *trans*-diacetate **17b** (120 mg, 61%) was isolated by preparative layer chromatography on silica gel using benzene/EtOAc = 95:5 as developing solvent. Recrystallization from MeOH/EtOAc gave **17b** as a solid; mp 201–205 °C; ^1H NMR (100 MHz) δ 8.4–8.8 (4 H, m), 7.5–7.9 (6 H, m), 6.38 (2 H, s), 1.94 (6 H, s); M^+ 370. Anal. Calcd for $C_{24}H_{18}O_4$: C, 77.82; H, 4.89. Found: C, 77.76; H, 4.86. The *trans*-diacetate **17b** was converted to the *trans*-diol **17a** under conditions that were used to convert **15b** to **15a**, except that the reaction was run under N_2 in order to avoid oxidation of the air-sensitive *trans*-dihydrodiol. The *trans*-dihydrodiol **17a** was obtained in quantitative yield: mp >185 °C dec; UV (MeOH) λ_{max} (ϵ) 254 (59 700), 261 (77 950), 287 (14 900); M^+ 286 (base peak). No quinone could be detected by analytical LC.

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Registry No.—**5**, 66787-94-8; **5** methyl ester, 66787-95-9; **6**, 66787-96-0; **7**, 66787-97-1; **8**, 66787-98-2; **9**, 66787-99-3; **10**, 66788-00-9; **11**, 66788-01-0; **12a**, 66788-02-1; **12b**, 66788-03-2; **13** isomer 1, 66808-48-8; **13** isomer 2, 66788-04-3; **14a**, 66788-05-4; **14b**, 66788-06-5; **15a**, 24909-10-2; **15b**, 66788-07-6; **16**, 66788-08-7; **17a**, 66788-09-8; **17b**, 66788-10-1; 8-hydroxy-8,9,10,11-tetrahydrocyclohepta[*cd*]pyrene, 66793-68-8; 9,10-epoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene, 66788-11-2; benzo[*e*]pyrene, 192-97-2.

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Syntheses of Dihydropyrenes and Triple-Layered [2.2]Metacyclophanes

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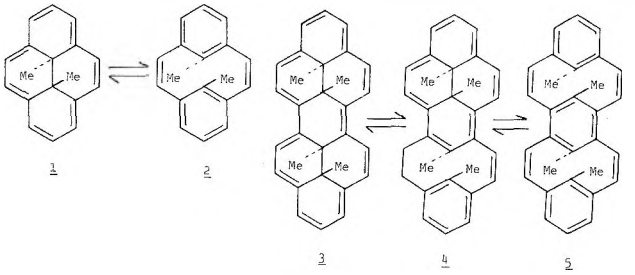
Two synthetic routes have been explored for the possible synthesis of a bridged [22]annulene (**3**) of the peropyrene type. Although the synthesis of **3** was not achieved, a number of *cis*- and *trans*-1,2,3-trisubstituted-15,16-dimethyldihydropyrenes were prepared. Also the triple-layered [2.2]metacyclophane derivative **24** has been synthesized and shown to have a staircase-type geometry.

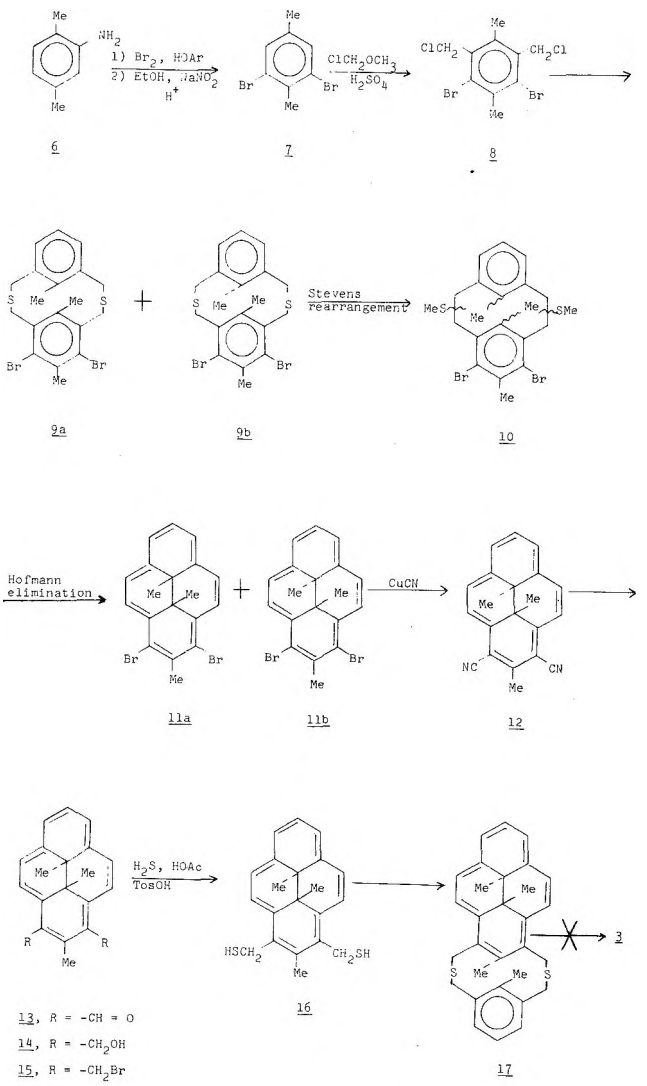
One of the important outstanding problems in Hückel molecular orbital theory is the experimental definition of whether, and at what ring size, the larger [4*n* + 2]annulenes will lose aromaticity and simply show polyene character. As has been discussed elsewhere,[1] bridged [4*n* + 2]annulenes are probably the best experimental models for testing this upper limit. In Haddon's system for empirically evaluating aromaticity by measuring effective ring currents, *trans*-15,16-dimethyldihydropyrene (**1**) is an exceptionally good example



of aromaticity in annulenes and was selected as the reference standard for comparing other molecules.[2] It seemed, therefore, that, in trying to assess the aromaticity of a bridged [22]annulene, a peropyrene structure such as **3**, having a double *trans*-15,16-dimethyldihydropyrene moiety, would be particularly appropriate. Aside from having the desirable features of the dihydropyrenes, structure **3** offers some intriguing possibilities for valence tautomerization. It is well known that the dihydropyrenes readily undergo valence tautomerization (**1** ⇌ **2**) both thermally and photochemically.[3] A similar valence tautomerization of **3** could yield both **4** and **5**, molecules whose relative thermodymamic stability would be of some interest.

The first approach we investigated for the synthesis of **3** is outlined in Scheme I and is based on methods previously developed for the synthesis of *trans*-dihydropyrene derivatives.[4] The steps in the conversion of 2,5-dimethylaniline (**6**) to **8** proceeded in good yield and require no comment. The coupling reaction of **8** with 2,6-bis(mercaptomethyl)toluene gave a mixture of the syn and anti isomers (**9a** and **9b**) of 2,11-dithia-5,7-dibromo-6,8,18-trimethyl[3.3]metacyclophane in an overall yield of 84%, but with a ratio of syn to anti isomers of 1.3:1.0. This is in sharp contrast to the parent example, where the ratio of syn to anti isomers is 1.0:7.0.[4] As has been discussed elsewhere,[5] the relative ratios of syn to anti isomers formed in these coupling reactions is very dependent on what substituents are present. Electron-withdrawing substituents, such as the bromine atoms present in **8**, greatly increase the relative amount of syn isomer formed, presumably due to charge-transfer stabilization of the transition state leading to the syn isomer. The formation of such a large fraction of the syn isomer was unfortunate, both because the anti isomer is the one needed as precursor for the synthesis of **3** and because of the additional difficulties in separation and purification of **11b** from the mixture.

Scheme I



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In practice, it proved expedient to carry along the mixture of isomers, **9a** and **9b**, through the Stevens rearrangement and the Hofmann elimination steps, and then effect the separation and purification at the dihydropyrene stage. In this way the *cis*- and *trans*-1,3-dibromo-2,15,16-trimethyl-15,16-dihydropyrenes, **11a** and **11b**, were isolated in the pure state in yields of 20 and 10%, respectively. Both are deep green, crystalline compounds, which can readily be distinguished by comparison of their NMR spectra with that of the parent *cis*- and *trans*-15,16-dimethyldihydropyrenes.[4] The chemical shift values for the protons of the internal methyls of **11a** are τ 11.97 and 11.89, whereas the protons of the internal methyl groups of **11b** appear at τ 13.98 and 13.93.

Although the von Braun reaction in using a pure sample of **11b** gave **12** in 77% yield, the more convenient use of the crude mixture of **11a** and **11b** in the von Braun reaction led to the desired trans isomer **12** in only 15% yield plus the corresponding cis isomer in 18% yield. Reduction of **12** with diisobutylaluminum hydride in benzene gave **13** in 96% yield and this, in turn, with sodium borohydride led to the diol **14** in 99% yield.

Normally, the next step would have been the conversion of the diol **14** to the corresponding dibromide **15**. However, we were surprised to find that none of the standard procedures for effecting this transformation were successful. In each case polymeric black tars resulted. Apparently, the dihydropyrene moiety is such a good electron donor that the dibromide **15**, when first formed, readily yields the corresponding carbonium ion, which undergoes self-alkylation leading to polymerization. To circumvent this the diol **15** was dissolved in acetic acid containing *p*-toluenesulfonic acid and saturated with hydrogen sulfide. Under these circumstances the carbonium ion derived from **15** is captured by the nucleophilic hydrogen sulfide and the desired dimercaptan **16** was formed in 47% yield.

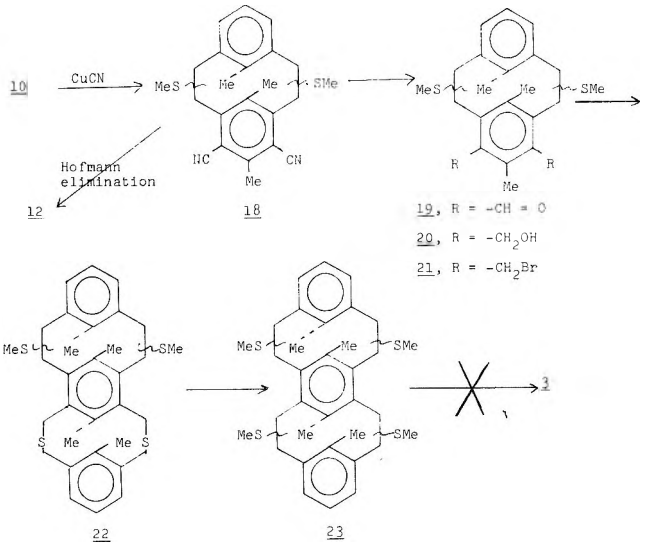
The coupling reaction between **16** and 2,6-bis(bromomethyl)toluene proceeded in high yield to give a mixture of the two possible *anti*-dithiacyclophanes of which **17** appeared to be the predominant isomer. The assignment of anti geometry to the mixture is based on the close correspondence of its NMR spectrum to that of 8,16-dimethyl-2,11-dithia[3.3]metacyclophane.[4] The protons of the internal methyl groups of **17** appear as two singlets at τ 14.17 and 13.58. Also, examination of molecular models suggests that the syn isomer analogous to **17** would be subject to severe steric interactions and so be unlikely to form.

Attempts to convert **17** to **3** by all of the standard methods of ring contraction and sulfur elimination were in each case unsuccessful. The reaction of **17** with dimethoxycarbonium fluoroborate[4] led to immediate tars, presumably via formation of a dihydropyrenyl carbonium ion followed by self-alkylation. However, both the benzyne–Stevens rearrangement[6] and the Wittig rearrangement[7] were also unsuccessful.

In view of our lack of success in effecting the conversion of **17** to **3** and the apparent instability of the dihydropyrene moiety toward the reaction conditions required in the final stages, we decided to try a modified approach starting from **10**, in which both dihydropyrene units would be introduced during the same final reaction. This modified approach is summarized in Scheme II.

When the mixture of stereoisomers from the Stevens rearrangement, depicted by the overall structure **10**, was subjected to the von Braun reaction, only the mixture of isomers having anti geometry, as shown by **18**, could be isolated and it was formed in 52% yield. In support of this assignment **18**, underwent a Hofmann elimination to give only *trans*-1,2-dicyano-2,15,16-trimethyldihydropyrene (**12**), a somewhat more efficient route for the synthesis of **12** than that described earlier. Since the final step in Scheme II was expected to lead

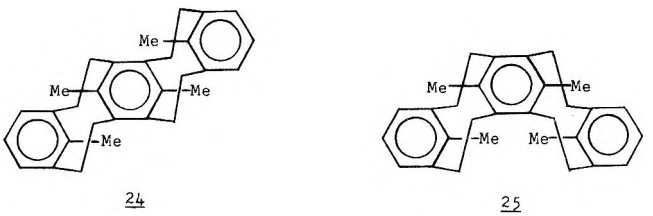
Scheme II

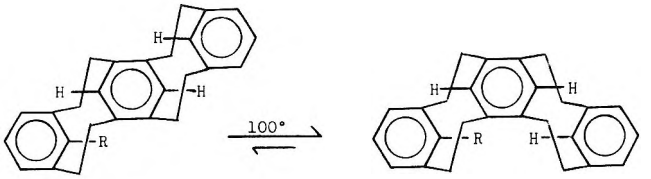


to only one isomer, it was decided not to try to separate the mixture of stereoisomers at this stage, but simply to carry through the intermediate steps with mixtures of stereoisomers.

The conversion, then, of **18** in successive steps to **19**, **20**, and **21** proceeded well following the usual pattern. The coupling of **21** with 2,6-bis(mercaptomethyl)toluene occurred in 65% yield to give the dithiacyclophane **22**. A Wittig rearrangement of **22**, using *n*-butyllithium followed by addition of methyl iodide, proceeded well, giving **23** in 89% yield. Although **23** was obtained as a complicated mixture of isomers, the lack of any signal in the region of τ 3.5, where the aromatic protons of *syn*-[2.2]metacyclophanes appear, rules out the presence of any isomers having syn geometry. Thus, the mixture of isomers represented by **23** appeared to be a suitable precursor for **3**. Unfortunately, however, the standard methods for removing sulfur with concomitant introduction of carbon–carbon double bonds, both the Hofmann elimination and the pyrolysis of the corresponding tetrasulfoxide, were completely unsuccessful in converting **23** to **3**.

As additional proof for the structural assignment made to **23**, it was subjected to desulfurization using Raney nickel. As expected, this gave the triple-layered [2.2]metacyclophane **24**. The question of whether the triple-layered cyclophane should be assigned the conformation shown by **24** or that of **25** was of some interest. It is now known that for benzene rings, in contrast to cyclohexane rings, it requires less energy to deform the ring to a boat than to a chair conformation.[8-10] This is due to the fact that the benzene π-orbital overlap is





26, R = -H
28, R = -Me
27, R = -H
29, R = -Me

more favorable in the boat than in the chair conformation. Umemoto, Otsubo, and Misumi provided the first experimental evidence for this preference when they prepared the two conformations, **26** and **27**, of the triple-layered [2.2]metacyclophane and showed that equilibration between these two conformations occurred readily at 100 °C with **27** being strongly favored.[11] In **27** all three benzene rings have boat conformations, whereas in **26** the central benzene ring is forced into a chair conformation. The driving force for the isomerization of **26** to **27** is the change in the central benzene ring from a chair to a boat conformation. Since Gschwend has shown that the energy barrier for conformational flipping for simple [2.2]metacyclophanes is about 33 kcal/mol,[12] it is remarkable that the isomerization of **26** to **27** should occur so readily.

Furthermore, this same study by the Osaka group showed that even with an internal methyl substituent, as in **28** and **29**, equilibration again occurred at 100 °C giving a mixture of **28** and **29** in a ratio of 1:17. In the case of **29**, a strong nuclear Overhauser effect was observed for the internal methyl and hydrogen substituents, which are forced into close proximity in the up–down conformation. In contrast, **28** does not exhibit a nuclear Overhauser effect. The differences in geometry between **28** and **29** are also evident in their NMR spectra; the signal for the internal methyl protons of **28** appear at τ 9.42, whereas in **29** they are seen at τ 8.93. Our product from the Raney nickel desulfurization of **23** was purified by sublimation at 150 °C and was a single compound. Its NMR spectrum showed the protons of the internal methyl groups as two singlets at τ 9.34 and 9.54. These values are in accord with that of **28** and permit the assignment of the staircase-type geometry of **24** to our tetramethyl derivative. Examination of molecular models suggests that the up–down conformation **25** would have severe, if not prohibitive, steric interactions between the internal methyl groups.

Experimental Section[13]

1,4-Dimethyl-2,6-dibromo-3,5-bis(chloromethyl)benzene (8) The bromination of 2,5-dimethylaniline was carried out as described by Bures and Meskan[14] and on a 4 M scale gave 2,4-dibromo-3,6-dimethylaniline, mp 58–59 °C (lit.[14] mp 61 °C), in 92% yield. This was then subjected to deamination following the procedure of Coleman and Talbot[15] to give 2,6-dibromo-*p*-xylene as a yellow oil [bp 82–88 °C (2 mm)] in 56% yield. A solution of 30.0 g of 2,6-dibromo-*p*-xylene in 75 mL of chloromethyl methyl ether was boiled gently under reflux while 30 mL of fuming sulfuric acid (30%) was added dropwise over a period of 30 min. A precipitate formed during the reaction and this was collected by filtration followed by a brief wash with water on the filter. The resulting solid was recrystallized from carbon tetrachloride to give 35.0 g (94%) of colorless needles: mp 185–187 °C; NMR, singlet at τ 5.2 (4 H, $-CH_2Cl$), and singlets at 7.30 and 7.40 (3 H each, $-CH_3$); mass spectrum *m/e* 361. Anal. Calcd for $C_{10}H_{10}Br_2Cl_2$: C, 33,26; H, 2.77. Found: C, 33.12; H, 2.75.

***syn*- and *anti*-2,11-Dithia-5,7-dibromo-6,9,18-trimethyl[3.3]metacyclophanes (9a and 9b).** A solution of 8.44 g of 1,4-dimethyl-2,6-dibromo-3,5-bis(chloromethyl)benzene (**8**) and 4.30 g of 2,6-bis(mercaptomethyl)toluene[4] in 700 mL of benzene was added dropwise with stirring to a boiling solution of 4.2 g of potassium hydroxide in 2 L of ethanol under a nitrogen atmosphere. After the addition was complete (3 days), the solvent was removed under reduced pressure and the residual solid was extracted with benzene. After concentration of the benzene extract, there separated 9.35 g (84%) of a colorless solid whose NMR spectrum showed it to be a mixture of the syn and anti isomers, **9a** and **9b**, in a ratio of 1.3:1.0. The two isomers could be separated by TLC, but it proved more convenient to allow the mixture to crystallize from benzene and then mechanically separate the syn (plates) and anti (needles) isomers.

In this way the syn isomer (**9a**) was isolated as colorless plates: mp 236–238 °C; NMR, an A_2B multiplet at τ 3.0–3.4 (3 H, ArH), two AB multiplets at 4.95 and 6.44 (4 H, J = 15 Hz, $ArCH_2-$) and at 5.93 and 6.15 (4 H, J = 15 Hz, $ArCH_2-$), and singlets at 7.32, 7.33, and 7.40 (3 H each, CH_3-); mass spectrum *m/e* 472. Anal. Calcd for $C_{19}H_{20}S_2Br_2$: C, 48.32; H, 4.27. Found: C, 48.41; H, 4.25.

The trans isomer (**9b**) was isolated as colorless needles: mp 234–236 °C; NMR, an A_2B multiplet at τ 2.6–2.9 (3 H, ArH), two AB multiplets at 5.94 and 6.30 (4 H, J = 15 Hz, $ArCH_2-$) and 6.26 and 6.30 (4 H, J = 15 Hz, $ArCH_2-$), and singlets at 7.11, 8.37, and 8.90 (3 H each, $-CH_3$); mass spectrum *m/e* 472. Anal. Calcd for $C_{19}H_{20}S_2Br_2$: C, 48.32; H, 4.27. Found: C, 48.41; H, 4.27.

Stevens Rearrangement to Give 10. To a solution of 13.7 g of the mixture of **9a** and **9b** from the above experiment in 400 mL of methylene chloride held at −20 °C was added portionwise with stirring 10.1 g of dimethoxycarbonium fluoroborate.[16] After several hours the solution was allowed to warm to room temperature and the solvent was removed by decantation. The crystalline residue was washed several times with methyl formate and dried to give 18.2 g (93%) of white crystals, mp 209–213 °C dec. Anal. Calcd for $C_{21}H_{26}S_2Br_2B_2F_8$: C, 37.31; H, 388. Found: C, 37.64; H, 3.90.

The bissulfonium salt (18.2 g) was dissolved in 300 mL of dry tetrahydrofuran and then 6.2 g of potassium *tert*-butoxide was added all at once. After addition of dilute aqueous hydrochloric acid, the organic layer was extracted with ether, dried, and concentrated to give 12.6 g (93%) of a pale yellow oil. The NMR spectrum of **10** was very complicated, showing it to be a mixture of stereoisomers of both syn and anti geometry. The high-resolution mass spectrum of **10** showed the parent molecular ion at 497.970 (calcd for $C_{21}H_{24}S_2Br_2$: 497.969). Anal. Calcd for $C_{21}H_{24}S_2Br_2$: C, 50.41; H, 4.83. Found: C, 50.54; H, 4.88.

Hofmann Elimination to Give 11a and 11b. To a solution of 12.6 g of **10** in 150 mL of methylene chloride held at 0 °C under a nitrogen atmosphere there was added 8.9 g of dimethoxycarbonium fluoroborate.[16] After the mixture had warmed to room temperature, it was stirred for 24 h and then 50 mL of ethyl acetate was added. The solvent was removed by decantation and the residue was washed with methyl formate and dried to give 16.0 g (90%) of a pale brown glass. Anal. Calcd for $C_{23}H_{30}S_2Br_2B_2F_8$: C, 39.24; H, 4.30. Found: C, 39.40; H, 4.47.

To a solution of 1.3 g of sodium hydride in 400 mL of dry tetrahydrofuran was added 15.0 g of the bissulfonium salt with stirring under a nitrogen atmosphere. In those runs where the solution did not turn an immediate deep green, the solvent was removed by decantation and replaced by fresh, dry tetrahydrofuran containing the appropriate amount of sodium hydride. When there was no longer any change in color, the solution was filtered and the filtrate was concentrated. The resulting green solid was taken up in petroleum ether (30–60 °C) and chromatographed over silica gel.

***trans*-1,3-Dibromo-2,15,16-trimethyldihydropyrene (11b)** was isolated from the first eluate fraction and, after recrystallization from pentane, was obtained as 800 mg (10%) of deep green, nearly black, crystals: mp 187–188 °C; NMR, an AB at τ 1.02 and 1.32 (4 H, J = 8 Hz, ArH), an A_2B at 1.42 (2 H, J = 8 Hz, ArH) and 1.93 (1 H, J = 8 Hz, ArH), and singlets at 6.58, 13.93, and 13.98 (3 H each, $-CH_3$); mass spectrum *m/e* 404, 389, and 374. Anal. Calcd for $C_{19}H_{16}Br_2$: C, 56.47; H, 3.99. Found: C, 56.50; H, 4.02.

***cis*-1,3-Dibromo-2,15,16-trimethyldihydropyrene (11a)** was isolated from the second fraction of eluate and, after recrystallization from pentane, was obtained as 1.60 g (20%) of deep green crystals: mp 178–180 °C; NMR, an AB at τ 0.83 and 1.28 (4 H, J = 8 Hz, ArH), an A_2B at 1.81 (2 H, J = 8 Hz, ArH) and 2.50 (1 H, J = 8 Hz, ArH), and singlets at 6.33, 11.89, and 11.97 (3 H each, $-CH_3$); mass spectrum *m/e* 404, 389, and 374. Anal. Calcd for $C_{19}H_{16}Br_2$: C, 56.47; H, 3.99. Found: C, 56.38; H, 3.89.

***cis*- and *trans*-1,3-Dicyano-2,15,16-trimethyldihydropyrenes (12).** The crude mixture of **11a** and **11b** (ratio of 2:1) from the Hofmann elimination reaction, weighing 4.66 g, was dissolved in 30 mL of *N*-methylpyrrolidone containing 11.3 g of cuprous cyanide and heated at 110 °C for 20 h under a nitrogen atmosphere. The warm dark solution was poured into 500 mL of a 1:1 mixture of water and concentrated aqueous ammonium hydroxide solution. After the solution had been stirred for 3 h, the solid was collected by filtration and dried. It was then mixed with silica gel, placed at the top of a silica gel column, and eluted with a 1:1 mixture of benzene and carbon tetrachloride.

***trans*-1,3-Dicyano-2,15,16-trimethyldihydropyrene (12)** was recovered from the first fraction of eluate and, after recrystallization from a benzene–hexane mixture, gave 290 mg (15%) of deep green plates: mp 197 °C; NMR, an AB at τ 0.95 and 1.14 (4 H, J = 8 Hz, ArH), an A_2B at 1.19 (2 H, J = 8 Hz, ArH) and 1.74 (1 H, J = 8 Hz, ArH), and singlets at 6.50, 13.94, and 13.98 (3 H each, $-CH_3$); mass spectrum *m/e* 296, 281, and 266. When the above experiment was repeated using pure **11b**, the yield of **12** was 77%. Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 84.95; H, 5.48; N, 9.24.

***cis*-1,3-Dicyano-2,15,16-trimethyldihydropyrene** was recovered from the second fraction of eluate and, after recrystallization from

a benzene–hexane mixture, gave 360 mg (18%) of deep green crystals: mp 185–187 °C; NMR, an AB at τ 0.74 and 0.99 (4 H, J = 8 Hz, ArH), an A_2B at 1.52 (2 H, J = 8 Hz, ArH) and 2.24 (1 H, J = 8 Hz, ArH), and singlets at 6.72, 11.88, and 11.96 (3 H each, $-CH_3$); mass spectrum m/e 296, 281, and 266. The cis isomer reacts readily with oxygen in the presence of light, even indirect laboratory lighting.[17] Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 84.87; H, 5.39; N, 9.32.

***trans*-1,3-Diformyl-2,15,16-trimethyldihydropyrene (13).** To a solution of 420 mg of **12** in 100 mL of dry benzene was added dropwise with stirring a 20% solution of diisobutylaluminum hydride in benzene. After the solution had been stirred at room temperature for 10 min, there was added successively 5 mL of methanol, 20 mL of dilute aqueous hydrochloric acid, and 500 mL of benzene. Hydrolysis of the aldimine was complete in about 30 min, whereupon the benzene layer was separated, dried, and concentrated to give 410 mg (96%) of deep green crystals: mp 190–192 °C; NMR, a singlet at τ −1.58 (2 H, –CHO), an AB at 0.60 and 1.28 (4 H, J = 8 Hz, ArH), an A_2B at 1.36 (2 H, J = 8 Hz, ArH) and 1.92 (1 H, J = 8 Hz, ArH), singlets at 6.54, 13.61, and 13.78 (3 H each, $-CH_3$); mass spectrum m/e 302, 287, and 272. Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.32; H, 5.94.

***trans*-1,3-Bis(hydroxymethyl)-2,15,16-trimethyldihydropyrene (14).** To a solution of 400 mg of **13** in 250 mL of dry tetrahydrofuran at room temperature was added 100 mg of sodium borohydride. After the mixture had been stirred for 4 h, it was cooled to 0 °C and dilute aqueous hydrochloric acid was added, followed by ether. The organic layer was separated, dried, and concentrated to give 400 mg (99%) of green crystals: mp 210–212 °C; NMR, an AB at τ 1.11 and 1.36 (4 H, J = 8 Hz, ArH), an A_2B at 1.44 (2 H, J = 8 Hz, ArH) and 1.97 (1 H, J = 8 Hz, ArH), an AB at 4.16 (2 H, J = 12 Hz, $ArCH_2OH$) and 4.30 (2 H, J = 12 Hz, $ArCH_2OH$), and singlets at 6.73, 13.99, and 14.08 (3 H each, $-CH_3$); mass spectrum m/e 306. Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.06; H, 7.16.

***trans*-1,3-Bis(mercaptomethyl)-2,15,16-trimethyldihydropyrene (16).** A solution of 165 mg of **14** in 150 mL of glacial acetic acid was saturated with dry hydrogen sulfide and 40 mg of *p*-toluenesulfonic acid was added in one portion. The mixture was stirred at room temperature for 3 h while bubbling hydrogen sulfide through the mixture. After addition of 200 mL of water, the mixture was extracted with benzene and the benzene extract was washed with water and dried. Concentration of the benzene extract followed by chromatography of the residual solid over deactivated silica gel using a 1:1 mixture of benzene–petroleum ether (30–60 °C) for elution gave 85 mg (47%) of green crystals: mp 103–105 °C; NMR, an AB at τ 1.37 and 1.41 (4 H, J = 8 Hz, ArH), an A_2B at 1.49 (2 H, J = 8 Hz, ArH) and 2.00 (1 H, J = 8 Hz, ArH), an ABX at 5.08 and 5.34 (4 H, J_{AB} = 14 and J_{AX} = 7 Hz, $ArCH_2SH$), a triplet at 8.04 (2 H, J = 7 Hz, –SH), and singlets at 6.86, 13.97, and 14.07 (3 H each, $-CH_3$); mass spectrum m/e 338. Anal. Calcd for $C_{21}H_{22}S_2$: C, 74.53; H, 6.55. Found: C, 74.23; H, 6.32.

Dithiacyclophane 17. A solution of 17 mg of **16** and 14 mg of 2,6-bis(bromomethyl)toluene in 35 mL of benzene was added dropwise with stirring under a nitrogen atmosphere to a solution of 30 mg of potassium hydroxide in 500 mL of ethanol held at room temperature. When the addition was complete (5 h), the solution was concentrated and the solid residue was extracted with benzene. Concentration of the benzene extract gave 27 mg (100%) of deep green crystals melting over a broad range. This appeared to be a mixture of the two possible anti isomers having the overall structure shown by **17**. Since the usual methods of separation and purification of these isomers by chromatography were not effective, the mixture of isomers was used directly in the attempts to synthesize **3**. The mixture showed an NMR spectrum having a multiplet in the region of τ 1.4–2.2 (ArH), a multiplet at 2.7–2.9 (ArH), two sets of AB patterns at 5.11 and 5.66 (J_{AB} = 15 Hz, $ArCH_2S$–) and 6.03 and 6.48 (J_{AB} = 14 Hz, $ArCH_2S$–), and singlets at 8.28, 8.73, 9.20, 13.58, and 14.17 (CH_3–); high-resolution mass spectrum m/e 454.180 (calcd for $C_{30}H_{30}S_2$: 454.179).

When a solution of the mixture of anti isomers corresponding to the **17** in methylene chloride was treated with dimethoxycarbonium fluoroborate, immediate formation of a black, polymeric tar occurred. So it was not possible to effect a normal Stevens rearrangement. Similarly, the benzyne–Stevens rearrangement procedure[6] gave no useful product. Furthermore, an attempt to effect a Wittig rearrangement[7] was likewise unsuccessful.

von Braun Reaction with 10 to Give 18. A solution of 2.47 g of the mixture of isomers corresponding to **10** and 8.0 g of cuprous cyanide in 60 mL of *N*-methylpyrrolidone was heated at 165 °C for 21 h. It was then poured into 400 mL of a 1:1 mixture of water and concentrated aqueous ammonium hydroxide. After the resulting mixture had been stirred with cooling for 3 h, the solid precipitate was collected by filtration, washed with water, and dried. The resulting solid was mixed with silica gel, placed at the top of a silica gel column, and eluted with methylene chloride. From the eluate there was isolated 1.01 g (52%) of a yellow oil: NMR, an A_2B multiplet at τ 2.2–3.0 (3 H, ArH), a multiplet at 5.8–6.9 (6 H, $ArCH_2$– and ArCH–), a singlet at 7.28 (3 H, $-CH_3$), a singlet at 7.72 (6 H, CH_3S–), and singlets at 8.6 and 9.4 (3 H each, CH_3–); high-resolution mass spectrum m/e 392.137 (calcd for $C_{23}H_{24}N_2S_2$: 392.138). From the NMR spectrum it is clear that **18**, although a mixture of stereoisomers, has entirely the anti geometry.

Treatment of **18** under the conditions for the Hofmann elimination, as described earlier, gave *trans*-1,3-dicyano-2,15,16-trimethyldihydropyrene (**12**) in 25% yield as deep green crystals, mp 197 °C, identical in all respects with the sample of **12** described previously.

Conversion of 18 to 19, 20, 21, and 22. To a solution of 1.01 g of **18** in 50 mL of dry benzene was added dropwise with stirring 5 mL of an 18% solution of diisobutylaluminum hydride in benzene. After the mixture had been stirred at room temperature, it was coooled and successive additions with stirring were made of 10 mL of methanol, 5 mL of water, and 30 mL of dilute aqueous hydrochloric acid. The organic layer was separated, washed with water, dried, and concentrated to give 500 mg (49%) of a pale orange oil: NMR, a singlet at τ −0.68 (2 H, –CHO), an A_2B multiplet at 2.2–3.1 (3 H, ArH), a broad multiplet at 4.7–8.2 (15 H, ArCH<, $ArCH_2$–, $-CH_3$, CH_3S–), and broad singlets at 8.7 and 9.5 (6H, $-CH_3$); high-resolution mass spectrum m/e 398.137 (calcd for $C_{23}H_{26}S_2O_2$: 398.137). The spectral data are fully in accord with the assignment of structure **19** to this oil.

A mixture of 500 mg of **19** and 45 mg of sodium borohydrde in 15 mL of dry tetrahydrofuran was stirred at room temperature for 3 h. It was then decomposed by the addition of dilute aqueous hydrochloric acid. The organic layer was extracted with ether, dried, and concentrated to give 507 mg (100%) of a pale yellow oil: NMR, a multiplet at τ 2.1–3.1 (3 H, ArH), a broad singlet at 5.10 (4 H, $-CH_2OH$), a multiplet at 5.0–7.9 (15 H, ArCH<, $ArCH_2$–, $-CH_3$, CH_3S–), a broad singlet at 8.24 (2 H, –OH), and broad singlets at 8.7 and 9.5 (3 H each, $-CH_3$); high resolution mass spectrum m/e 402.168 (calcd for $C_{23}H_{30}S_2O_2$: 402.169). The spectral data are fully in accord with the assignment of structure **20** to this oil.

To a stirred solution of 107 mg of **20** in 15 mL of dry benzene there was added dropwise a solution of 63 mg of phosphorus tribromide in 3 mL of benzene. After the mixture had been stirred for 2 h, it was washed with ice water, dried, and concentrated to give 94 mg (67%) of a yellow oil: NMR, a multiplet at τ 2.1–3.0 (3 H, ArH), a multiplet at 5.28 (4 H, $-CH_2Br$), a multiplet at 4.6–7.0 (6 H, ArCH<, $ArCH_2$–), a multiplet at 7.0–7.8 (9 H, CH_3–), broad singlets at 8.7 and 9.5 (6 H, CH_3–); mass spectrum m/e 526, 528, and 530 (the relative peak intensities correspond to the expected bromine isotope distribution for $C_{23}H_{28}S_2Br_2$). These spectral data are in accord with the assignment of structure **21** to this oil.

A solution of 94 mg of **21** and 32 mg of 2,6-bis(mercaptomethyl)-toluene in 20 mL of benzene was added dropwise with stirring to a solution of 98 mg of potassium hydroxide in 500 mL of ethanol. When the addition was complete (5 h), the mixture was stirred an additional 12 h and then concentrated. The residue was taken up in benzene and chromatographed over silica gel to give 65 mg of a pale yellow oil: NMR, a multiplet at τ 2.1–3.1 (6 H, ArH), a multiplet at 5.3–8.0 (20 H, ArCH<, $ArCH_2$–, CH_3S–), and a series of broad singlets at 8.5–9.6 (12 H, $-CH_3$); high-resolution mass spectrum m/e 550.185 (calcd for $C_{32}H_{38}S_4$: 550.186). These spectral data are fully in accord with the assignment of structure **22** to this product.

Wittig Rearrangement of 22 to Give 23. To a solution of 51 mg of **22** in 3 mL of dry tetrahydrofuran there was added by syringe 0.10 mL of a 2 N solution of *n*-butyllithium in hexane. After 10 min, 0.03 mL of methyl iodide was added, followed by 5 mL of water. The organic layer was extracted with methylene chloride, washed with water, dried, and concentrated to give 48 mg (89%) of a yellow oil; NMR, a multiplet at τ 2.1–3.1 (6 H, ArH), a multiplet at 5.9–8.0 (12 H, ArCH<, $ArCH_2$–), a series of singlets at 7.8–7.9 (12 H, CH_3S–), and a series of singlets at 8.4–9.6 (12 H, CH_3–); mass spectrum m/e 578. These data are in accord with the assignment of structure **23** to this oil.

Triple-Layered [2.2]Metacyclophane 24. A solution of 48 mg of **23** in 40 mL of a 3:1 mixture of absolute alcohol and benzene containing commercial Raney nickel was boiled under reflux for 18 h. After removal of the Raney nickel and concentration of the filtrate, the residue was taken up in hexane and chromatographed over silica gel. The main fraction of eluate gave 2.5 mg (8%) of colorless crystals. These were purified by sublimation at 150 °C (10^{-4} mm) to give white crystals: mp 320 °C (sealed tube); NMR, an A_2B multiplet at τ 2.88 (4 H, d, J_{AB} = 7 Hz, ArH) and 3.20 (2 H, t, J_{AB} = 7 Hz, ArH), a multiplet at 6.5–7.9 (16 H, $ArCH_2$–), and singlets at 9.34 and 9.54 (6 H each, CH_3–); high-resolution mass spectrum m/e 394.265 (calcd for

$C_{30}H_{34}$: 394.266).

Acknowledgment. We thank the National Science Foundation for their support of this investigation.

Registry No.—**8,** 66788-12-3; **9a,** 66793-69-9; **9a** bis(methylsulfonium) derivative BF_4 salt, 66788-15-6; **9b,** 66808-49-9; **9b** bis(methylsulfonium) derivative BF_4 salt, 66788-15-6; **9b,** 66808-49-9; **9b** bis(methylsulfonium) derivative BF_4 salt, 66808-11-5; **10,** 66792-73-2; **10** bismethylsulfonium derivative BF_4 salt, 66792-80-1; **11a,** 66788-16-7; **11b,** 66788-17-8; *cis*-**12,** 66788-18-9; **12,** 66788-19-0; **13,** 66788-20-3; **14,** 66788-21-4; **16,** 66788-22-5; **17** isomer 1, 66788-23-6; **17** isomer 2, 66808-12-6; **18,** 66792-74-3; **19,** 66792-75-4; **20,** 66792-76-5; **21,** 66792-77-6; **22,** 66792-78-7; **23,** 66810-82-0; **24,** 66788-24-7; 2,6-dibromo-*p*-xylene, 66788-13-4; 2,6-bis(mercaptomethyl)toluene, 41563-67-1; dimethoxycarbonium fluoroborate, 18346-68-4; 2,6-bis(bromomethyl)toluene, 41563-68-2.

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Syntheses of *syn*-[2.2]Metacyclophanes and Triple-Layered *anti*-[2.2]Metacyclophanes

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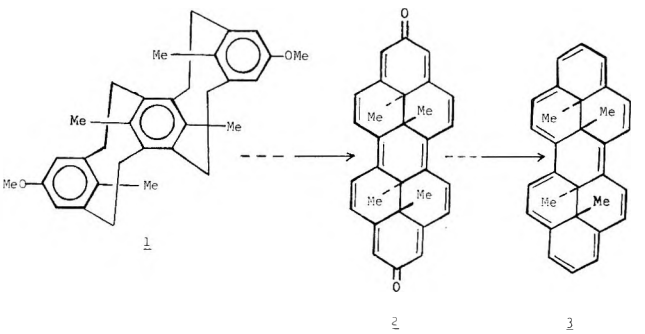
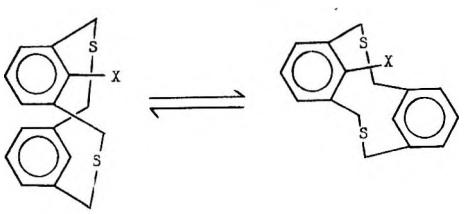
A study has been made of the effect of substituents in influencing the relative amounts of syn and anti isomers formed in the coupling reaction to give substituted 2,11-dithia[3.3]metacyclophanes. Photolytic extrusion of sulfur from *syn*-2,11-dithia-5,7-dicyano-15-methoxy-6,9,18-trimethyl[3.3]metacyclophane (**11**) has led to the first examples of simple *syn*-[2.2]metacyclophanes. Using the standard methods of 2,11-dithia[3.3]metacyclophane formation followed by ring contraction with sulfur extrusion we have been able to prepare the triple-layered *anti*-[2.2]metacyclophane **1**. Oxidation of **1** readily yields the bisdienone **28,** demonstrating the role of the central benzene ring in such triple-layered *anti*-[2.2]metacyclophanes as a transmitter of electronic effects.

The molecule shown by structure **3** has been proposed as a good model for testing the theoretical prediction that the larger [4*n* + 2]annulenes will lose their aromaticity and simply exhibit polyene character. In an accompanying paper,[1] we have described attempts to synthesize **3** starting either with preformed dihydropyrene derivatives or using the standard sulfur methods developed for synthesizing dihydropyrenes. Unfortunately, **3** does not appear to survive the reaction conditions required for its generation by these routes. An alternate possibility for synthesizing **3** is to employ the quinone approach originally used for the preparation of *trans*-15,16-dimethyldihydropyrene.[2] In this approach the key steps are the conversion of a triple-layered *anti*-[2.2]metacyclophane **1** to quinone **2** and this, in turn, to the peropyrene derivative **3.** In the present paper we describe our experiences in exploring this approach to **3.**



1 2 3

The synthesis of **1** requires anti geometry, and so the factors affecting the ratio of syn to anti isomers in metacyclophane formation were of immediate concern to us. Vögtle, Weider, and Förster have described the effect of substituents on the syn–anti equilibrium of 2,11-dithia[3.3]metacyclophanes, where conformational flipping is readily possible.[3] For example, the equilibrium between **4** and **5** lies completely on the side of the syn conformer **4,** presumably due to the more favorable charge-transfer interaction possible with the syn geometry. However, reduction of the nitro group in **4** to give the amino derivative **6** leads to an equilibration that is completely on the side of the anti conformer **7.**



4, X = $-NO_2$ **5,** X = $-NO_2$
6, X = $-NH_2$ **7,** X = $-NH_2$

With bulky groups such as methyl at the 9 and 18 positions,

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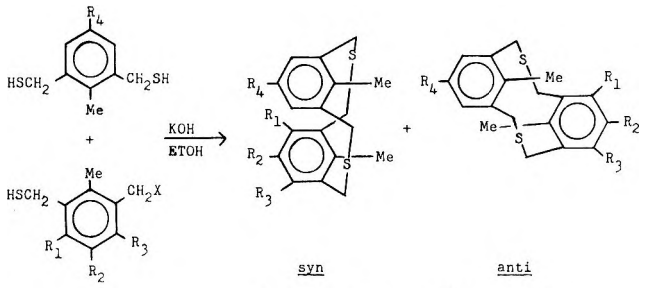


syn anti

10, R_1=R_3= -Br; R_2= $-CH_3$; R_4= $-OCH_3$

11, R_1=R_3= -CN; R_2= $-CH_3$; R_4= $-OCH_3$

equilibration of the syn and anti isomers of 2,11-dithia[3.3]-metacyclophanes is no longer possible. Thus, for these compounds the ratio of syn to anti isomers will be determined by their relative rates of formation. Again, however, charge-transfer interaction should preferentially lower the energy of activation for formation of the syn isomer and so substituents should play an important role in influencing the relative amounts of syn and anti isomers formed. This is found to be true, and the data available from this and other studies are summarized in Table I.

As can be seen, the ratio of syn to anti isomers varies widely depending upon the substituents present, going from 1:7 for the unsubstituted case to 10:1 where one ring has an electron-donating methoxyl and the other ring has electron-withdrawing cyano groups. Since for our purposes we required both anti geometry and the presence of a methoxyl group in one ring and two cyano groups in the other ring, the 10:1 distribution in the coupling reaction was quite discouraging. However, this distribution was clearly the result of kinetic control and it seemed possible that equilibration under thermodynamic control at a later stage might be much more favorable for providing the anti isomer.

Our first task then was providing 3,11-dithia[3.3]metacyclophanes with the appropriate substitution pattern, regardless of the relative ratios of syn and anti isomers. The coupling reaction of 2,6-bis(mercaptomethyl)-4-methoxytoluene and 2,6-bis(chloromethyl)-3,5-dibromo-1,4-dimethylbenzene occurred in 71% yield to give **10**, having a syn to anti ratio of isomers of 2.5:1.0 as shown in Table I. Unfortunately, the replacement of bromide by cyanide in the von Braun reaction proceeded very poorly with **10**; the syn isomer of **10** gave the syn isomer of **11** in only 5% yield, whereas the anti isomer of **10** gave the anti isomer of **11** in 24% yield. To circumvent this the cyano precursor **15** for the coupling reaction was prepared as outlined in Scheme I.

Although the coupling of **15** with 2,6-bis(mercaptomethyl)-4-methoxytoluene then provided a more efficient route to **11**, the ratio of syn to anti isomers in this coupling reaction was 10:1, as shown in Table I. It was important, therefore, in selecting a route for ring contraction and expulsion of sulfur to choose one that might be expected to give increased amounts of the anti isomer. The photochemical expulsion of sulfur in the presence of trimethyl phosphite is

Scheme I

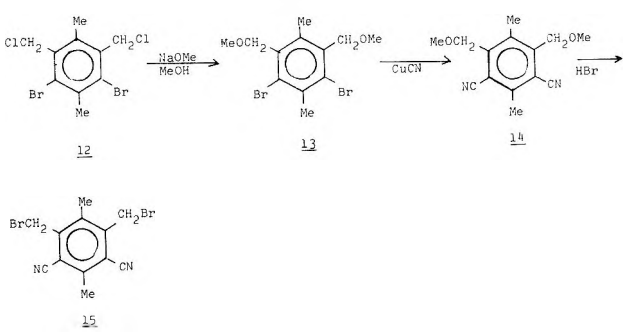
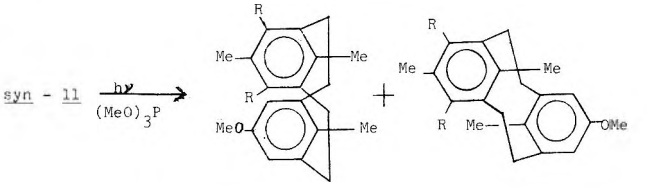


Table I. Effect of Substituents on the Relative Amounts of Syn and Anti Isomers Formed in the Coupling Reaction

compd	substituents R_1	R_2	R_3	R_4	syn/anti ratio
7[4]	H	H	H	H	1:7
8[5]	H	H	H	NO_2	1:1
9[1]	Br	CH_3	Br	H	1.3:1
10	Br	CH_3	Br	OCH_3	2.5:1
11	CN	CH_3	CN	OCH_3	10:1

known to involve an intermediate diradical[6-8] and so this was the method selected. Irradiation of the syn isomer of **11** in the presence of trimethyl phosphite gave the *syn*-[2.2]metacyclophane **16** in 20% yield and the corresponding anti isomer **17** in 40% yield.



16, R = -CN

18, R = -CH=O

19, R = $-CH_2OH$

20, R = $-CH_2OCH_3$

17, R = -CN

21, R = -CH=O

22, R = $-CH_2OH$

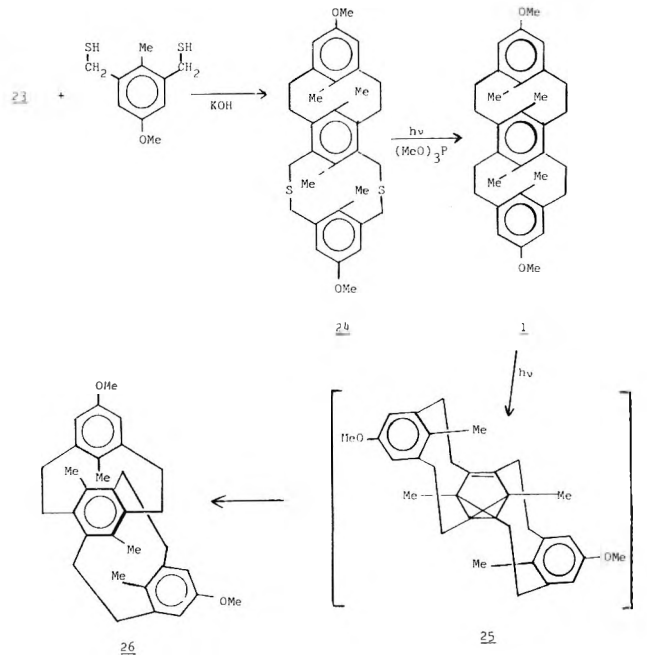
23, R = $-CH_2Br$

To our knowledge the isolation of **16** is the first reported example of a simple *syn*-[2.2]metacyclophane.[9] Previously, we had tried to prepare *syn*-8,16-dimethyl[2.2]metacyclophane by the Raney nickel desulfurization of a *syn*-bis(methylthio)-8,16-dimethyl[2.2]metacyclophane, but the product was entirely the *anti*-8,16-dimethyl[2.2]metacyclophane.[4] Similarly, treatment of [2.2.2](1,3,5)cyclophan-1-ene with osmium tetroxide at 0 °C gave entirely the *anti*-5,13-diformyl[2.2]metacyclophane and none of the syn isomer.[10] Intuitively, one would expect the strain energy of *syn*-[2.2]-metacyclophanes to be comparable to that of [2.2]paracyclophane, and Boyd has shown from heats of combustion that the relative strain energies of [2.2]paracyclophane, [2.2]meta-paracyclophane, and *anti*-[2.2]metacyclophane are 32.6, 24.5, and 13.5 kcal/mol, respectively.[11] However, despite the strong driving force for a syn to anti isomerization in the [2.2]metacyclophane series, this would not be expected to occur spontaneously, for Gschwend has shown that the energy barrier to conformational flipping in *anti*-[2.2]metacyclophane is 33.2 kcal/mol,[12] and for derivatives having methyl substituents at the 8 and 16 positions, the barrier must be very much higher.

One possible explanation for the stability of **16** could be that there is an exceptionally strong charge-transfer interaction due to the presence of the two cyano groups. It was of interest, therefore, to make a series of derivatives in which the cyano groups were replaced by other substituents, including electron-donating groups. This was readily done. Reduction of **16** with diisobutylaluminum hydride gave the corresponding diformyl derivative **18**, and sodium borohydride reduction of **18** gave the diol **19**. Treatment of **19** with methanol containing a trace of hydrogen chloride immediately gave the corresponding methyl ether **20**. The syn and anti isomers of [2.2]-metacyclophanes are readily distinguished by their NMR spectra and all of these transformation products, **18**, **19**, and **20**, are clearly syn isomers and are stable at ambient temperatures.

Reich and Cram first showed that heating [2.2]paracyclophanes at 200 °C leads to ring opening and isomerization via diradical intermediates.[13] If *syn*-[2.2]metacyclophanes have comparable strain energies to those of [2.2]paracyclophanes, it would be expected that they might show a similar thermal

Scheme II



isomerization. This has been found to be true. When a sample of the syn isomer **16** was heated above its melting point (194–196 °C) in a sealed capillary and held at that temperature for a period of time, the sample recrystallized and, on NMR analysis, was found to have undergone a quantitative conversion to the anti isomer **17.** Similarly, the *syn*-diformyl derivative **18** on being heated at 215 °C was converted quantitatively to the corresponding anti isomer **21.** Thermal isomerization of the syn isomers **19** and **20** to their corresponding anti isomers was also effected, but was accompanied by considerable decomposition. Apparently, the syn geometry in the [2.2]metacyclophane series strongly promotes thermal carbonium ion formation followed by self-alkylation.

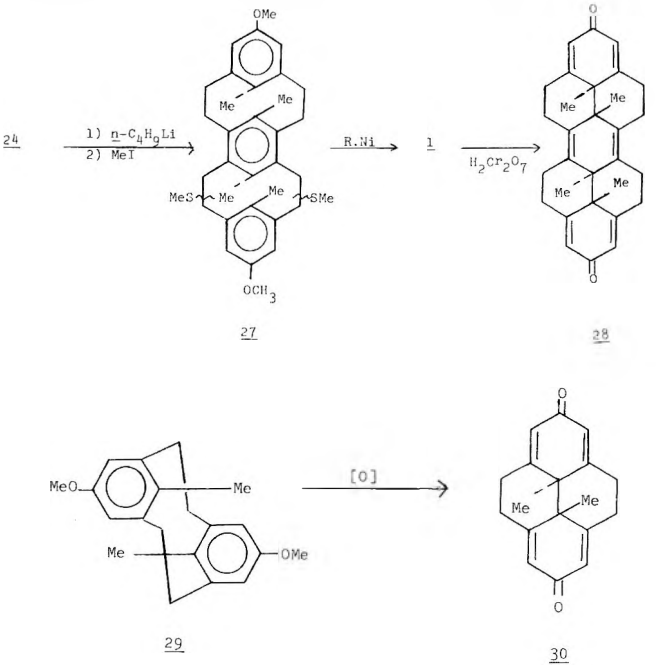
From these data it can be concluded that the influence of substituents on the relative ratios of *syn*- and *anti*-[2.2]metacyclophanes is a result of their effect on reaction rates and that thermodynamically *anti*-[2.2]metacyclophanes are greatly favored over *syn*-[2.2]metacyclophanes regardless of the nature of the substituents. Furthermore, the combination of photochemical extrusion of sulfur followed by thermal isomerization is a practical, efficient route for converting *syn*-2,11-dithia[3.3]metacyclophanes completely to *anti*-[2.2]metacyclophanes.

With the way now clear for preparing the appropriately substituted *anti*-[2.2]metacyclophane **17,** the overall synthetic approach to **1** could be continued. Following the same procedures used with **16,** the transformation of **17** to **21** and then on to **22** proceeded well and in high yield. Treatment of **22** with phosphorus tribomide then gave **23.** A coupling reaction between **23** and 2,6-bis(mercaptomethyl)-4-methoxytoluene gave the dithiacyclophane **24** as a single product in 56% yield (Scheme II). The assignment of a staircase geometry to **24** is based both on its NMR spectrum, which clearly fits an anti isomer, and the assumption that an up–down conformation would require prohibitive steric interactions between the internal methyl groups.

In an attempt to effect ring contraction with sulfur extrusion, a solution of **24** in trimethyl phosphite was irradiated using a medium-pressure mercury lamp. A single product was isolated in 51% yield having the correct composition and molecular weight expected for **1.** However, the spectral properties of the product were inconsistent with those to be expected for a triple-layered *anti*-[2.2]metacyclophane. Its ultraviolet absorption spectrum showed maxima at 211 (ε 53 000), 238 (14 500), and 287 nm (3500), but with none of the longer wavelength absorptions characteristic of the *anti*-[2.2]metacyclophanes of this series. Its NMR spectrum shows the four aromatic protons as an AB pattern at τ 3.44 and 3.52 (J_{AB} = 3 Hz) instead of the singlet to be expected for **1.** Also, there is no signal in the region of τ 9.5 where the internal methyl protons of an *anti*-[2.2]metacyclophane should occur. However, these spectral data are in good accord with those reported by Kannen, Umemoto, Otsubo, and Misumi for triple-layered [2.2]metaparacyclophanes.[14] We have, therefore, assigned structure **26** to this product and its formation is logically explained as a photochemical isomerization of the initially formed **1** going via the benzvalene intermediate **25** to the final product **26.**

Attempts to obtain **1** by using shorter irradiation times with **24** were unsuccessful. However, when a low-pressure mercury lamp was substituted for the medium-pressure lamp, irradiation of **24** did give **1** in low yield. Apparently, the photochemical isomerization of **1** to **26** is wavelength dependent and is favored by the longer wavelengths of light emitted by the medium-pressure lamp. As expected, the ultraviolet absorption spectrum of **1** had, in addition to maxima at 207 (ε 13 000) and 259 nm (6600), bands at 310 (1000) and 340 nm (500) as is characteristic for the *anti*-[2.2]metacyclophanes in this series. Likewise, the four aromatic protons of **1** appear as a singlet at τ 3.28 and the internal methyl protons as two singlets at τ 9.38 and 9.41.

Because of the poor yield in the photochemical conversion of **24** to **1,** an alternate method for this transformation was sought. When **24** was subjected to a Wittig rearrangement, a mixture of stereoisomers corresponding to **27** was formed in



93% yield. Raney nickel desulfurization of **27** then led to **1** but, again, in disappointingly small yield.

An unusual feature of *anti*-5,13-dimethoxy-8,16-dimethyl[2.2]metacyclophane (**29**) is its easy oxidation under mild conditions to the bisdienone **30.**[2] Presumably the first step in this oxidation is the formation of a radical cation which is delocalized over both aromatic rings.[15] Of immediate interest, then, was whether the central aromatic ring of **1** would enter into such a delocalization process and allow the formation of the extended bisdienone **28.** In fact, treatment of **1** with an acetone solution of chromic acid reagent for a few minutes at room temperature effected a complete conversion of **1** to **28.** The central benzene ring in triple-layered *anti*-[2.2]metacyclophanes having a staircase conformation is clearly a very

effective transmitter of electronic effects between the benzene rings at each end.

In the case of **30**, treatment with *N*-bromosuccinimide led smoothly in high yield to the corresponding quinone.[2] However, treatment of **28** with *N*-bromosuccinimide gave only extensive decomposition and none of the desired quinone **2**. Unfortunately, lack of material precluded exploring other possible routes for the conversion of **28** to **2**.

Experimental Section[16]

2,6-Bis(mercaptomethyl)-4-methoxytoluene. To a stirred solution of 1.52 g of thiourea in 59 mL of ethanol was added 3.08 g of 2,6-bis(bromomethyl)-4-methoxytoluene,[2,17] and the mixture was boiled under reflux for 1 h. After removal of the solvent under reduced pressure, a solution of 6.5 g of potassium hydroxide in 25 mL of water was added to the residual solid and the resulting mixture was boiled under reflux for 3 h. When the solution had cooled, it was acidified and extracted with ether. The ether extract was washed with water, dried, and concentrated to give 2.05 g (96%) of a clear oil: NMR, a singlet at τ 3.2 (2 H, ArH), a singlet at 6.20 (3 H, $-OCH_3$), a doublet at 6.25 (4 H, J = 7 Hz, $ArCH_2-$), a singlet at 7.65 (3 H, $ArCH_3$), and a triplet at 8.35 (2 H, J = 7 Hz, -SH); mass spectrum *m/e* 214.047 (calcd for $C_{10}H_{14}OS_2$: 214.049). Anal. Calcd for $C_{10}H_{14}OS_2$: C, 56.07; H, 6.59. Found: C, 55.93; H, 6.52.

***syn*- and *anti*-5,7-Dibromo-6,9,18-trimethyl-15-methoxy-2,11-dithia[3.3]metacyclophane (10).** A solution of 2.03 g of 2,6-bis(mercaptomethyl)-4-methoxytoluene and 3.42 g of 2,6-dibromo-3,5-bis(chloromethyl)-1,4-dimethylbenzene[1] in 250 mL of benzene was added dropwise with stirring to a boiling solution of 1.6 g of potassium hydroxide in 1.0 L of ethanol. When the addition was complete (24 h), the solution was concentrated and the residual solid was extracted with dichloromethane. Concentration of the dichloromethane extract was followed by chromatography of the residue over silica gel using a 1:2 mixture of benzene–petroleum ether (30–60 °C) as eluent. The first fraction of eluate gave 2.42 g (51%) of the syn isomer of **10** as white needles: mp 254–256 °C; NMR, a singlet at τ 3.47 (2 H, ArH), an AB pattern at 6.30 and 5.20 (4 H, J = 15 Hz, $ArCH_2-$), a singlet at 6.08 (4 H, $ArCH_2-$), a singlet at 6.27 (3 H, $-OCH_3$), and three singlets at 7.42, 7.46, and 7.55 (3 H each, $-CH_3$); mass spectrum *m/e* 502. Anal. Calcd for $C_{20}H_{22}Br_2OS_2$: C, 47.82; H, 4.41. Found: C, 47.52; H, 4.33.

The second fraction of eluate gave 940 mg (20%) of the anti isomer of **10** as white crystals: mp 235–237 °C; NMR, a singlet at τ 3.05 (2 H, ArH), an AB pattern at 6.37 and 6.27 (4 H, J = 14 Hz, $ArCH_2-$), an AB at 6.21 and 6.07 (4 H, J = 14 Hz, $ArCH_2-$), a singlet at 6.17 (3 H, $-OCH_3$), and singlets at 6.32, 8.58, and 8.68 (3 H each, $-CH_3$); mass spectrum *m/e* 502. Anal. Calcd for $C_{20}H_{22}Br_2OS_2$: C, 47.82; H, 4.41. Found: C, 47.59; H, 4.47.

2,6-Dibromo-3,5-bis(methoxymethyl)-1,4-dimethylbenzene (13). A solution of 27.0 g of sodium methoxide in 200 mL of methanol was added dropwise with stirring to a solution of 68.6 g of **12** in 450 mL of dry benzene. When the addition was complete, the resulting solution was boiled under reflux for 11 h. After removal of the inorganic precipitate by filtration, the filtrate was washed with water and concentrated to give 66.1 g (98%) of a colorless solid, mp 122–123 °C. A sample recrystallized from methanol gave soft needles: mp 122.5–123.5 °C; NMR, a singlet at τ 5.28 (4 H, $ArCH_2-$), a singlet at 6.58 (6 H, $-OCH_3$), and singlets at 7.31 and 7.48 (3 H each, $-CH_3$). Anal. Calcd for $C_{12}H_{16}Br_2O_2$: C, 40.94; H, 4.58. Found: C, 40.65; H, 4.48.

2,6-Dicyano-3,5-bis(methoxymethyl)-1,4-dimethylbenzene (14). To a solution of 66.0 g of **13** in 200 mL of *N*-methylpyrrolidone was added 50.4 g of cuprous cyanide and the mixture was heated at 170 °C for 66 h. It was then poured into a cold solution of 300 mL of concentrated ammonium hydroxide and 300 mL of water. The gray precipitate was collected by filtration, washed with water, and dried. It was then taken up in dichloromethane and chromatographed over silica gel to give 27.5 g (60%) of colorless crystals. A sample recrystallized from 2-propanol gave white crystals: mp 116–117 °C; NMR, a singlet at τ 5.28 (4 H, $ArCH_2-$), a singlet at 6.53 (6 H, $-OCH_3$), and singlets at 7.21 and 7.51 (3 H each, $-CH_3$). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.38; H, 6.60. Found: C, 68.64; H, 6.39.

2,6-Dicyano-3,5-bis(bromomethyl)-1,4-dimethylbenzene (15). A solution of 10.0 g of **14** in 30 g of a 30% solution of hydrogen bromide in acetic acid was stirred at room temperature for 48 h. It was then poured into 200 mL of ice water and extracted with dichloromethane. After the dichloromethane extract had been washed with water, it was dried and concentrated. The residual solid was taken up in a 2:1 dichloromethane–hexane mixture and chromatographed over silica gel to give 8.12 g (52%) of white crystals: mp 168–170 °C; NMR, a singlet at τ 5.39 (4 H, $ArCH_2-$), and singlets at 7.22 and 7.49 (3 H each, $-CH_3$); mass spectrum *m/e* 341.919 (calcd for $C_{12}H_{10}Br_2N_2$: 341.919). Anal. Calcd for $C_{12}H_{10}Br_2N_2$: C, 42.11; H, 2.92. Found: C, 42.01; H, 2.73.

***syn*- and *anti*-5,7-Dicyano-6,9,18-trimethyl-15-methoxy-2,11-dithia[3.3]metacyclophane (11).** A solution of 17.75 g of **15** and 11.10 g of 2,6-bis(mercaptomethyl)-4-methoxytoluene in 1 L of benzene was added dropwise with stirring to a solution of 8.55 g of potassium hydroxide in 6 L of ethanol boiling under reflux. When the addition was complete (5.5 days), the solution was concentrated and the residual semisolid was extracted with hot chloroform. The chloroform extract was concentrated and the residue was chromatographed over silica gel using benzene as eluent.

The first fraction of eluate gave 4.63 g (23%) of the syn isomer of **11** as colorless crystals: mp 276–277 °C; NMR, a singlet at τ 3.56 (2 H, ArH), an AB pattern at 5.39 and 6.17 (4 H, J = 16 Hz, $ArCH_2-$), a singlet at 6.04 (4 H, $ArCH_2-$), a singlet at 6.22 (3 H, $-OCH_3$), and singlets at 7.37, 7.42, and 7.55 (3 H each, $-CH_3$); mass spectrum *m/e* 394.116 (calcd for $C_{22}H_{22}N_2OS_2$: 394.116). When a sample of the syn isomer of **10** was subjected to the von Braun reaction, as described for the preparation of **14**, the product, formed in only 5% yield, was identical in all respects with this specimen. Anal. Calcd for $C_{22}H_{22}N_2OS_2$: C, 66.99; H, 5.62. Found: C, 67.25; H, 5.55.

The second fraction of eluate gave 505 mg (2%) of the anti isomer of **11** as colorless crystals: mp 291–292 °C; NMR, a singlet at τ 3.09 (2 H, ArH), a multiplet at 5.92–6.38 (8 H, $ArCH_2-$), a singlet at 6.16 (3 H, $-OCH_3$), and singlets at 7.55, 8.56, and 8.68 (3 H each, $-CH_3$); mass spectrum *m/e* 394.119 (calcd for $C_{22}H_{22}N_2OS_2$: 394.116). When a sample of the anti isomer of **10** was subjected to the von Braun reaction, as described for the preparation of **14**, the product, formed in 24% yield, was identical in all respects with this specimen. Anal. Calcd for $C_{22}H_{22}N_2OS_2$: C, 66.99; H, 5.62. Found: 66.91; H, 5.57.

Photochemical Extrusion of Sulfur to Give *syn*- and *anti*-4,6-Dicyano-5,8,16-trimethyl-13-methoxy[2.2]metacyclophane (16 and 17). A suspension of 1.79 g of the syn isomer of **11** in 100 mL of trimethyl phosphite was irradiated with a 450-W medium-pressure Hanovia lamp for 46 h. The homogeneous solution was then poured onto 200 g of crushed ice and stirred at room temperature for 2 h. The solid, which had precipitated, was collected by filtration, washed with water, and extracted with dichloromethane. The dichloromethane extract was washed with water, dried, and concentrated to give 3 g of a clear oil. This was chromatographed over silica gel using dichloromethane as eluent.

The product from the first fraction of eluate was recrystallized from a mixture of dichloromethane–petroleum ether (30–60 °C) to give 510 mg (33%) of the anti isomer **17** as colorless crystals: mp 291–292 °C; NMR, a singlet at τ 3.24 (2 H, ArH), a singlet at 6.21 (3 H, $-OCH_3$), multiplets at 6.90–7.36 and 6.36–6.56 (8 H, $ArCH_2-$), and singlets at 7.31, 9.21, and 9.41 (3 H each, $-CH_3$); UV (tetrahydrofuran), maxima at 218 (ϵ 49 000), 245 (20 000), and 338 nm (1200); mass spectrum *m/e* 330.172 (calcd for $C_{24}H_{22}N_2O$: 330.173), 315, and 300. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71. Found: C, 79.80; H, 6.62.

The product from the second fraction of eluate was recrystallized from ether to give 247 mg (17%) of the syn isomer **16** as colorless crystals: mp 194–196 °C; NMR, a singlet at τ 3.90 (2 H, ArH), a singlet at 6.36 (3 H, $-OCH_3$), a multiplet at 6.46–7.08 (8 H, $ArCH_2-$), and singlets at 7.63, 7.78, and 7.90 (3 H each, $-CH_3$); UV (tetrahydrofuran), maxima at 232 (ϵ 37 000), 292 (2700), and 346 nm (520); mass spectrum *m/e* 330, 315, and 300. Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 79.75; H, 6.57; N, 8.24.

A sample of the syn isomer **16** was sealed under vacuum in a capillary tube and heated just above its melting point for 5 h. At the end of this time **16** was completely converted to the anti isomer **17**, identical in all respects with the sample obtained above.

***anti*-4,6-Diformyl-5,8,16-trimethyl-13-methoxy[2.2]metacyclophane (21).** To a solution of 746 mg of **17** in 22 mL of dry benzene was added at room temperature 4.8 mL of a 20% solution of diisobutylaluminum hydride in benzene. After the solution had stood at room temperature for 2 h, additions were made successively with stirring of 3.5 mL of methanol, 3.5 mL of water, and 10 mL of aqueous 10% hydrochloric acid. The organic layer was extracted with benzene, washed with water, dried, and concentrated. The residual solid was recrystallized from a benzene–hexane mixture to give 744 mg (98%) of pale yellow prisms: mp 191–192 °C; NMR, a singlet at τ − 0.75 (2 H, ArCHO), a singlet at 3.35 (2 H, ArH), a singlet at 6.22 (3 H, $-OCH_3$), multiplets at 6.21–6.32 and 6.86–7.60 (8 H, $ArCH_2-$), and singlets at 7.32, 9.24, and 9.42 (3 H each, $-CH_3$); UV (tetrahydrofuran), maxima at 217 (ϵ 38 000), 253 (2600), and 352 nm (1700); mass spectrum *m/e* 336. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.49; H, 7.16.

***syn*-4,6-Diformyl-5,8,16-trimethyl-13-methoxy[2.2]metacy-**

clophane (18). A 405-mg sample of **16** was reduced with diisobutylaluminum hydride following the same procedure described above for preparing **21.** Chromatography of the product over silica gel using dichloromethane as eluent gave 243 mg (59%) of yellow needles: mp 208–210 °C (sealed capillary); NMR, a singlet at τ −0.38 (2 H, ArH), a singlet at 4.15 (2 H, ArH), two multiplets at 6.14–6.75 and 7.04–7.30 (8 H, $ArCH_2$–), a singlet at 6.48 (3 H, $-OCH_3$), and singlets at 7.57, 7.50, and 7.90 (3 H each, $-CH_3$); UV (cyclohexane), maxima at 212 (ϵ 25 000), 240 (16 000), and 360 nm (440); mass spectrum *m/e* 336.174 (calcd for $C_{22}H_{24}O_3$: 336.173), 321, and 306.

A sample of the syn isomer **18**, sealed under vacuum in a capillary tube, was heated at 215 °C for 5 h. When the tube was cooled, the contents was shown to be completely identical with the anti isomer **21.**

***anti*-4,6-Bis(hydroxymethyl)-5,8,16-trimethyl-13-methoxy-[2.2]metacyclophane (22).** To a stirred solution of 879 mg of **21** in 22 mL of a 2:1 mixture of tetrahydrofuran–2-propanol was added 65 mg of sodium borohydride. After the mixture had been stirred at room temperature for 3.5 h, 10 mL of aqueous 5% hydrochloric acid was added. The organic layer was extracted with chloroform, washed with water, dried, and concentrated to give 889 mg (100%) of white needles: mp 227–230 °C; NMR (Me_2SO-d_6), a singlet at τ 3.16 (2 H, ArH), a singlet at 5.25 (4 H, $-CH_2OH$), a singlet at 6.20 (3 H, $-OCH_3$), two multiplets at 6.4–6.7 and 7.0–7.8 (8 H, $ArCH_2$–), and singlets at 7.57, 9.29, and 9.50 (3 H each, $-CH_3$); mass spectrum *m/e* 340.201 (calcd for $C_{22}H_{28}O_3$: 340.204). Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.47; H, 8.01.

***syn*-4,6-Bis(hydroxymethyl)-5,8,16-trimethyl-13-methoxy-[2.2]metacyclophane (19) and *syn*-4,6-Bis(methoxymethyl)-5,8,16-trimethyl-13-methoxy[2.2]metacyclophane (20).** A 122-mg sample of **18** was reduced with sodium borohydride as described for the preparation of **22.** After crystallization from methanol, there was isolated 117 mg (95%) of white crystals: mp 172–173 °C (sealed capillary); NMR, singlets at τ 4.20 (2 H, ArH), 5.48 (4 H, $ArCH_2OH$), and 6.48 (3 H, $-OCH_3$), two multiplets at 6.50–6.75 and 7.14–7.36 (8 H, $ArCH_2$–), and singlets at 7.82 and 7.84 (9 H, $-CH_3$); UV (tetrahydrofuran), maxima at 275 (ϵ 2500) and 297 nm (1400); mass spectrum *m/e* 340.

When a sample of **19** was heated at 200 °C, the NMR spectrum of the starting material was quickly replaced by that of **22,** but the thermal isomerization was accompanied by decomposition. Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.07; H. 8.19.

A 110-mg sample of **19** in 5 mL of methanol was treated with one drop of concentrated hydrochloric acid. It was then poured into an aqueous solution of sodium bicarbonate and extracted with dichloromethane. After concentration, the residual oil was chromatographed over silica gel using chloroform as eluent. The main fraction of eluate gave **20** as a colorless oil: NMR, singlets at τ 4.20 (2 H, ArH), 5.77 (4 H, $ArCH_2OCH_3$), 6.48 (3 H, $-OCH_3$), and 6.61 (6 H, $-OCH_3$), two multiplets at 6.6–6.8 and 7.2–7.4 (8 H, $ArCH_2$–), and singlets at 7.8., 7.86, and 7.94 (9 H, $-CH_3$); mass spectrum *m/e* 368.236 (calcd for $C_{24}H_{32}O_3$: 368.235).

A sample of **20** heated above 200 °C quickly had its NMR spectrum replaced by a new one, apparently corresponding to the anti isomer of **20,** but considerable decomposition occurred.

***anti*-4,6-Bis(bromomethyl)-5,8,16-trimethyl-13-methoxy-[2.2]metacyclophane (23).** To a stirred suspension of 720 mg of **22** in 22 mL of dry benzene there was added with stirring 0.25 mL of phosphorus tribromide. After the solution had stood at room temperature for 1 h, it was poured into 50 mL of water and the organic layer was extracted with benzene. The benzene extract was washed successively with water, aqueous bicarbonate, and water before it was dried and concentrated. The residual oil was chromatographed over silica gel using dichloromethane as eluent. The product from the main fraction of eluate was recrystallized from a 1:4 mixture of benzene–hexane to give 423 mg (41%) of white prisms: mp 160–163 °C; NMR, singlets at τ 3.25 (2 H, ArH), 5.25 (4 H, $-CH_2Br$), and 6.21 (3 H, $-OCH_3$), two multiplets at 6.55–6.78 and 6.92–7.48 (8 H, $ArCH_2$), and singlets at 7.58, 9.33, and 9.47 (3 H each, $-CH_3$); mass spectrum *m/e* 466.035 (calcd for $C_{22}H_{26}OBr_2$: 466.033). Compound **23** is unstable to oxygen and light, but can be stored in the dark under nitrogen.

4^2-Methyl-4^5-methoxy-4[1,3],$8^{3,6}$-dimethyl-8^u[1,5,2,4],11^2-methyl-11^5-methoxy-11^u[1,3]-tribenzospiro[7.5]-2,6-dithiatridecaphane[18] (24). A solution of 76 mg of **23** and 35 mg of 2,6-bis(mercaptomethyl)-4-methoxytoluene in 60 mL of benzene was added dropwise with stirring to a solution of 35 mg of potassium hydroxide in 125 mL of ethanol. When the addition was complete (9 h), the mixture was concentrated and the residue was extracted with dichloromethane. After the dichloromethane extract had been washed with water, dried, and concentrated, the residual solid was chromatographed over silica gel using dichloromethane as eluent. The product from the main fraction of eluate was recrystallized from a benzene–hexane mixture to give 47 mg (56%) of colorless crystals: mp 254–257 °C; NMR, singlets at τ 3.06 (2 H, ArH), 3.48 (2 H, ArH), 6.18 (3 H, $-OCH_3$), and 6.21 (3 H, $-OCH_3$), multiplets at 6.04–6.25 and 6.30–6.42 (8 H, $ArCH_2$–) and multiplets at 6.48–6.75 and 7.04–7.48 (8 H, $ArCH_2$–), and singlets at 8.74, 8.77, 9.24, and 9.58 (3 H each, $-CH_3$); UV (tetrahydrofuran), maxima at 207 (ϵ 41 000), 247 (25 000), 303 (3320), and 327 nm (640); mass spectrum *m/e* 518.229 (calcd for $C_{32}H_{38}O_2S_2$: 518.231).

3^2-Methyl-3^5-methoxy-3[1,3],$6^{3,6}$-dimethyl-6^u[1,5,2,4],9^2-methyl-9^5-methoxy-9^u[1,3]-tribenzospiro[5.5]undecaphane[18] (26). A suspension of 118 mg of **24** in 100 mL of trimethyl phosphite was irradiated for 27 h using a 450-W medium-pressure Hanovia lamp. The solution was then poured onto 200 g of crushed ice and stirred at room temperature for 2 h. The organic matter was extracted with dichloromethane, washed with water, dried, and concentrated. The residual oil was then chromatographed over silica gel using dichloromethane as eluent. The main fraction of eluate gave 53 mg (51%) of a colorless oil: NMR, an AB pattern at τ 3.44 and 3.52 (4 H, J = 3 Hz, ArH), a singlet at 6.21 (6 H, $-OCH_3$), two multiplets at 6.64–7.56 and 7.80–8.62 (16 H, $ArCH_2$–), and singlets at 8.04 and 9.94 (6 H each, $-CH_3$); UV (tetrahydrofuran), maxima at 211 (ϵ 53 000), 238 (14 500), and 287 nm (3500); mass spectrum *m/e* 454, 439, 424, 409, 394, and 379. Anal. Mol wt calcd for $C_{32}H_{38}O_2$: 454.287. Found (high-resolution mass spectrum): 454.285.

3^2-Methyl-3^5-methoxy-3[1,3],$6^{3,6}$-dimethyl-6^u[1,5,2,4],9^2-methyl-9^5-methoxy-9^u[1,3]-tribenzospiro[5.5]undecaphane[18] (1). A. Via the Wittig Rearrangement of 24 to 27 and Desulfurization. To a stirred solution of 42 mg of **24** in 3 mL of dry tetrahydrofuran was added 0.125 mL of a 1.5 M solution of *n*-butyllithium in hexane at room temperature. After the solution had been stirred for 10 min, 0.2 mL of methyl iodide was added. The mixture was then poured into 10 mL of water and extracted with dichloromethane. After the dichloromethane extract had been washed with water, dried, and concentrated, it gave 41 mg (93%) of a mixture of isomers of **27** as a yellow oil: NMR, a singlet at τ 3.28 (4 H, ArH), multiplets at 5.96–6.44 and 7.00–7.80 (14 H, ArCH< and $ArCH_2$–), a singlet at 7.85 (6 H, $-SCH_3$), and four singlets at 9.00–9.55 (3 H each, $-CH_3$); mass spectrum *m/e* 546 and 499.

To a solution of 41 mg of **27** in 10 mL of a 1:1 absolute ethanol–benzene mixture was added a spatula of commercial Raney nickel and the mixture was boiled under reflux for 11 h. The catalyst was removed by filtration and washed with dichloromethane. The combined dichloromethane washings were concentrated and the solid residue was purified by preparative thin-layer chromatography using benzene as eluent. The band at R_f 0.5 gave 2.6 mg of **1** as colorless crystals: NMR, a singlet at τ 3.28 (4 H, ArH), a singlet at 6.22 (6 H, $-OCH_3$), multiplets at 6.50–6.70 and 7.00–7.40 (16 H, $ArCH_2$), and two singlets at 9.38 and 9.41 (6 H each, $-CH_3$); UV (tetrahydrofuran), maxima at 207 (ϵ 13 000), 259 (6600), 310 (1000), and 340 nm (500); mass spectrum, *m/e* 454, 439, 424, 409, 394, 379, and 364. Anal. Mol wt calcd for $C_{32}H_{38}O_2$: 454.287. Found (high-resolution mass spectrum): 454.289.

B. Via Irradiation of 24. A suspension of 21 mg of **24** in 0.5 mL of trimethyl phosphite in a 5-mm quartz tube was irradiated using a low-pressure Rayonet mercury resonance lamp for 2 days. The solution was then poured into water, stirred at room temperature for 2 h, and extracted with dichloromethane. After the dichloromethane extract had been washed with water, it was dried and concentrated. Preparative thin-layer chromatography over silica gel using dichloromethane as eluent gave a band at R_f 0.6 which yielded 2 mg (11%) of a colorless solid, whose spectral properties agreed in all respects with the specimen obtained in A.

Oxidation of 1 to Give the Bisdienone 28. To a stirred suspension of 4 mg of **1** in 0.5 mL of acetone was added 0.01 mL of a prepared chromic acid reagent.[2] After the deep green solution had been stirred at room temperature for 5 min, 2 mL of water and 2 mL of dichloromethane were added. The aqueous layer was separated and extracted with dichloromethane. The combined dichloromethane extract and organic layer was washed successively with aqueous bicarbonate solution and water. The dichloromethane solution was then dried and concentrated to give 3.4 mg (92%) of a yellow oil: NMR, a singlet at τ 3.75 (4 H, C(=O)CH=C<), a broad multiplet at 6.90–7.70 (16 H, $-CH_2$–), and two singlets at 8.81 and 8.83 (6 H each, $-CH_3$); UV (tetrahydrofuran), maxima at 223 (ϵ 22 000), 277 (23 000), 332 (1800), and 355 nm (1400); mass spectrum *m/e* 424, 409, 394, 379, and 364. Anal. Mol wt calcd for $C_{30}H_{32}O_2$: 424.240. Found (high-resolution mass spectrum): 424.236.

Acknowledgment. We thank the National Science Foundation for their support of this investigation.

Registry No.—**1**, 66793-10-0; *syn*-**10**, 66793-11-1; *anti*-**10**, 66808-40-0; *syn*-**11**, 66793-12-2; *anti*-**11**, 66808-41-1; **12**, 66788-12-3; **13**, 66793-13-3; **14**, 66793-14-4; **15**, 66793-15-5; **16**, 66793-16-6; **17**, 66808-42-2; **18**, 66793-17-7; **19**, 66793-18-8; **20**, 66793-19-9; *anti*-**20**, 66808-43-3; **21**, 66808-44-4; **22**, 66808-45-5; **23**, 66793-20-2; **24**, 66793-21-3; **26**, 66793-22-4; **27**, 66792-72-1; **28**, 66793-23-5; 2,6-bis(mercaptomethyl)-4-methoxytoluene, 66793-24-6; 2,6-bis(bromomethyl)-4-methoxytoluene, 14542-73-5.

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(16) Elemental and mass spectral analyses were determined by Dr. R. Wielesek, University of Oregon Microanalytical Laboratories. Melting points are uncorrected and were taken with a Mel-Temp apparatus, visible and ultraviolet spectra were measured with a Cary 15, NMR spectra were measured using deuteriochloroform with tetramethylsilane as an internal standard and were obtained with a Varian HA-100 or XL-100 instrument, and all mass spectra were taken using a CEC Model 21-110 spectrometer at 70 eV.
(17) We thank Dr. F. Häfliger and the Geigy Research Laboratories for a generous gift of 2,6-bis(bromomethyl)-4-methoxytoluene.
(18) At present there is no accepted system of nomenclature for the multilayered cyc ophanes. The name given to compounds **24**, **26**, and **1** follow from the system proposed by H. Lehner (*Monatsh. Chem.*, **107**, 565 (1976)). However, Lehner did not provide for the conformational isomerism possible in the triple-layered [2.2]metacyclophane, and so to his system we have added the use of superscripts u and o to designate whether that aromatic ring is under or over the previous ring. This follows the pattern of up–down nomenclature used by Misumi (*Mem. Inst. Sci. Ind. Res., Osaka Univ.*, **33**, 53 (1976).

Chemical Behavior of *cis*-15,16-Dimethyldihydropyrene

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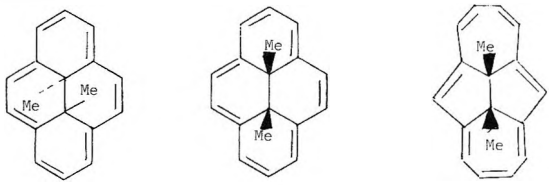
The synthesis of *cis*-15,16-dimethyldihydropyrene derivatives has been reexamined and 2-nitro-*cis*-15,16-dimethyldihydropyrene (**8**) has been prepared both by nitration of *cis*-15,16-dimethyldihydropyrene (**2**) and by independent synthesis. Acetylation of *cis*-15,16-dimethyldihydropyrene gives both the 1- and 2-acetyl derivatives (**10** and **11**) in a ratio of 2:1. In contrast to the trans series, *cis*-15,16-dimethyldihydropyrene (**2**) readily reacts with oxygen to give a nonaromatic diepoxide.

The development of the dithiacyclophane–sulfur extrusion route for the synthesis of *trans*-15,16-dimethyldihydropyrene (**1**) made possible the concomitant synthesis of *cis*-15,16-dimethyldihydropyrene (**2**), albeit in poor yield.[1] For purposes of comparing the chemical properties of the *cis*-



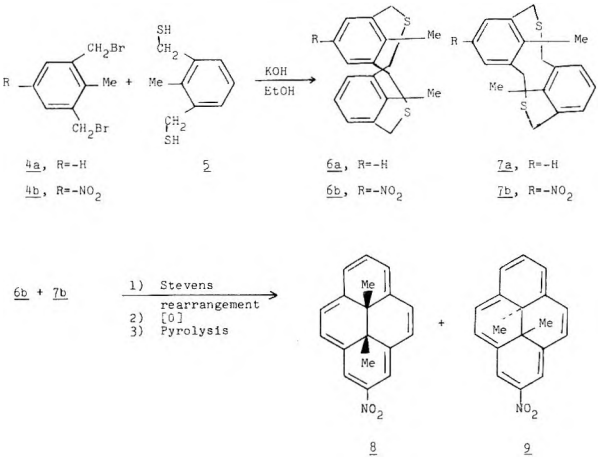
1 2 3

and *trans*-15,16-dimethyldihydropyrenes, as well as making a comparison of the physical and chemical properties of **2** with 1,6:8,13-ethanediylidene[14]annulene (**3**),[2,3] where both types of molecules have the same saucer-shaped geometry but different perimeter contours, we needed additional quantities of *cis*-15,16-dimethyldihydropyrene.

The difficulty in the previous synthesis was the coupling reaction of **4a** and **5** which, although it proceeds in about 75% overall yield, gives the syn and anti isomers of 9,18-dimethyl-2,11-dithia[3.3]metacyclophane (**6a** and **7a**) in a ratio of about 1:7.[1] For the synthesis of **2** only the syn isomer is useful and so the unfavorable syn to anti isomer distribution in the coupling reaction is a severe disadvantage. Subsequently, it was found that substituents present in **4** or **5** affect the ratio of syn to anti isomers formed and the role of substituents in such coupling reactions is discussed in an accompanying paper.[5] On the assumption that the presence of a nitro group, as in **4b**, would improve the syn to anti isomer ratio and that the nitro group could be removed as a final step, we undertook the synthesis of 2-nitro-*cis*-15,16-dimethyldihydropyrene (**8**), as shown in Scheme I.

To obtain the requisite 2,6-bis(bromomethyl)-4-nitrotoluene (**4b**), 2-methylisophthalaldehyde was nitrated and then converted by standard procedures to **4b**. The coupling reaction of **4b** and **5** proceeded in 47% overall yield, giving a mixture whose NMR spectrum showed the ratio of syn to anti isomers (**6b**/**7b**) to be 1:1. Since the Stevens rearrangement

Scheme I



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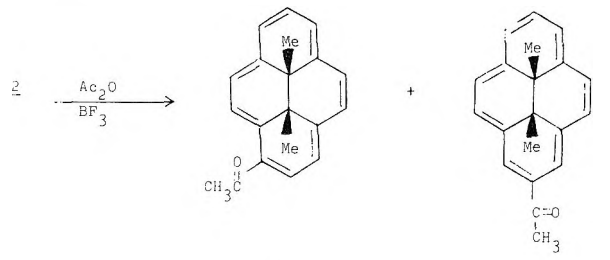
of *syn*-2,11-dithia[3.3]metacyclophanes gives mixtures of both the syn and anti isomers of the corresponding [2.2]metacyclophanes,[1] separation was not attempted at this stage but, instead, the mixture was carried through the complete sequence of Stevens rearrangement, oxidation of the product to the corresponding disulfoxide, and pyrolysis of this to give the cis and trans isomers of 2-nitro-15,16-dimethyldihydropyrene (**8** and **9**).

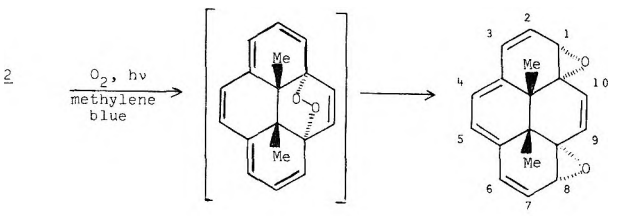
Although **8** and **9** could readily be separated and characterized, they were obtained in exceedingly poor yield and this is not a useful route for preparing *cis*-15,16-dihydropyrenes. In order to obtain samples of **2** for study, we then repeated the original synthesis.[1] As expected, nitration of **2** proceeded smoothly in 88% yield to give **8**, identical in all respects with the specimen obtained previously by independent synthesis.

However, in contrast to *trans*-15,16-dimethyldihydropyrene, which undergoes initial electrophilic substitution only at the 2 position,[6] *cis*-15,16-dimethyldihydropyrene (**2**) reacts with acetic anhydride in the presence of boron trifluoride etherate to give a mixture of the 1-acetyl and 2-acetyl derivatives **10** and **11** in a ratio of 2:1. The correct assignment of structure in each case was readily apparent from its ^1H NMR spectrum.



10 **11**

Also, in contrast to *trans*-15,16-dimethyldihydropyrene, the cis isomer **2** slowly reacts with air, and to be preserved it must be stored in the dark under vacuum. Since the reaction of **2** with oxygen is promoted by light, it seemed probable that singlet oxygen was involved. When a solution of **2** in chloroform containing methylene blue was irradiated with an ordinary tungsten lamp in the presence of oxygen, conversion of **2** to a new product containing two oxygen atoms was complete in 180 s. The composition, molecular weight, and spectra of this new oxygenated product, formed in essentially quantitative yield, are in full accord with its assignment of structure **13**. This is also a logical result. Attack on **2** by singlet oxygen would be expected to give **12** which, in turn, by thermal rearrangement would lead to **13**.



12 **13**

The ultraviolet absorption spectrum of **13** has a long wavelength band at 333 nm (ϵ 7750), as would be expected for such a conjugated tetraene.[7] In the NMR spectrum of **13** the symmetry of the molecule is evidenced by the fact that the protons of the internal methyl groups appear as a singlet (τ 8.61) as do the vinyl protons at the 4 and 5 positions and at the 9 and 10 positions (τ 3.56 and 4.09). The protons at the 1 and 8 positions appear as a doublet of doublets at τ 6.53, in good analogy to other examples of cyclic vinyl epoxides.[8]

Under the same reaction conditions used for the conversion of **2** to **13**, *trans*-15,16-dimethyldihydropyrene (**1**) remains unchanged. Apparently, the internal methyl groups of **1** provide sufficient steric hindrance that reaction with singlet oxygen does not occur. In the case of the cis isomer **2** approach of singlet oxygen from the side anti to the methyl groups is free of steric hindrance.

Experimental Section[9]

2,6-Bis(bromomethyl)-4-nitrotoluene (4b). A. 2-Methyl-5-nitroisophthalaldehyde. A solution of 4.82 g of 2-methylisophthalaldehyde[1] in 29 mL of concentrated sulfuric acid was added dropwise with stirring to a solution of 17.3 g of ammonium sulfate and 5.8 mL of 90% nitric acid in 28 mL of concentrated sulfuric acid held at 0 °C. When the addition was complete, the mixture was stirred for an additional 3.5 h and then was poured onto 250 g of ice. After the mixture had warmed to room temperature, the precipitate was collected by filtration, washed with water, and dried. This gave 5.63 g (90%) of a cream-colored solid, mp 98–100 °C. A sample, after recrystallization from a dichloromethane–hexane mixture, gave crystals: mp 101–101.5 °C; NMR, singlets at τ −0.50 (2 H, –CHO), 1.15 (2 H, ArH), and 6.95 (3 H, $-CH_3$). Anal. Calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.72; H, 3.69; N, 7.62.

B. 2,6-Bis(hydroxymethyl)-4-nitrotoluene. A solution of 170 mg of 2-methyl-5-nitroisophthalaldehyde in 5 mL of tetrahydrofuran was added with stirring to a suspension of 75 mg of sodium borohydride in 10 mL of tetrahydrofuran. After the resulting mixture had been stirred at room temperature for 6 h, it was decomposed by addition of 3 mL of dilute hydrochloric acid followed by 5 mL of brine. The organic layer was extracted with ether, washed with water, dried, and concentrated. The residual solid was recrystallized from 2-propanol to give 87 mg (50%) of pale yellow crystals: mp 140–142 °C; NMR, singlets at τ 1.73 (2 H, ArH), 5.17 (4 H, $-CH_2OH$), and 7.64 (3 H, $-CH_3$); mass spectrum *m/e* 197.070 (calcd for $C_9H_{11}NO_4$: 197.069). Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.75; H, 5.82; N, 6.96.

C. 2,6-Bis(bromomethyl)-4-nitrotoluene. A solution of 2.61 g of 2,6-bis(hydroxymethyl)-4-nitrotoluene in 15 g of a 30% solution of hydrogen bromide in acetic acid was stirred at room temperature for 16 h. The suspension was diluted with water and the precipitate was collected by filtration. The resulting dry solid was chromatographed over silica gel using a 1:1 mixture of benzene–hexane as eluent. The main fraction of eluate gave 1.91 g (45%) of colorless crystals: mp 154–155 °C; NMR, singlets at τ 1.80 (2 H, ArH), 5.44 (4 H, $-CH_2Br$), and 7.47 (3 H, $-CH_3$); mass spectrum *m/e* 325, 323, and 321. Anal. Calcd for $C_9H_9NO_2Br_2$: C, 33.44; H, 2.79. Found: C, 33.25; H, 3.01.

Coupling of 4b and 5 to Give the Syn and Anti Isomers 6b and 7b. A solution of 2.92 g of 2,6-bis(mercaptomethyl)toluene[1] and 5.14 g of 2,6-bis(bromomethyl)-4-nitrotoluene (**4b**) in 750 mL of benzene was added dropwise with stirring to a boiling solution of 2.7 g of potassium hydroxide in 3 L of ethanol. When the addition was complete (5 days), the solution was concentrated and the residual solid was extracted with dichloromethane. After the dichloromethane extract had been washed with water and dried, it was concentrated and the residual solid was chromatographed over silica gel using a 1:1 mixture of dichloromethane–petroleum ether (30–60 °C) as eluent. The main fraction of eluate gave 2.55 g (47%) of a colorless solid melting over a broad range. The NMR spectrum of the mixture showed the signals of the syn and anti isomers (**6b** and **7b**) sufficiently separated so that the spectrum of each could be individually analyzed. The syn isomer **6b** showed a singlet at τ 2.50 (2 H, ArH), a singlet at 3.35 (3 H, ArH), a doublet at 5.97 (4 H, J = 15 Hz, $ArCH_2$–), a doublet at 6.09 (4 H, J = 15 Hz, $ArCH_2$), and singlets at 6.36 and 7.48 (3 H each, CH_3–). The anti isomer **7b** showed a singlet at τ 1.81 (2 H, ArH), a multiplet at 2.62–2.90 (3 H, ArH), a singlet at 6.28 (8 H, $ArCH_2$–), and singlets at 8.59 and 8.71 (3 H each, $-CH_3$). The integration values indicated the syn to anti isomer ratio to be 1:1. The mass spectrum of the mixture showed *m/e* 313.115 (calcd for $C_{18}H_{19}NO_2S_2$: 313.114).

2-Nitro-*cis*-15,16-dimethyldihydropyrene (8) and 2-Nitro-*trans*-15,16-dimethyldihydropyrene (9). A. Stevens Rearrangement of 6b and 7b. A solution of 2.55 g of the 1:1 mixture of **6b** and **7b** in 74 mL of dichloromethane was added dropwise with stirring to a suspension of 3.20 g of dimethoxycarbonium fluoroborate[10] in 10 mL of dry dichloromethane held at −20 °C under a nitrogen atmosphere. After the mixture had been stirred for 5 h, 40 mL of methyl formate was added with stirring and the precipitate was collected by filtration. This gave 3.75 g (92%) of the bis(sulfonium fluoroborate) as a tan solid, mp 220 °C dec. The bis(sulfonium fluoroborate) was added in one portion with stirring to a suspension of 500 mg of sodium hydride in 300 mL of tetrahydrofuran. After the mixture had been stirred at room temperature for 9 h, it was decomposed by the addition

of water and aqueous hydrochloric acid. The organic layer was extracted with ether, washed with water, dried, and concentrated. Chromatography of the residue over silica gel using a 1:1 mixture of dichloromethane–petroleum ether (30–60 °C) as eluent gave 2.4 g (93%) of a yellow oil. The NMR spectrum of the oil was complicated, but appropriate for the expected mixture of isomers. The protons for the internal methyl groups of the *anti*-[2.2]metacyclophane isomers appeared in the region of τ 8.96–9.42, whereas the corresponding methyl protons of the syn isomers appeared in the region of τ 7.2–7.6. The comparative integration values for these areas indicated the ratio of syn to anti isomers to be 1:3. Since attempts to separate the individual isomers were not fruitful, the mixture was employed directly in the next step.

B. Oxidation of the Stevens Rearrangement Product. To a solution of 110 mg of the mixture of isomers from the Stevens rearrangement in 10 mL of dichloromethane was added 125 mg of *m*-chloroperbenzoic acid and the mixture was stirred at room temperature for 16 h. The solution was then decanted from the solid, washed with water, dried, and concentrated. The residual oil was again taken up in dichloromethane, washed with aqueous base followed by water, dried, and concentrated. This gave 124 mg (100%) of a pale yellow oil. The complicated NMR spectrum of the oil showed the protons of the internal methyl groups of the anti isomers at τ 9.0–9.4 and those of the syn isomers at τ 7.5–8.0, with the integration values for these regions indicating again a ratio of syn to anti isomers of 1:3.

C. Pyrolysis of the Disulfoxide Mixture. The pyrolysis was conducted in the normal apparatus used for sulfone pyrolyses with the preheater set at 150 °C and the oven at 500 °C.[11] A sample of 100 mg of the disulfoxide mixture from the above experiment was placed in the pyrolysis apparatus and the pressure was reduced to 1 Torr. After 2 h the pyrolysate was collected and purified by preparative thin-layer chromatography over silica gel (silica gel PF254) using a 1:1 mixture of benzene–petroleum ether (30–60 °C) for elution.

The first purple band (R_f 0.35) gave 4.6 mg of deep purple crystals: mp 172–173 °C; identical in all respects with an authentic sample of 2-nitro-*trans*-15,16-dimethyldihydropyrene (**9**).[6]

The second purple band (R_f 0.20) gave 2 mg of 2-nitro-*cis*-15,16-dimethyldihydropyrene (**8**) as deep purple crystals: mp 140–145 °C; NMR, singlet at τ 0.72 (2 H, ArH), two doublets at 0.90 and 1.90 (2 H each, J = 7.5 Hz, ArH), doublet at 1.61 (2 H, J = 8 Hz, ArH), a triplet at 2.23 (1 H, J = 8 Hz, ArH), and singlets at 11.89 and 11.98 (3 H each, $-CH_3$); UV (cyclohexane), maxima at 288 (ϵ 5400), 342 (35 200), 378 (17 400), 484 (12 700), 562 (1170), and 617 nm (1370); mass spectrum *m/e* 277, 262, 247, and 201. Anal. Mol wt calcd for $C_{18}H_{15}NO_2$: 277.110. Found (high-resolution mass spectrum): 277.108.

2-Nitro-*cis*-15,16-dimethyldihydropyrene was also prepared independently. A solution of 1.8 mg of *cis*-15,16-dimethyldihydropyrene[1] and 1.9 mg of cupric nitrate trihydrate in 0.5 mL of acetic anhydride was stirred at 0 °C for 1 h. Ice (2 g) was then added and the mixture was allowed to warm to room temperature with stirring. After extraction of the mixture with ether, the ether extract was washed successively with aqueous bicarbonate solution and water, dried, and concentrated. The residue was chromatographed over silica gel using dichloromethane as eluent to give 2.1 mg (88%) of deep purple crystals, identical in all respects with the specimen of 2-nitro-*cis*-15,16-dimethyldihydropyrene (**8**) described above.

1- and 2-Acetyl-*cis*-15,16-dimethyldihydropyrene (10 and 11). To a solution of 2.0 mg of *cis*-15,16-dimethyldihydropyrene (**2**)[1] in 1 mL of acetic anhydride held at 0 °C was added 5 drops of boron trifluoride etherate with stirring. After the mixture had been stirred for 10 min, 2 mL of water was added and the mixture was allowed to warm and was stirred at room temperature for 2 h. The organic constituents were extracted with dichloromethane and the dichloromethane extract was washed successively with aqueous bicarbonate solution and water, dried, and concentrated. The residual green solid was purified by thin-layer chromatography over silica gel using dichloromethane for elution.

The first band (R_f 0.4) gave 1 mg (40%) of 1-acetyl-*cis*-15,16-dimethyldihydropyrene (**10**) as deep green crystals: NMR, doublets at τ 0.35 and 1.13 (1 H each, J = 8 Hz, ArH), a singlet at 1.17 (2 H, ArH), an AB pattern at 1.73 and 1.91 (2 H, J = 8 Hz, ArH), a doublet at 1.67 (2 H, J = 8 Hz, ArH), a triplet at 2.37 (1 H, J = 8 Hz, ArH), a singlet at 7.06 (3 H, $-C(=O)CH_3$), and singlets at 11.94 and 11.97 (3 H each, $-CH_3$); (cyclohexane), maxima at 358 (ϵ 12 000), 423 (1200), 442 (1000), 570 (100), and 616 nm (100). Anal. Mol wt calcd for $C_{20}H_{18}O$: 274.136. Found (high-resolution mass spectrum): 274.139.

The second band (R_f 0.3) gave 0.5 mg of 2-acetyl-*cis*-15,16-dimethyldihydropyrene as deep green crystals: NMR, a singlet at τ 1.04 (2 H, ArH), an AB pattern at 0.98 and 1.20 (4 H, J = 8 Hz, ArH), a doublet at 1.69 (2 H, J = 8 Hz, ArH), a triplet at 2.32 (1 H, J = 8 Hz, ArH), a singlet at 7.06 (3 H, $-C(=O)CH_3$), and singlets at 11.85 and 11.96 (3 H, each, $-CH_3$); UV (cyclohexane), maxima at 262 (ϵ 12 000), 333 (13 000), 367 (9300), 467 (2600), 570 (100), and 617 nm (200). Anal. Mol. wt calcd for $C_{20}H_{18}O$: 274.136. Found (high-resolution mass spectrum): 274.138.

Oxidation of *cis*-15,16-Dimethyldihydropyrene (2) to 13. A stream of oxygen was slowly bubbled through a solution of 1.0 mg of *cis*-15,16-dimethyldihydropyrene (**2**)[1] in 0.2 mL of chloroform containing a trace of methylene blue while the solution was irradiated with an ordinary 250-W incandescent lamp. After 180 s the solution was removed and chromatographed over silica gel. From the main fraction of eluate there was isolated 1.1 mg (100%) of a yellow oil: NMR, a singlet at τ 3.56 (2 H, –CH=C<), a doublet of doublets at 3.70 (2 H, J = 2 Hz, J^1 = 9 Hz, –CH=C<), a doublet of doublets at 4.03 (2 H, J = 2 Hz, J^1 = 9 Hz, –CH=C<), a singlet at 4.09 (2 H, –CH=CH–), a doublet of doublets at 6.53 (2 H, J = 2, J^1 = 4 Hz, C–CHOC<), and a singlet at 8.61 (6 H, $-CH_3$); UV (ethanol), maxima at 207 (ϵ 10 300), 223 (8720), 230 (10 700), 239 (14 800), 249 (7300), 261 (8250), 272 (9940), 303 (3550), 317 (5230), and 333 nm (7750). Anal. Mol wt calcd for $C_{18}H_{16}O_2$: 264.115. Found (high-resolution mass spectrum): 264.114.

The same product was obtained when oxygen was bubbled through a chloroform sclution of **2** in the absence of methylene blue, but the reaction required hours for completion.

Acknowledgment. We thank the National Science Foundation for their support of this investigation.

Registry No.—**2**, 52028-44-1; **4b**, 66901-98-2; **5**, 41563-67-1; **6b**, 66901-99-3; **6b** bis-*S*-Me derivative tetrafluoroborate salt, 66966-28-7; **6b** bissulfoxide bis-*S*-Me derivative tetrafluoroborate salt, 66902-32-7; **6b** Stevens rearrangement product, 66902-31-6; **7b**, 66966-21-0; **7b** bis-*S*-Me derivative tetrafluoroborate salt, 66902-07-6; **7b** bissulfoxide bis-*S*-Me derivative tetrafluoroborate salt, 66902-33-8; **7b** Stevens rearrangement product, 66966-22-1; **8**, 66902-00-9; **9**, 13979-82-3; **10**, 66902-01-0; **11**, 66902-02-1; **13**, 66902-03-2; 2-methyl-5-nitroisophthalaldehyde, 66902-04-3; 2-methylisophthalaldehyde, 51689-50-0; 2,6-bis(hydroxymethyl)-4-nitrotoluene, 66902-05-4; dimethoxycarbonium fluoroborate, 18346-68-4.

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Synthesis of Bridgehead Hydroxyl-Substituted Benzobicyclo[3.2.1]octenes and -octadienes via an Acyloin Rearrangement in the Benzobicyclo[2.2.2]octene Ring System

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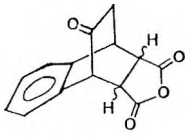
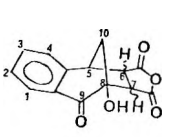
Maleic anhydride and 1,2-naphthalenediol, on heating to 180 °C, produced a mixture of the benzobicyclo[3.2.1]-octene derivative **2** and the benzobicyclo[2.2.2]octene derivative **3**. This was the result of Diels–Alder addition to form **3**, followed by extensive rearrangement of **3** to **2**. Purified compound **3** was converted to **2** in high yield via an acyloin rearrangement; this process occurred thermally or with acid or base catalysis. The utility of this rearrangement for the preparation of bridgehead hydroxyl-substituted benzobicyclo[3.2.1]octenes and -octadienes was demonstrated by the conversion of the anhydride **2** to the bisdecarboxylated hydroxy ketones **4** and **5** and the amino alcohol **6**. Presence of the bicyclo[3.2.1] ring system was confirmed crystallographically for the hydrochloride salt of **6**.

Benzobicyclo[2.2.2]- and -[3.2.1]octenes, -octadienes, and -octatrienes bearing bridgehead hydroxyl substituents are uncommon. Only one benzobicyclo[3.2.1]octadiene[1] and two benzobicyclo[2.2.2]octene[2] and -octatriene[3] examples are known. We report the synthesis of a bridgehead hydroxyl-substituted benzobicyclo[2.2.2]octene and its facile conversion to bridgehead hydroxyl-substituted benzobicyclo[3.2.1]octene and -octadiene derivatives via an acyloin rearrangement. Rearrangements in the benzobicyclo[2.2.2]octene, -octadiene, and -octatriene ring systems are well known and have been initiated by a cationic species (H^+, Br^+, Cl^+, NO^+)[4a–c] or by solvolysis of a sulfonate ester,[4d,e] producing a carbonium ion, or by irradiation;[4f,g,h] ours is the first example of an acyloin rearrangement in this ring system.

The Diels–Alder addition of maleic anhydride to 2-naphthol, producing **1**, has previously been reported as an entry



1



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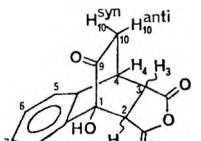
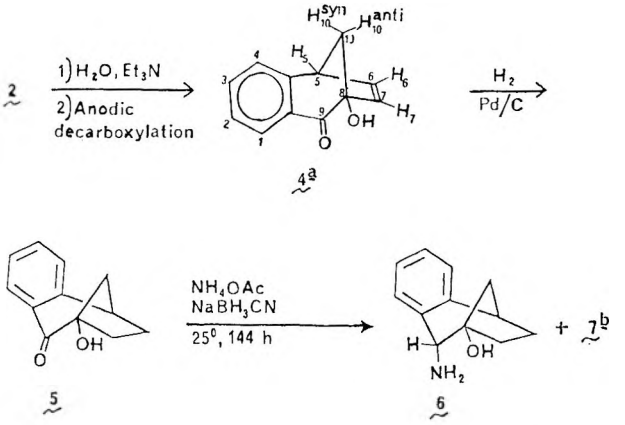


3

into the benzobicyclo[2.2.2]octene ring system.[5] When we attempted to extend this procedure by adding maleic anhydride to 1,2-naphthalenediol at 180 °C under inert atmosphere, we observed the formation of two isomeric products, **2** (major) and **3**, which were separable by column chromatography or by fractional recrystallization. Compound **2** was subsequently hydrolyzed and subjected to anodic decarboxylation to produce the olefin **4**. Catalytic hydrogenation of **4** to **5** followed by reductive amination gave the amine **6** (see Scheme I). All assigned structures were consistent with observed IR and NMR spectra, and the presence of the benzobicyclo[3.2.1]octene skeleton was confirmed by X-ray structure determination of the hydrochloride salt of **6**.

The minor product of the Diels–Alder reaction was the expected adduct **3**. The infrared spectrum of **3** was very similar to that of **1**; in particular, **3** had a ketone carbonyl absorption at 1735 cm^{-1} (cf. 1730 cm^{-1} observed for **1**). In addition, IR showed that the hydroxyl group is strongly intramolecularly hydrogen bonded, consistent with the presence of an α-hydroxy ketone. In the NMR spectrum of **3**, the methylene protons H_{10} appeared as a pair of doublets. $H_{10}{}^{anti}$ had a chemical shift of δ 2.68, while $H_{10}{}^{syn}$, which is shielded by the aromatic ring, appeared at δ 2.57. The aromatic protons of **3** appeared as a multiplet between 7.2 and 7.7 ppm. The mass spectral fragmentation patterns of **1** and **3** showed a number

Scheme I



2 **4**[a] **5** **6** + **7**[b]

[a] The terms "syn" and "anti" are used relative to the aromatic ring. [b] Compound **7** constituted < 5% of the amine product and was not identified.

of similarities; significant among these was the appearance of a peak at M − 42, consistent with the retro-Diels–Alder loss of ketene. The UV spectrum provided further evidence for the assigned structure of **3**; it showed maxima at 255 and 292 nm, compared to literature values[6] of 265 and 295 nm for compound **1**.

In comparison, the major product **2** had a carbonyl absorption at 1690 cm^{-1} in the infrared and a strong UV maximum absorption at 251 nm (ϵ 12 600), indicative of a conjugated ketone. Intramolecular hydrogen bonding of the hydroxyl group was again observed by infrared spectroscopy, indicating the rearranged structure **2**. In contrast to the mass spectra of **1** and **3**, compound **2** showed no M − 42 fragment; this observation is also consistent with the presence of a rearranged carbon skeleton.

The yield and the product ratio in the Diels–Alder reaction were found to be dependent upon the purity of both the naphthalenediol and the maleic anhydride. Higher proportions of **3** relative to **2** and higher overall yields were observed when the naphthalenediol was dried over $MgSO_4$ and recrystallized from carbon disulfide and when commercial maleic anhydride (containing as much as 14% maleic acid) was sublimed prior to use. Table I lists yields and product ratios which were obtained under various conditions. Prolonged heating led to increased yields of **2** at the expense of **3**; this is consistent with initial formation of **3** and subsequent acyloin rearrangement to **2**.

Characteristic of acyloin rearrangements, the conversion of **3** to **2** occurs thermally and with acid and base catalysis. The

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Table I. Product Ratios Obtained in the Diels–Alder Addition of Maleic Anhydride to 1,2-Naphthalenediol

conditions	ratio of 3 to 2[a]	% overall yield
commercial maleic anhydride,[b] 170 °C, 20 min	13:87	42.6
sublimed maleic anhydride, 180 °C, 20 min	25:75	61.3
sublimed maleic anhydride, 180–190 °C, 5 min	44:56	70.5

[a] Product ratios were determined by IR as described in the text. [b] This material was found to contain 14% maleic acid.

Table II. First-Order Rate Constants for the Rearrangement of 3 to 2 at 82 °C (Acetonitrile at Reflux)

conditions	k, h^{-1}
CH_3CN, Δ[a]	$2.46\ (\pm 0.22) \times 10^{-3}$
CH_3CN, p-TsOH, Δ[b]	$2.98\ (\pm 0.15) \times 10^{-3}$

[a] 202.8 mg of **3** in 75 mL of CH_3CN. [b] 204.2 mg of **3** + 3.2 mg of p-TsOH in 75 mL of CH_3CN.

crystalline hydroxy ketone **3** underwent rearrangement to **2** at its melting point. The reaction proceeded more slowly at 82 °C (acetonitrile at reflux) and was conveniently monitored by infrared spectroscopy. The changes in ketone carbonyl absorbance of **3** and **2** were linear with concentration over the range 0–37 mg/mL in acetonitrile solution. Table II lists first-order rate constants for the rearrangement in acetonitrile at reflux under neutral conditions and with added p-toluenesulfonic acid. The base-catalyzed rearrangement was complicated by competing condensation reactions, which interfered with the determination of rate constants; changes in the infrared spectra were, however, consistent with base catalysis. Rearrangement of **2** to **3** was not observed; this suggests that **2** is considerably more stable than **3** due to conjugation of the ketone carbonyl group. This is not always the case; Colard et al., for example, reported an instance (see Figure 1) in which a conjugated acyloin was less stable than its nonconjugated isomer.[8] Ring strain effects would probably favor the bicyclo[2.2.2] system over the bicyclo[3.2.1] system, according to results obtained with several equilibrating dibenzobicyclo[3.2.1]- and -[2.2.2]octadiene systems.[9]

Further evidence for the structure of **2** was afforded by conversion to the bicyclo[3.2.1]octadienone **4**. Following hydrolysis, compound **2** readily underwent electrolytic decarboxylation[10] in pyridine to produce **4** in 49% yield from the anhydride. In the NMR spectrum of **4**, the aromatic proton ortho to the carbonyl group (H_1) was deshielded relative to the other aromatic protons. The vinyl protons H_6 and H_7 appeared as a doublet of doublets and a doublet, respectively. The bridgehead proton H_5 appeared as a broad multiplet at δ 3.81. The methylene protons H_{10} produced a doublet of doublets centered at δ 2.90 and a doublet at δ 2.53. Irradiation of the bridgehead proton H_5 caused the methylene protons to appear as two doublets due to geminal coupling (J = 10 Hz). It was determined from a Dreiding model of **4** that H_5 should couple with H_{10}^{anti} (H–C–C–H dihedral angle ≈40°) but not with H_{10}^{syn} (H–C–C–H dihedral angle ≈80°), permitting the assignment of the peaks at δ 2.90 to H_{10}^{anti}, and the doublet at δ 2.53 to H_{10}^{syn}. The shielding effect on H_{10}^{syn} by the carbonyl and/or aromatic systems lends further support to these assignments.

Attempted anodic decarboxylation of **3** gave a low yield of a mixture of two ketones (Scheme II). The major product was compound **4**; the presence of carbonyl absorption at 1740 cm^{-1} in the ketone mixture suggested that the minor product was compound **8**. The product ratio of **4** to **8** was estimated to be about 4:1 on the basis of the IR carbonyl absorptions. The susceptibility of **8** to rearrangement prevented thin layer or gas chromatographic isolation of a pure sample uncontaminated with **4**.

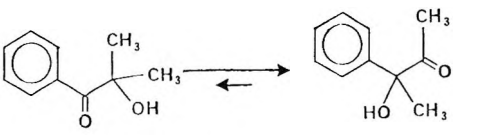
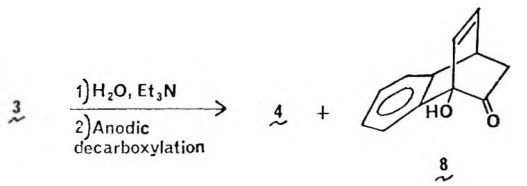
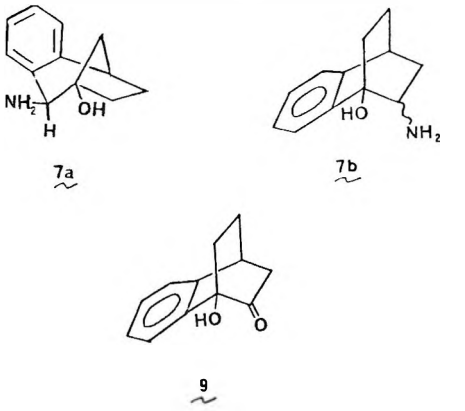


Figure 1.

Scheme II



The facile acyloin rearrangement of a benzobicyclo[2.2.2]-octene affords a convenient procedure for the synthesis of bridgehead hydroxyl-substituted benzobicyclo[3.2.1]octenes and -octadienes. For example, ketone **4** was readily hydrogenated to **5**, which underwent reductive amination with ammonium acetate and sodium cyanoborohydride.[11] The reductive amination afforded a mixture of two amines, separable by LC. The major product, comprising 95% of the isolated



product, was shown to be the amine **6** by X-ray crystallographic analysis of the hydrochloride salt.[12] The minor product was not isolated in sufficient quantity to identify. It is likely that it was either **7a** (the stereoisomer of **6**) or **7b** (arising from contamination of the ketone **5** with a small amount of the bicyclo[2.2.2]octenone **9**).

Experimental Section

Infrared spectra were recorded on a Beckman IR-33 spectrophotomer. NMR spectra were obtained on a Varian T-60, EM360, or HA-100 spectrometer using tetramethylsilane as internal standard. UV spectra were recorded on a Cary 14 spectrophotometer. Melting points were determined on a Thomas-Hoover Uni-melt and are uncorrected. Mass spectra were obtained on a Varian CH5 spectrometer. Elemental analyses were performed on an F&M Model 185 by Mr. Tho Nguyen of The University of Kansas.

9-Keto-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2,3-dicarboxylic Anhydride (1). This material was prepared as described by Takeda et al.;[6] IR (KBr) 3075, 3025, 2980, 2950, 1865 and 1775 (anhydride C=O), 1730 (ketone C=O), 1470, 1450, 1395, 1345, 1285, 1255, 1235 (sh), 1215, 1195, 1170, 1140, 1095, 1060, 995, 970, 930, 900, 825, 805, 755, 735, 705, 680 cm^{-1}; NMR (Me_2SO-d_6) δ 7.35 (s, 4, aromatic), 3.43 (d, 1), 2.93 (m, 1), 2.44–2.68 (m, 2), 2.28–2.41 (m, 1), 2.03 (m, 1); mass spectrum m/e (rel intensity) 242 (19, M^+), 215 (7), 214 (48), 200 (2), 141 (6), 129 (11), 128 (100), 127 (5), 115 (6).

1,2-Naphthalenediol.[13] To a stirred solution of sodium dithionite (300 g, 1.72 mol) in distilled water (3.75 L) at 25 °C was added 1,2-

Table III

product (2) concn, M	time, h
Run 1: 202.8 mg of 3 Dissolved in 75 mL of CH_3CN at Reflux	
0.21×10^{-3}	16.50
0.31	37.92
1.45	76.50
2.27	116.00
Run 2: 204.2 mg of 3 + 3.2 mg of *p*-TsOH in 75 mL of CH_3CN at Reflux	
0.21×10^{-3}	16.67
0.72	38.08
1.96	76.67
2.79	116.17

naphthoquinone (50.0 g, 0.316 mol). The solution turned gray, then black, and then clarified as a small amount of tar formed. The mixture was stirred for 15 min and was filtered to remove the tar. The solution was saturated with NaCl and cooled to −5 °C for 30 min. The cream-colored precipitate was collected by filtration and immediately dissolved in 1.5 L of hot CS_2. The solution was dried with $MgSO_4$, filtered, and concentrated to 100 mL on a steam bath under a stream of argon. Upon cooling, 21.5 g (42.4%) of naphthalenediol was collected as purple-brown crystals, mp 103–105 °C (lit.[13] mp 104 °C). This material was of adequate purity for the Diels–Alder reaction; however, white crystals could be obtained by sublimation.

Reaction of Maleic Anhydride with 1,2-Naphthalenediol. Maleic anhydride was sublimed prior to use. 1,2-Naphthalenediol was freshly prepared as described above. Under argon atmosphere, a mixture of maleic anhydride (16.7 g, 0.170 mol) and 1,2-naphthalenediol (16.7 g, 0.104 mol) was heated at 180–190 °C for 5 min. The mixture was taken up in 150 mL of hot ethyl acetate and the solution was concentrated in vacuo to give a brown semisolid mass. This was shaken with 800 mL of ether and allowed to stand for 30 min. Filtration afforded 19.0 g (70.6%) of a mixture of the products 3 and 2 in a ratio of 44:56 as determined by IR analysis. A 2.9-g portion of the product mixture was separated by medium-pressure liquid chromatography on silica (Merck, 230–400 mesh), column size 25 × 1000 mm, eluting with hexane–ethyl acetate (3:2) at a pressure of 40 psi. The first 700 mL was discarded; the bicyclo[3.2.1] product 2 was contained in the next 150 mL. Another 350 mL was discarded, and the following 500 mL contained the bicyclo[2.2.2] product 3, contaminated with traces of 2; 3 was further purified by a recrystalization from toluene–ethyl acetate: mp 187–192 °C; UV λ_{max} (CH_3CN) 226 (ε 4350), 255 (347), 292 nm (377); IR (KBr) 3480 (OH), 2982, 1850 and 1775 (anhydride C=O), 1735 (ketone C=O, log ε 6.13), 1264, 1234, 1163, 1082, 1053 (sh), 1016, 934, 862, 763 (sh), 754 (sh), 740, and 732 cm^{-1}; NMR (CD_3CN) δ 7.2–7.7 (m, 4, aromatic), 4.63 (s, 1, OH), 3.92 (m, 2 of H_2, H_3, and H_4), 3.61 (m, 1 of H_2, H_3, and H_4), 2.68 (d, 1, H_{10}^{anti}), and 2.57 (d, 1, H_{10}^{syn}); mass spectrum *m/e* (rel intensity) 258 (M^+, 8), 231 (5), 230 (38), 216 (2), 160 (4), 157 (8), 156 (6), 144 (26), 133 (9), 132 (100), 131 (37), 129 (6), 128 (9), 116 (6), 115 (15), 103 (12), 77 (10), 51 (5). Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.11; H, 3.90. Found: C, 65.36; H, 3.87.

Compound 2: mp 204.5–205.5 °C; UV λ_{max} (C_2H_5OH) 251 (ε 12 600), 290 (1770), 297 nm sh (1740); IR (KBr) 3458 (OH), 1855 and 1775 (anhydride C=O), 1690 (ketone C=O, log ε 5.97), 1604, 1296, 1265 (sh), 1242 (sh), 1228, 1212 (sh), 1192, 1100, 1077, 929, 920 (sh), 771, 725, and 628 cm^{-1}; NMR (CD_3CN) δ 8.01–8.35 (m, 1, H_1), 7.35–7.95 (m, 3, H_2, H_3, H_4), 4.60 (s, 1, OH), 3.92 (t, 1, bridgehead), 3.57 (d, 1, methine), 3.26 (d, 1, methine), and 2.30 (m, 2, methylene); mass spectrum *m/e* (rel intensity) 258 (M^+, 20), 231 (15), 230 (88), 204 (7), 203 (7), 202 (30), 196 (7), 188 (11), 186 (30), 185 (15), 184 (27), 172 (5), 170 (8), 169 (6), 168 (27), 161 (6), 160 (48), 159 (5), 158 (21), 157 (27), 156 (27), 145 (14), 144 (100), 143 (8), 141 (5), 140 (7), 139 (6), 133 (13), 132 (91), 131 (100), 130 (13), 129 (27), 128 (30), 127 (15), 116 (16), 115 (36), 114 (5), 104 (7), 103 (36), 102 (15), 89 (9), 83 (8), 79 (8), 78 (30), 77 (45), 76 (12), 75 (8), 70 (10), 69 (6), 66 (7), 65 (9), 64 (21), 63 (16), 57 (12), 55 (15), 53 (7), 52 (9), 51 (30), 50 (10), 45 (7). Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.11; H, 3.90. Found: C, 65.11; H, 3.82.

Rearrangement of 1-Hydroxy-9-keto-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2,3-dicarboxylic Anhydride (3) to 8-Hydroxy-9-keto-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-6,7-dicarboxylic Anhydride (2). Method A. Compound 3 (47 mg, 0.18 mmol) was heated under an argon atmosphere at 170–180 °C for 10 min. The product was cooled and crystallized from ethyl acetate–ether to yield 2 (41 mg, 87.2%), mp 205–206 °C, identical to an authentic sample by IR and mixed melting point.

Method B. The changes in ketone carbonyl absorbances of 3 and 2 were found to be linear with concentration over the concentration range 0–37 mg/mL in acetonitrile solution. Compound 3 was dissolved in acetonitrile at reflux with or without added *p*-toluenesulfonic acid. Periodically aliquots were withdrawn and the extent of rearrangement determined from the IR spectrum. First-order rate constants were determined by linear least-squares analysis of the concentration vs. time data. Experimental data for two runs are listed in Table III.

8-Hydroxy-8,9-dihydro-5,8-methano-5*H*-benzocyclohepten-9-one (4). A mixture of the anhydride 2 (1.25 g, 4.84 mmol), Et_3N (1.25 mL), and distilled water (10 mL) was heated at reflux for 30 min. This solution was added to pyridine (95 mL) in a water-jacketed electrolysis cell fitted with a rubber stopper through which a thermometer and a concentric pair of cylindrical platinum gauze electrodes of matched surface area (outer electrode 4-cm diameter × 5-cm long) had been inserted. The magnetically stirred solution was cooled to 18 °C, and an initial current of 0.8 A was applied to the solution, resulting in an observable evolution of gas within ~60 s. The solution was maintained at 17–23 °C, and within several hours became dark brown. The reaction was terminated after 24 h (final current 0.5 amp), although a slow evolution of gas was observable. The black solution was concentrated in vacuo to 5–10 mL, combined with concentrates from three other runs, and further concentrated in vacuo to give a viscous black oil. Dry column chromatography of this oil on a 5 cm × 50 cm column packed with silica (Woelm, activity III, 500 g) developed with $CHCl_3$ afforded 1.78 g (49.3%) of 4 as a pale yellow oil (isolated by extraction with ethyl acetate of a 28.8-cm long band beginning 8.8 cm from the base of the column and visualized by UV): IR ($CHCl_3$) 3630 and 3512 (OH), 2968, 2900, 1689 (ketone), 1600, 1450, 1381, 1359, 1324, 1286, 1226, 1135, 1116, 1090, 1055, 1029, 957, 932, 891, and 861 cm^{-1}; UV λ_{max} (C_2H_5OH) 246 (ε 8040), 295 (706) nm; NMR ($CDCl_3$) 7.83–8.23 (m, 1, aromatic), 7.00–7.83 (m, 3, aromatic), 6.66 (d of d, 1, H_6, J_{6-5} = 5 Hz, J_{6-7} = 6 Hz), 5.96 (d, 1, H_7, J_{7-6} = 6 Hz), 4.47 (s, 1, OH), 3.81 (m, 1, H_5), 2.70–3.10 (d of d, 1, H_{10}^{anti}, $J_{10^{a}-10^{s}}$ = 10 Hz, $J_{10^{a}-5}$ = 5 Hz), and 2.53 (d, 1, H_{10}^{syn}, $J_{10^{s}-10^{a}}$ = 10 Hz). A high-resolution mass spectrum gave a parent ion of 186.06845 (calcd 186.06802).

Electrolytic Decarboxylation of 1-Hydroxy-9-keto-1,4-ethano-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic Anhydride (3). Anhydride 3 (357 mg, 1.38 mmol) was stirred in distilled water (4 mL) and Et_3N (1 mL) at room temperature for 10.5 h. The mixture was added to 100 mL of pyridine and the electrolysis reaction was carried out as described above. Medium-pressure liquid chromatography was carried out on silica (Merck, 230–400 mesh), column size 15 × 1000 mm, eluting with hexane–ethyl acetate (8:1) at a pressure of 40 psi. After a 550-mL forerun, 100 mL of eluate was collected and evaporated to leave 102 mg (39.7%) of a pale yellow oil. The IR spectrum was identical with that of 4 with an additional peak at 1740 cm^{-1}. The NMR was identical with that of 4 with additional absorption from δ 3.3 to 3.6. Using the ketone carbonyl absorbance vs. concentration correlations for anhydrides 3 and 2, the ratio of 8 to 4 was estimated to be about 1:4. The following chromatographic procedures failed to achieve separation of the mixture: thin-layer chromatography using Merck silica plates (solvents, ratio, R_f of ketone mixture: benzene–$CHCl_3$, 1:1, 0.21; hexane–$CHCl_3$, 1:1, 0.06; hexane–EtOAc, 4:1, 0.37; hexane–benzene–EtOAc, 20:4:1, 0.08; hexane–EtOAc–$CHCl_3$, 21:2:2, 0.17; benzene, 0.11; $CHCl_3$, 0.33; hexane–EtOAc, 1:1, 0.77); gas chromatography on a 6 ft × 0.125 in. column of 5% FFAP on Chromasorb G at 140–200 °C; medium-pressure liquid chromatography on silica (Merck, 230–400 mesh) using hexane–EtOAc, 20:1, column size 15 × 1000 mm, at 40 psi.

8-Hydroxy-6,7,8,9-tetrahydro-5,8-methano-5*H*-benzocycloheptene-9-one (5). Ketone 4 (1.87 g, 10.0 mmol) in EtOH (15 mL) was hydrogenated over 5% Pd/C (320 mg) on a Parr Shaker at an initial pressure of 33 psi for 10 min, at which time 1 equiv of hydrogen had been consumed. The solution was filtered and the solvent removed in vacuo, leaving 1.86 g (98.9%) of a colorless oil: IR ($CHCl_3$) 3630 and 3510 (OH), 2964, 2886, 1682 (ketone), 1600, 1446 (br), 1376, 1320, 1291, 1263, 1130, 1114, 1084, 987, 947, and 894 cm^{-1}; NMR ($CDCl_3$) δ 7.84–8.14 (m, 1, aromatic), 7.07–7.84 (m, 3, aromatic), 4.15 (s, 1, OH), 3.29–3.53 (m, 1, bridgehead), and 0.80–3.20 (m, 6, aliphatic); UV (EtOH) λ_{max} 220 (ε 627), 246 (ε 8040), and 295 nm (ε 706). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.42. Found: C, 76.59; H, 6.36.

Reductive Amination of 5. The hydroxy ketone 5 (849 mg, 4.51 mmol) was stirred in 13.5 mL of absolute methanol with ammonium acetate (3.48 g, 45.1 mmol). Sodium cyanoborohydride (199 mg, 3.16 mmol) was added and the mixture was stirred at room temperature for 7 days. The mixture was cooled on an ice bath and concentrated HCl was added dropwise until the pH was <2. Methanol was removed in vacuo. Distilled water (6 mL) and 1 N HCl (4 mL) were added. The solution was extracted with 4 × 15 mL of ether. The ether layers were washed with 2 × 20 mL of 5% $NaHCO_3$ solution, dried with $MgSO_4$,

and evaporated to give 80 mg (9.4%) of the starting material **5**. The acidic aqueous portion was adjusted to pH 10 with solid NaOH and was extracted with 5 × 15 mL of ether. The ether layers were combined, dried with $MgSO_4$, and evaporated to give a brown semisolid mass. Trituration with ether (10 mL) provided 570 mg (66.8%) of an off-white solid. LC (Partisil 10/25, 25 cm × 4.6 mm column, methanol, flow rate = 5 mL/min) afforded separation into two components. A 147-mg sample was dissolved in 0.3 mL of CH_3OH and injected onto the column in 10-μL portions; collecting and evaporating the fractions yielded 141 mg of **6**: retention time 9.8 min; mp 101–102 °C; IR (KBr) 3355, 3290, 3075 (br), 3030 (sh), 2955, 2875, 2855 (sh), 1595, 1485, 1450, 1365, 1320, 1260, 1215, 1190, 1165, 1140, 1115, 1090, 1065, 1005, 980, 970 (sh), 935, 905, 755, and 725 cm^{-1}; NMR ($CDCl_3$) δ 6.90–7.50 (m, 4, aromatic), 4.03 (s, 1, methine), 2.97–3.15 (m, 1, bridgehead), and 0.80–2.38 (m, 6, aliphatic); mass spectrum *m/e* (rel intensity) 190 (M + 1, 7), 189 (M^+, 47), 188 (17), 173 (12), 172 (91), 171 (8), 157 (7), 145 (9), 144 (24), 143 (14), 133 (11), 132 (100), 131 (16), 130 (55), 129 (34), 128 (45), 127 (8), 118 (9), 117 (38), 116 (29), 115 (54), 103 (9), 92 (11), 91 (9), 90 (5), 89 (7), 77 (12), 65 (7), 51 (7). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.37; H, 8.04; N, 7.39.

Dry HCl gas was passed over the surface of a solution of **6** in ether. The solid product, **6**·HCl, was collected by filtration. Recrystallization from isopropyl alcohol gave crystals (mp 257 °C) suitable for X-ray analysis: IR (KBr) 3270, 3190, 3035, 2975 (sh), 2950, 2840, 2665 (sh), 2605 (sh), 1630, 1595, 1510, 1490 (sh), 1465 (sh), 1445, 1355, 1305, 1260, 1250, 1200, 1070, 765, and 725 cm^{-1}.

LC also provided 4.8 mg of an unidentified amine with a retention time of 16.9 min; its hydrochloride had mp 220 °C dec.

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Registry No.—**1**, 4428-22-2; **2**, 66792-54-9; **3**, 66792-55-0; **4**, 66792-51-6; **5**, 66792-52-7; **6**, 66808-36-4; **6** HCl, 66279-25-2; **8**, 66792-53-8; 1,2-naphthalenediol, 574-00-5; 1,2-naphthoquinone, 524-42-5; maleic anhydride, 108-31-6.

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Use of the Trimethylsilyl Group in Synthesis. Preparation of Sulfinate Esters and Unsymmetrical Disulfides[1a]

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Alkoxytrimethylsilanes and sulfinyl chlorides have been shown to couple efficiently to afford sulfinate esters; kinetic data indicate that a nonionic transition state is involved. The parallel reaction between aralkylthiotrimethylsilanes and sulfenyl chlorides gives unsymmetrical disulfides. An attempt to prepare sulfenate esters by the reaction of a sulfenyl chloride and an alkoxytrimethylsilane gave no reaction; in fact, sulfenate esters were shown to be cleaved by either chlorotrimethylsilane or trimethylsilyl cyanide to yield sulfenyl chlorides or thiocyanates, respectively. The reaction of *tert*-butyl hypochlorite with an alkylthiosilane gave disulfide.

A variety of silicon derivatives have seen widespread and growing use in the past few years[2] as protective groups and synthetic mediators. For instance, it is well known[2h,3] that acid chlorides react smoothly with alkoxysilanes to produce esters in good yield. Heteroatom analogues of this reaction could be of great utility; however, incomplete synthetic information and virtually no detailed mechanistic data are available for this reaction class[2h,4] (eq 1), which in principle encompasses

$$RCCl + (CH_3)_3SiOR' \longrightarrow RCOR' + (CH_3)_3SiCl$$

an impressive number of important functionalities. We wish to report on two facile syntheses using the trimethylsilyl group.

$$RXCl + (CH_3)_3SiYR' \rightarrow RXYR' + (CH_3)_3SiCl \quad (1)$$

X = O, NR, S, S=O, PR, P(=O)R; Y = O, NR, S

When sulfinyl chlorides are treated with aralkoxytrimethylsilanes (eq 2), sulfinate esters (1) are cleanly produced in very good yield (Table I).[6]

$$RSCl + R'OSi(CH_3)_3 \longrightarrow \underset{\mathbf{1}}{RSOR'} + (CH_3)_3SiCl \quad (2)$$

R′ = R = aralkyl

The precursor alcohols may be conveniently silylated[7] with hexamethyldisilazane using imidazole as catalyst. One equivalent of the alkoxytrimethylsilane is added to an equivalent of a sulfinyl chloride and the reaction is allowed to proceed at room temperature. The progress of the reactions may be conveniently followed by ^1H NMR spectroscopy, the singlet for chlorotrimethylsilane increasing at the expense of the peak for the trimethylsilyl group of the alkoxytrimethylsilane. Chlorotrimethylsilane may be easily removed by

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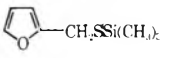
Table I. Preparation of Sulfinate Esters

sulfinate ester (1)	registry no.	yield, %	bp (torr) [mp], °C	n_D^{22}	ρ_{22}
(a) $CH_3S(O)OC_2H_5$	819-75-0	81	85–87 (80)[a]	1.4357[a]	
(b) $CH_3S(O)OCH_2C_6H_5$	35896-44-7	88	105–106 (1.5)[b]	1.5412[b]	1.164
(c) $C_6H_5S(O)OC_2H_5$	1859-03-6	83	87–88 (0.5)[c]	1.5351[c]	1.148
(d) $C_6H_5S(O)OCH_2C_6H_5$	29624-04-2	95	150 (0.025)[d]	1.5888[d]	1.148
(e) $C_6H_5CH_2S(O)OC_2H_5$	42300-72-1	54	83–84 (0.25)[e]	1.5370[e]	
(f) $C_6H_5CH_2S(O)OCH_2C_6H_5$	3358-25-6	48	[49–50][f]		

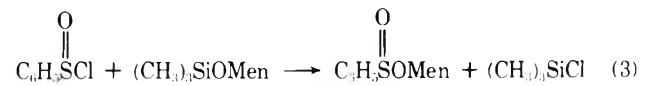
[a] Lit.[5a] 57–58 °C (25 Torr); n_D^{25} 1.4333. [b] Lit.[5b] 105 °C (0.03 Torr); n_D^{20} 1.5380. [c] Lit.[5c] 64–65 (0.06 Torr); n_D^{20} 1.5370. [d] Lit.[5b] 135–137 °C (0.05 Torr); n_D^{18} 1.5887. [e] Lit.[5d] 69–71 °C (0.025 Torr); n_D^{22} 1.5362. [f] Lit.[5e] 51–52 °C.

Table II. Preparation of Unsymmetrical Disulfides

disulfide (5)	registry no.	silyl thioether used	registry no.	yield, %	bp (torr) [mp], °C	n_D^{23}
(a) $C_6H_5CH_2SSC_6H_4$-CH_3-p	16601-19-7	$C_6H_5CH_2SSi(CH_3)_3$	14629-67-5	85	[33–34][a]	
(b) $C_6H_5SSC_3H_7$	20126-55-0	$C_3H_7SSi(CH_3)_3$	18143-79-8	67	71–73 (0.1)[b]	1.5838
(c) $C_6H_5SSC_3H_7$		$C_6H_5SSi(CH_3)_3$	4551-15-9	87	71–73 (0.1)[b]	1.5840
(d) $C_6H_5CH_2SSC_2H_5$	21230-16-0	$C_6H_5CH_2SSi(CH_3)_3$		86	69–71 (0.2)[c]	1.5841
(e) p-$CH_3C_6H_4SSC_6H_5$	29627-34-7	$C_6H_5SSi(CH_3)_3$		*d*		
(f) 	57500-00-2		1578-37-6	80	60–61 (0.8)	1.5661

[a] Lit.[12a] 34–35 °C. [b] Lit.[11f] 87–93 °C (0.1 Torr). [c] Lit.[12b] 75 °C (0.1 Torr). [d] 1:2:1 mixture by GLC.[13]

rotary evaporation. One useful application of this reaction involves the synthesis of menthylsulfinates, precursors of chiral sulfoxides.[8] By combining benzenesulfinyl chloride (**2**) and neat menthoxytrimethylsilane (**3**) the crude diastereomeric (**4**) mixture was obtained in 91% yield (eq 3). Crystal-



(3)

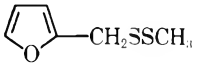
lization of the product from methanol gave the desired diastereomer in over 95% optical purity.[9] This approach should be useful in those cases where simple methoxide displacement on the sulfinyl chloride is ineffective.

We reasoned that other sulfur halides, such as sulfenyl chlorides, should be reactive toward alkylthiotrimethylsilanes.[10]

$$R'SCl + RSSi(CH_3)_3 \rightarrow R'SSR + (CH_3)_3SiCl \quad (4)$$

This was realized in that a variety of unsymmetrical disulfides **5**[10] were prepared in isolated yields averaging over 80% (Table II). In aralkyl and dialkyl cases only trace amounts of the symmetrical moieties are produced.[13] In a typical procedure a CCl_4 solution of the sulfenyl chloride (prepared in situ) is added dropwise to the alkylthiotrimethylsilane at 0 °C. The rapid discharge of the color of the sulfenyl chloride is used to monitor the reaction. After isolation of the product disulfide, no trace of the symmetrical disulfide was noted by TLC.

Of special interest was the synthesis of the mixed disulfide **5f**, reported to be a prime odor constituent of freshly baked



5f

bread.[14] We prepared this compound by the silicon exchange reaction using furfurylthiotrimethylsilane and methanesulfenyl chloride. It was also prepared by the sulfenimide route[11f,g] from either *N*-(methylthio)phthalimide or *N*-(methylthio)succinimide and furfuryl mercaptan. In each of the three syntheses a colorless liquid was obtained in ~75% yield. Gas chromatographic analysis, TLC, and MS revealed a single substance in each case under conditions which would have revealed the symmetrical species. In no case, under a variety of evaluation conditions, did the odor of the unsymmetrical species even remotely resemble the smell of baked bread. The spectral properties of our product appear to agree well with the published data; however, the disagreement as to the odor pinpoints the difficulty in evaluation of problems of this kind, particularly when the target compounds can undergo disproportionation readily.

Of considerable interest would be an effective synthetic route to sulfenate esters **6**.

RSOR

6

While the reaction of arylsulfenyl chlorides with alkoxide gives the desired ArSOR,[15] no general, reproducible technique is available for the preparation of the dialiphatic derivatives. When various alkoxytrimethylsilanes were reacted with arylsulfenyl chlorides, only starting materials were isolated.[16] In contrast, the reverse reaction involving treatment of methyl benzenesulfenate or o-nitrobenzenesulfenate with trimethylchlorosilane gave the corresponding sulfenyl chlorides.[17]

$$ArSOCH_3 + ClSi(CH_3)_3 \rightarrow ArSCl + CH_3OSi(CH_3)_3$$

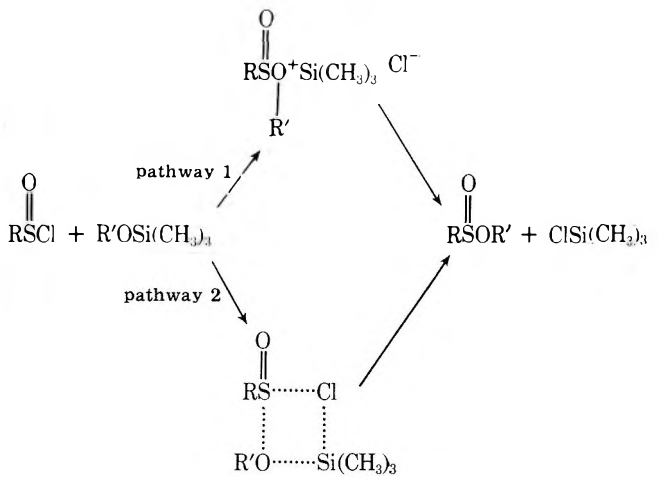
This result suggested that sulfenates could be conveniently converted to thiocyanates by reaction with trimethylsilyl cyanide.[18]

$$C_6H_5SOCH_3 + NCSi(CH_3)_3 \rightarrow C_6H_5SCN + CH_3OSi(CH_3)_3$$

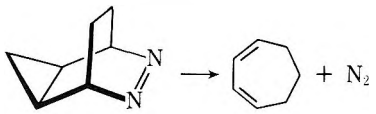
The reaction was essentially quantitative to form phenyl thiocyanate uncontaminated with the isothiocyanate.[19]

We felt that the mechanism of the exchange reaction was of considerable interest in that there appears to be a substantial number of synthetically useful silicon–halide interchange reactions of this general type (eq 1).[2b,h,4] Two distinct mechanistic pathways can be envisioned for the reaction of sulfinyl chlorides with trimethylsilyl ethers (Scheme I). In pathway 1, a charged intermediate is portrayed by attack of the ether oxygen on the electrophilic sulfinyl sulfur.[21] In the

Scheme I



second possibility, a four-center transition state is suggested which is associated with a minimum of charge generation.[24] A study of the effect of solvent polarity on reaction rate was helpful in differentiating these possibilities. If pathway 1 were operative, a rate increase of some several hundred would be expected in going from hydrocarbon solvents to methylene chloride,[26] while for the second, only a small change should be noted. A useful comparison in this regard obtains in the cheleotropic decomposition of the cheleotropic decomposition of **7**. This reaction has been



7

studied over a wide variety of solvent polarities from isooctane to 96% ethanol; a rate change of only 15-fold was noted.[27]

The rate of the silicon–halide interchange reaction was studied in five solvents (Table III) and a rate increase of only ninefold was found. This would be approximately the expected change if the transition state were nonionic.[28] In addition, such a transition state should be sensitive to steric factors. Consistent with this is the observation that when ethoxytrimethylsilane is used, an overall rate decrease of a factor of about 10 is observed, the same relative rates for each solvent being maintained.

We have found a number of formally analogous reactions between phosphorus and sulfur halides with trimethylsilyl derivatives of oxygen, nitrogen, and sulfur functions.[4e,29] These are under active investigation in our laboratory.

Experimental Section[30]

Preparation of the Silylated Alcohols. The required silylated alcohols were synthesized by essentially the same procedure. The alcohol (1.0 mol), hexamethyldisilazane (0.62 mol), and imidazole (0.5 g) were refluxed for 8 h. Distillation at reduced pressure (aspirator) removed the residual hexamethyldisilazane. Distillation of the residue under vacuum gave the product as a colorless oil. $(CH_3)_3SiOCH_3$: 53%; bp 57–58 °C (760 mm) [lit.[31] bp 67 °C (760 mm)]. $(CH_3)_3SiOC_2H_5$: 64%; bp 66–74 °C (760 mm) [lit.[32] bp 75 °C (760 mm)]. $(CH_3)_3SiOCH_2C_6H_5$: 88%; bp 82 °C (8.5 mm) [lit.[33] bp 92 °C (19 mm)]. $(CH_3)_3SiOC_{10}H_{19}$ (menthyl): 79%; bp 59–60 °C (0.35 mm).

Preparation of the Silylated Thiols. The procedure employed was as above.[34] $(CH_3)_3SiSCH_2C_5H_5$: 65%; bp 74–76 °C (0.6 mm); NMR (CCl_4) δ 0.3 [9 H, s, $Si(CH_3)_3$], 3.7 (2 H, s, CH_2), 7.2 (5 H, m, C_6H_5). $(CH_3)_3SiSC_6H_5$: 66%; bp 43–44 °C (1.1 mm) [lit.[34] bp 72–74 °C (3 mm)].

Preparation of Sulfinyl Chlorides. Methane and benzenesulfinyl chloride were prepared by the low temperature chlorination of the disulfide in the presence of acetic anhydride[35] in methylene chloride as solvent.[36] $CH_3(SO)Cl$: 70%; bp 46–48 °C (20 mm) [lit.[35] bp 47–48 °C (15 mm)]. $C_6H_5(SO)Cl$: 98%; n_D^{22} 1.6053 (lit.[35] n_D^{25} 1.6062).

α-Toluenesulfinyl chloride was prepared similarly by the chlorination of benzyl thiolacetate.[37] $C_6H_5CH_2(SO)Cl$: 90%; n_D^{22} 1.5784 (lit.[37] n_D^{25} 1.5872).

Table III.[a] Relative Rates of the Reaction $C_6H_5(SO)Cl + ROSi(CH_3)_3 \rightarrow C_6H_5(SO)OR + (CH_3)_3SiCl$

solvent	ε	10^5k, L mol^{-1} s^{-1} (R = C_2H_5)	k_{rel} (R = C_2H_5)	10^5k, L mol^{-1} s^{-1} (R = CH_3)
C_6D_{12}	2.02	3	1	
CCl_4	2.24	5	2	72
C_6H_6[b]	2.30	7	2	110
$CDCl_3$	4.81	16	5	150
CH_2Cl_2[b]	9.08	27	9	310

[a] The reaction was monitored by ^1H NMR spectroscopy (T = 36 ± 1 °C) using equal concentrations of substrate. [b] Added HCl increased the rate only by ~30%.

Benzyl Thiolacetate. Benzylthiotrimethylsilane (7.8 g, 0.04 mol) and acetyl chloride (4.7 g, 0.06 mol) were stirred together for 4 days. A small amount of solid material which had accumulated was collected and the volatiles were removed in vacuo. The resulting clear, colorless liquid was distilled under reduced pressure to give pure benzyl thiolacetate (6.1 g, 92%); bp 82–85 °C (1.75 mm) [lit.[38] 75–76 °C (0.8 mm)]; n_D^{24} 1.5581 (lit.[38] n_D^{25} 1.5565).

Sulfinate Esters. The procedure for the preparation of these materials was essentially the same for each member. Essential data are collected in Table I. Any deviations from the sample procedure (below) are cited.

Ethyl Methanesulfinate. Methanesulfinyl chloride (9.85 g, 0.10 mol) was introduced into a dry flask fitted with a pressure-equalizing dropping funnel. Ethoxytrimethylsilane (71.8 g, 0.10 mol) was placed in the dropping funnel and the apparatus was flushed with nitrogen. The ethoxytrimethylsilane was added dropwise over a period of 10 min, with constant stirring. The reaction appeared to be virtually complete overnight. Trimethylchlorosilane was removed by rotary evaporation and the resulting oil was distilled under reduced pressure: 8.7 g (81%); bp 85–87 °C (80 mm) [lit.[5a] 57–58 °C (25 mm)]; n_D 1.4357 (lit.[5a] n_D^{25} 1.4333).

Benzyl Benzenesulfinate. The reaction was carried out in the same way as for methyl methanesulfinate using benzenesulfinyl chloride (8.03 g, 0.05 mol) and benzyloxytrimethylsilane (9.0 g, 0.05 mol). Purification was achieved by column chromatography using Merck 7734 silica gel (70 g) and a column of diameter 2.5 cm. The eluant was a 30:70 percent mixture by volume of ethyl acetate and carbon tetrachloride. The appropriate fractions were concentrated by rotary evaporation and then subjected to a high vacuum (0.1 mm) for 1.5 h to remove last traces of solvent: yield 11.0 g (95%).

Benzyl α-Toluenesulfinate. α-Toluenesulfinyl chloride (5.82 g, 0.033 mol) was introduced into a round-bottom flask fitted with a pressure-equalizing dropping funnel. Benzyloxytrimethylsilane (6.00 g, 0.033 mol) was placed in the dropping funnel and the apparatus was flushed with nitrogen. The benzyloxytrimethylsilane was added over a period of about 10 min and the reaction mixture was stirred for 5 days; a white precipitate gradually formed. The reaction mixture was concentrated by rotary evaporation, several portions of carbon tetrachloride were added, and the mixture was evaporated again to ensure that trimethylchlorosilane was completely removed. The crystals were collected and washed with a small amount of diethyl ether. The crude material (4.0 g, 48%) was recrystallized from ethyl acetate: mp 49–50 °C (lit.[5e] mp 51–52 °C).

(−)-Methyl (−)-(*S*)-Benzenesulfinate. Benzenesulfinyl chloride (8.02 g, 0.05 mol) and *l*-menthoxytrimethylsilane (11.4 g, 0.05 mol) were mixed in a 50-mL round-bottom flask and the contents was stirred for 48 h. A very small amount of solid separated out and NMR showed the reaction to be about 95% completed. The reaction mixture was concentrated by rotary evaporation to remove trimethylchlorosilane; a slightly yellowish colored oil was obtained. This oil was taken up in methanol (40 mL) and the methanolic solution was cooled using dry ice. The resulting crystals were collected and washed with cold methanol. On standing the crystalline material changed to an oil–crystal mixture (6.35 g, 91%) which was then crystallized from methanol. This procedure was repeated and the crystals were washed using cold pentane: mp 37–40 °C (lit.[9b] 49–51 °C); $[\alpha]_D$ −195.3° (c 2.0, acetone) [lit.[9] $[\alpha]_D$ −205.5° (c 2.0, acetone)].

Unsymmetrical Disulfides. The procedure for the preparation of these compounds is the same for each one. Yields and properties are presented in Table II.

Benzyl *p*-Tolyl Disulfide. A solution of *p*-tolyl disulfide (6.16 g,

0.025 mol) in 50 mL of CCl_4, protected from moisture by a calcium chloride drying tube, was cooled to 0 °C, and sulfuryl chloride (3.38 g, 0.025 mol) was added followed by 3 drops of triethylamine. The red color of the sulfenyl chloride appeared immediately on mixing the reagents. The conversion was complete after 2 h by NMR analysis. This solution was then added dropwise to a solution of benzylthiotrimethylsilane (9.8 g, 0.05 mol) cooled in an ice–salt bath. The loss of color of the sulfenyl chloride was used as an end point for the reaction. The volatiles were removed by rotary evaporation, leaving a white solid which was crystallized from methanol to give 10.5 g (85%); mp 33–34 °C (lit.[12a] 34–35 °C).

Furfuryl Methyl Disulfide. Furfuryl mercaptan (1.14 g, 0.01 mol) was silylated in CCl_4 (25 mL) solution by treatment with 1-(trimethylsilyl)imidazole[39] (1.40 g, 0.01 mol). Imidazole was removed by filtration and the filtrate was treated dropwise with methanesulfenyl chloride[40] (0.94 g, 0.01 mol) in CCl_4 (25 mL) at 0 °C. After the addition was complete the volatiles were removed by rotary evaporation and the residue was distilled in vacuo to give 1.62 g (80%): bp 60–61 °C (0.8 mm); n_D^{23} 1.5661; $d^{22}{}_{22}$ 1.0796. The spectral properties (NMR, IR, MS) were identical with those in the literature.[14]

The Attempted Preparation of an Unsymmetrical Diaryl Disulfide. The reaction was carried out as above, using di-*p*-tolyl disulfide (3.08 g, 0.0125 mol), sulfuryl chloride (1.687 g, 0.0125 mol), and phenylthiotrimethylsilane (4.55 g, 0.025 mol). VPC analysis of the resulting reaction mixture indicated a 1:2:1 mixture of symmetrical/unsymmetrical/symmetrical disulfides, respectively.

Preparation of Furfuryl Methyl Disulfide from *N*-(Methylthio)succinimide. Furfuryl thiol (1.15 g, 0.01 mol) and *N*-(methylthio)succinimide (1.5 g, 0.01 mol) were refluxed in benzene (25 mL) for 72 h, after which time NMR showed the reaction to be complete. The reaction mixture was allowed to cool to room temperature and succinimide (0.88 g, 89%) was collected by filtration. After the filtrate was concentrated by rotary evaporation, the residue was distilled under reduced pressure to give 1.26 g (79%) of a colorless liquid, the properties of which were identical with those of the compound prepared by the sulfuryl chloride–alkylthiotrimethylsilane route.

Methyl Benzenesulfenate. A solution of diphenyldisulfide (21.8 g, 0.1 mol) in 200 mL of CCl_4, protected from moisture by a calcium chloride drying tube and cooled to 0 °C, was treated with sulfuryl chloride (13.5 g, 0.1 mol) followed by a few drops of triethylamine. The reaction mixture, which immediately turned red, was stirred for 2 h. The solvent was then removed by rotary evaporation, leaving benzenesulfenyl chloride as an oily, dark red liquid, which was used without further purification. The benzenesulfenyl chloride (28.8 g, 0.2 mol) was added dropwise to a solution of sodium methoxide [prepared from sodium (4.56 g, 0.2 mol) and methanol (200 mL)] cooled to −20°C. When the addition was completed, the solution was allowed to warm to room temperature. Methanol was removed by rotary evaporation and the residue was filtered of solid material. The filtrate was distilled under reduced pressure to give 2.8 g (10%): bp 49–51 °C (0.3 mm) [lit.[41] 88–89 °C (0.4 mm)].

Methyl *o*-Nitrobenzenesulfenate. A solution of sodium methoxide [prepared from sodium (0.46 g, 0.02 mol) and methanol (20 mL)] was added dropwise to a stirred solution of *o*-nitrophenylsulfenyl chloride (3.8 g, 0.02 mol) in 40 mL of methanol cooled in an ice bath. Addition was completed over a period of 20 min and stirring was then continued for a further hour. The reaction mixture was cooled to −20 °C and the resulting solid was collected by filtration. The product was recrystallized twice from methanol (1.24 g, 34%): mp 49–50 °C (lit.[42] 54 °C).

Reaction between Methyl *o*-Nitrobenzenesulfenate and Trimethylchlorosilane. Methyl *o*-nitrobenzenesulfenate (0.050 g, 0.27 mol) and trimethylchlorosilane (0.050 g, 0.43 mol) were introduced into an NMR tube containing deuterated chloroform (0.5 mL). NMR indicated that the reaction was >90% complete after 2 weeks and comparison of this spectrum with that of an authentic sample of *o*-nitrophenylsulfenyl chloride showed the two to be identical.

Reaction between Methyl Benzenesulfenate and Trimethylchlorosilane. Methyl benzenesulfenate (0.21 g, 1.9 mol) and trimethylchlorosilane (0.25 g, 2.2 mol) were mixed in an NMR tube. NMR indicated that the reaction was complete after 2 h. Comparison of the NMR spectrum with that of an authentic sample of benzenesulfenyl chloride shows that the features in the range δ 7.0–8.0 are identical.

Reaction between Methyl Benzenesulfenate and Trimethylsilyl Cyanide. Methyl benzenesulfenate (1.1 g, 7.9 mol) was dissolved in carbon tetrachloride (5 mL) and the solution was cooled to −20 °C using an acetone/dry ice bath. Trimethylsilyl cyanide (0.81 g, 7.9 mol) dissolved in carbon tetrachloride (5 mL) was added dropwise from a dropping funnel over a period of 10 min. The reaction mixture was allowed to warm to room temperature and the reaction was monitored by NMR. After 18 h the reaction was complete; carbon tetrachloride was removed by rotary evaporation. Vacuum distillation of the resulting residue gave a clear colorless liquid: bp 50–51 °C (1.0 mm) [lit.[43] 89–90 °C (8 mm)]; n_D^{26} 1.5704 (lit.[43] n_D^{25} 1.5712).

Reaction between *tert*-Butyl Hypochlorite and Benzylthiotrimethylsilane. Benzylthiotrimethylsilane (5.88 g, 0.03 mol) was dissolved in CCl_4 (25 mL) on a 50-mL round-bottom flask. *tert*-Butyl hypochlorite[44] (1.62 g, 0.015 mol) was added dropwise over 10 min; NMR showed the reaction was complete in 12 h. The *tert*-butoxytrimethylsilane was shown (NMR) to be present in the reaction mixture. The mixture was reduced in volume by rotary evaporation and the resulting dibenzyl disulfide recrystallized from ethanol (2.65 g, 62%): mp 68–71 °C; mmp 68–70 °C.

Reaction between *tert*-Butylhypochlorite and Phenylthiotrimethylsilane. The reaction was carried out as above. Diphenyl disulfide was formed (1.52 g, 47%): mp 60–61 °C; mmp 60–61 °C.

Acknowledgment. We thank the National Research Council of Canada and the Danish Natural Science Research Council (C.L.) for financial support of this work.

Registry No.—$HOCH_3$, 67-56-1; HOC_2H_5, 64-17-5; $HOCH_2C_6H_5$, 100-51-6; $HOC_{10}H_{19}$, 2216-51-5; $(CH_3)_3SiOCH_3$, 1825-61-2; $(CH_3)_3SiOC_2H_5$, 1825-62-3; $(CH_3)_3SiOCH_2C_6H_5$, 14642-79-6; $(CH_3)_3SiOC_{10}H_{19}$, 66808-39-7; $CH_3(SO)Cl$, 676-85-7; $C_6H_5(SO)Cl$, 4972-29-6; $C_6H_5CH_2(SO)Cl$, 41719-05-5; C_6H_5SCN, 5285-87-0; hexamethyldisilazane, 999-97-3; acetyl chloride, 75-36-5; benzylthiolacetate, 32362-99-5; (−)-menthyl (*S*)-benzenesulfinate, 34513-32-1; *p*-tolyl disulfide, 103-19-5; furfuryl mercaptan, 98-02-2; *N*-(methylthio)succinimide, 63742-19-8; diphenyl disulfide, 882-33-7; benzenesulfenyl chloride, 931-59-9; methyl benzenesulfenate, 28715-70-0; methyl o-nitrobenzenesulfenate, 15666-75-8; *o*-nitrophenylsulfenyl chloride 7669-54-7; trimethylchlorosilane, 75-77-4; trimethylsilyl cyanide, 7677-24-9; dibenzyl disulfide, 150-60-7.

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Dinitromethane[1]

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Alkali salts of dinitromethane were obtained in high yields in the saponification of methyl cyanodinitroacetate or methyl dinitroacetate, prepared in the nitration of methyl cyanooximinoacetate and methyl malonate, respectively. These salts were used in the synthesis of fluorodinitromethane, fluorodinitroethanol, dinitroethanol, 2,2-dinitropropanediol, and dimethyl 4,4-dinitropimelate.

Potassium dinitromethane was first prepared by Villiers[2] in 1884 by reduction of bromodinitromethane, which was obtained[3] in low yields in the nitration of 2,4,6-tribromoaniline. Free dinitromethane,[4] an unstable pale yellow oil, decomposes readily at ambient temperatures. Dinitromethane was also obtained in low yields in the nitration of halogenated olefins, such as trichloroethylene.[5] More recently potassium dinitromethane was prepared[6] in 23% yield by the Ter Meer reaction[7] of chloronitromethane.

$$CH_3NO_2 + Cl_2 \rightarrow ClCH_2NO_2 \xrightarrow{KNO_2\text{–}KOH} K^+{}^-CH(NO_2)_2$$

Dinitromethane salts are also obtained from the alkali salts of dinitroethanol,[7] which are available in good yields in the oxidative nitration[8] of nitroethanol.

The present investigation resulted from a need for a more practical synthesis of dinitromethane salts. New routes to the compound were investigated based on methyl dinitroacetate and methyl cyanodinitroacetate.

The nitration of malonates was first investigated by Bouveault and Wahl[9] in 1903, who reported the synthesis of ethyl dinitroacetate with little experimental details. Kissinger and Ungnade[10] prepared a number of alkyl dinitroacetates in 10–20% yields in the nitration of alkyl malonates.

We obtained methyl malonate by a modification of a reported procedure;[11] yields were improved by 30% and the isolation procedure was simplified. The nitration of this monoester with nitrogen tetroxide, 100% nitric acid, nitric–sulfuric acid, and red fuming nitric acid was investigated. The best yield of methyl dinitroacetate, 55–60%, was obtained using an excess of 20% red fuming nitric acid in methylene chloride at 3–7 °C.

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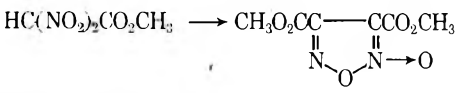
$$HO_2CCH_2CO_2CH_3 + HNO_3 \rightarrow HC(NO_2)_2CO_2CH_3$$

A side reaction product of these nitrations, 3,4-bis(carbomethoxy)furazan 2-oxide,[12] could be readily separated.

On storage at ambient temperature for several days, methyl dinitroacetate gradually decomposed to the furazan derivative.



The alkali salts of methyl dinitroacetate, however, were found to be storable at ambient temperatures. When treated with aqueous alkalies at 70–80 °C, the salts underwent saponification to give the corresponding salts of dinitromethane in 90–95% yields.

$$Na^{+-}C(NO_2)_2CO_2CH_3 + 2NaOH \xrightarrow[\Delta]{H_2O} Na^{+-}CH(NO_2)_2 + Na_2CO_3 + CH_3OH$$

Potassium dinitromethane is sparingly soluble in water, whereas the sodium salt is very soluble. Both salts can be stored without any noticeable decomposition for several weeks at ambient temperatures. These salts are sensitive to impact, and in larger scale work aqueous solutions of the sodium salt were used for safe handling.

Ammonium dinitromethane, previously reported by metathesis reaction,[4] was obtained by heating methyl dinitroacetate with ammonium hydroxide.

$$HC(NO_2)_2CO_2CH_3 + NH_4OH \xrightarrow{\Delta} NH_4^{+-}CH(NO_2)_2$$

Fluorodinitromethane was previously reported[13] by fluorination of aqueous ammonium dinitromethane. Aqueous sodium dinitromethane was fluorinated to give fluorodinitromethane in 75–80% yields.

$$Na^{+-}CH(NO_2)_2 + F_2 \xrightarrow{(H_2O)} FCH(NO_2)_2$$

Fluorodinitromethane was also obtained in ca. 60% yield in the fluorination of aqueous alkali salts of methyl dinitroacetate. Methyl fluorodinitroacetate is thus hydrolyzed under the reaction conditions.

$$K^{+-}C(NO_2)_2CO_2CH_3 + F_2 \xrightarrow{(H_2O)} [FC(NO_2)_2CO_2CH_3] \xrightarrow{H_2O} FC(NO_2)_2H + CO_2 + CH_3OH$$

The analogous fluorination of the ethyl ester,[14] however, yielded a mixture of fluorodinitromethane and ethyl fluorodinitroacetate.

Dialkyl dinitromalonates have not been previously reported,[15] but mononitromalonates are known.[16] We found that dimethyl nitromalonate undergoes slow nitration in nitric–sulfuric acid to give dimethyl dinitromalonate in 20–25% yields.

$$NO_2CH(CO_2CH_3)_2 + HNO_3\text{–}H_2SO_4 \rightarrow (NO_2)_2C(CO_2CH_3)_2$$

The compound was identified by its elemental analysis and NMR spectrum. Dimethyl dinitromalonate reacted with methanolic potassium hydroxide to give methyl potassium dinitroacetate, which on acidification yielded the previously reported methyl dinitroacetate.

$$(NO_2)_2C(CO_2CH_3)_2 + KOH \xrightarrow{CH_3OH} K^{+-}C(NO_2)_2CO_2CH_3 \xrightarrow{H_3O^+} HC(NO_2)_2CO_2CH_3$$

The second route to dinitromethane was based on cyanodinitromethide salts. The nitration of methyl cyanoacetate with the mixed acid was reported[17] to give low yields (20–30%) of the dinitro derivative. Much better yields of methyl cyanodinitroacetate, 80–85%, were reported[17] in the nitration of methyl cyanooximinoacetate, available quantitatively in the nitrosation of cyanoacetate with sodium nitrite–phosphoric acid.

$$NCCH_2CO_2CH_3 + NaNO_2 \xrightarrow{H_3PO_4} NCC(=NOH)CO_2CH_3 \xrightarrow[H_2SO_4]{HNO_3} NCC(NO_2)_2CO_2CH_3$$

Methyl cyanodinitroacetate in methylene chloride solution reacted with water at ambient temperatures to give the known[17] dinitroacetonitrile.

$$NCC(NO_2)_2CO_2CH_3 + H_2O \rightarrow NCC(NO_2)_2H + CO_2 + CH_3OH$$

When an aqueous solution of dinitroacetonitrile salts was heated with 2 mol of an alkali hydroxide, the nitrile underwent saponification to give the alkali salt of dinitromethane, the alkali carbonate, and ammonia.

$$NCC(NO_2)_2^-Na^+ + 2NaOH \xrightarrow[\Delta]{H_2O} Na^+CH(NO_2)_2 + Na_2CO_3 + NH_3$$

The rate of this reaction was conveniently followed by the disappearance of the nitrile UV absorption at 350 nm. The reaction was completed in ca. 2 h at 80–85 °C, and the yield of dinitromethane salts was practically quantitative. At 105 °C the saponification was completed in 15–20 min.

Sodium dinitromethane solution, obtained in this one-pot reaction, was used directly in the synthesis of other geminal dinitro compounds. Formaldehyde (1 mol) was added, and the resulting sodium dinitroethanol[18] was fluorinated according to a reported procedure[19] to give fluorodinitroethanol in 70–80% yields.

$$Na^{+-}CH(NO_2)_2 + CH_2O \rightarrow Na^{+-}C(NO_2)_2CH_2OH \xrightarrow[H_2O]{F_2} FC(NO_2)_2CH_2OH$$

Similarly, sodium dinitromethane solution was used directly in the synthesis of 2,2-dinitropropanediol. Formaldehyde (2 mol) was added, and the alkaline solution was then neutralized with acetic acid to give the diol.[6]

$$K^{+-}CH(NO_2)_2 + CH_2O \underset{\Delta}{\rightleftarrows} K^{+-}(NO_2)_2CH_2OH \underset{OH^-}{\overset{CH_2O}{\rightleftarrows}} HOCH_2C(NO_2)_2CH_2OH$$

Dinitromethane salts react with 2 mol of α,β-unsaturated carbonyl compounds to give the corresponding Michael condensation products.[7] When the crude sodium dinitromethane solution above was treated with 2 mol of methyl acrylate, dimethyl 4,4-dinitropimelate[20] was obtained in 65% yield.

$$Na^{+-}CH(NO_2)_2 + 2CH_2{=}CHCO_2CH_3 \rightarrow (NO_2)_2C(CH_2CH_2CO_2CH_3)_2$$

Fluorination of sodium dinitroacetonitrile was reported[21] to give fluorodinitroacetonitrile, which was hydrolyzed to fluorodinitroacetamide. We found that fluorodinitroacetonitrile can be hydrolyzed to fluorodinitromethane in 75–80% yields. A 1,1,2-trichloro-1,2,2-trifluoroethane solution of the nitrile was stirred with concentrated hydrochloric acid at ambient temperature for 10–12 h to give fluorodini-

troacetamide. The resulting hydrochloric acid solution of the amide was heated at 80–85 °C for 2 h to give fluorodinitromethane.

$$Na^+{}^-C(NO_2)_2CN + F_2 \xrightarrow{H_2O} FC(NO_2)_2CN$$

$$\xrightarrow{HCl} FC(NO_2)_2CONH_2 \xrightarrow[\Delta]{HCl} FC(NO_2)_2H$$

Fluorodinitromethane and fluorodinitroethyl methyl carbonate, rather than fluorodinitroacetonitrile, were the fluorination products of aqueous sodium dinitroacetonitrile containing small amounts of methanol.

Experimental Section

Caution. Because of the explosive nature of many compounds described in this paper, safety shielding is strongly recommended in all the experimental work. Salts of dinitromethane should be handled with utmost care: remotely and in small quantities.

Methyl Malonate. To a stirred solution of 132 g (1.0 mol) of dimethyl malonate in 250 mL of methanol at room temperature was added dropwise (15 min) with occasional cooling a solution of 66 g (1.0 mol) of 85% potassium hydroxide in 150 mL of methanol. After 15 min, the mixture was acidified with 1 mol of concentrated hydrochloric acid and filtered. The filter cake (KCl) was washed with two 25-mL portions of methanol. The combined filtrate and washing were concentrated on a rotating evaporator, and the residual liquid was dissolved in 150 mL of methylene chloride. The solution was filtered from a small amount of salts. The filtrate was distilled to give 95 g (80% yield) of methyl malonate: bp 90 °C (0.5 mm); NMR ($CDCl_3$) δ 3.44 (s, 2 H), 3.75 (s, 3 H), and 11.1 (s, COCH).

Methyl malonate was also obtained in 85% yield when diethyl malonate instead of dimethyl malonate was used. Ethyl malonate was obtained in 85% yield from diethyl malonate followed the above procedure but using ethanol as the solvent.

Methyl Dinitroacetate. To a stirred and cooled solution of 80 g of 20% red fuming nitric acid in 60 mL of methylene chloride at −5 °C was added 25 g of methyl malonate. After 3 h at 5–7 °C, the reaction mixture was drowned in 150 mL of ice–water. The methylene chloride solution was washed with three 75-mL portions of ice–water, dried, and concentrated on a rotary evaporator to leave 21 g of crude methyl dinitroacetate (60% yield). An analytical sample was obtained by distillation: bp 37–38 °C (0.02 mm) [reported[17] bp 38 °C (0.02 mm)]; NMR ($CDCl_3$) δ 4.00 (s, 6 H) and 6.75 (s, 1 H).

3,4-Bis(methoxycarbonyl)furazan 2-Oxide. The title compound was isolated from crude methyl malonate nitration mixtures from which methyl dinitroacetate was removed by extraction with aqueous sodium bicarbonate. The crude 3,4-bis(methoxycarbonyl)furazan 2-oxide was distilled to give a pale yellow liquid: bp 93 °C (0.25 mm); NMR ($CDCl_3$) δ 3.96 (s) and 4.02 (s). Anal. Calcd for $C_6H_5N_2O_6$: C, 35.65; H, 2.99; N, 13.86. Found: C, 35.40; H, 2.81; N, 13.61.

Potassium Dinitromethane. A. From Methyl Potassium Dinitroacetate. To a stirred solution of 1.5 g of potassium hydroxide in 15 mL of water was added 4.05 g (0.02 mol) of methyl potassium dinitroacetate, and the mixture was heated at 65–70 °C for a few minutes. The deep orange-red solution turned turbid and began to deposit some yellow solid. The mixture was cooled to 0–5 °C. The yellow crystalline solid was collected and washed with two 5-mL portions of ice–water. Air-dried solid amounted to 2.6 g (90% yield), mp 220 °C (expl) (reported[4] mp 216 °C dec).

B. From Potassium Dinitroacetonitrile. A stirred suspension of 3.4 g (0.02 mol) of potassium cyanodinitromethide in 15 mL of 10% aqueous potassium hydroxide was heated at 90–95 °C for 2 h. Ammonia odor, strong at the beginning, gradually faded away. The yellow solution was cooled to 0–5 °C. The yellow crystalline solid was collected and washed with two 5-mL portions of ice–water: 2.5 g (85% yield); mp 220 °C (expl).

Ammonium Dinitromethane. To a stirred suspension of 4.1 g (0.025 mol) of methyl dinitroacetate in 10 mL of water was added 10 mL of 14% ammonium hydroxide, and the mixture was heated in an open Erlenmeyer flask at 85–90 °C for 1.5 h. The solution was cooled in a refrigerator overnight, and a yellow crystalline solid was collected. The filter cake was washed with 2 mL of ice–water. The air-dried yellow solid weighed 2.4 g (77% yield): mp 110 °C dec (reported[4] mp 105 °C); IR (Nujol mull) no C=O.

Potassium Dinitroethanol. A suspension of 1.0 g of potassium dinitromethane obtained from methyl potassium dinitroacetate in 5 mL of 10% aqueous formaldehyde was heated at 90–95 °C for a few minutes, and the solution was cooled to 0–5 °C. A yellow solid was collected and washed with ice–water. The air-dried material weighed 0.9 g, mp 152 °C dec alone or when mixed with an authentic sample of potassium dinitroethanol.[6]

In another experiment, a suspension of potassium dinitroethanol obtained from potassium dinitromethane was fluorinated at 0–5 °C with elementary fluorine. The aqueous fluorination mixture was extracted with methylene chloride. Fluorodinitroethanol, bp 33–34 °C (0.1 mm), was isolated from the extract and identified by its published[19] physical properties.

Fluorodinitromethane. A. From Potassium Dinitromethane. A stirred suspension of 3.1 g (0.02 mol) of potassium dinitromethane in 25 mL of water was fluorinated with elemental fluorine following a previously described technique.[19] When all of the yellow potassium salt was consumed, the fluorination mixture was extracted with five 10-mL portions of methylene chloride. The combined extracts were dried and distilled to give 2.0 g of fluorodinitromethane, bp 36–37 °C (20 mm) [reported[13] bp 35–38 °C (20 mm)].

B. From Methyl Dinitroacetate. A suspension of potassium salt of methyl dinitroacetate (150 g, 0.75 mol) in 1400 mL of water was fluorinated at 0–5 °C with 0.65 mol of fluorine over a 7-h period. The aqueous reaction mixture was extracted with ten 150-mL portions of methylene chloride. The combined extracts were dried with anhydrous sodium sulfate and concentrated using an 18 in Vigreux column. The amount of product present in the distillation residue was determined by fluorine NMR spectroscopy using benzotrifluoride as the standard. There was obtained 60 g of fluorodinitromethane, 65% yield based on methyl potassium dinitroacetate.

C. From Fluorodinitroacetonitrile. A mixture of 13.4 g (0.09 mol) of fluorodinitroacetonitrile in 50 mL of 1,1,2-trichloro-1,2,2-trifluoroethane and 15 mL of concentrated hydrochloric acid was stirred for 10 h at room temperature. The fluorine NMR signal at φ 91.4 for fluorodinitroacetonitrile disappeared, and a strong signal for fluorodinitroacetamide at φ 101 appeared in the hydrochloric acid phase. The phases were separated, and the hydrochloric acid solution was heated at 80–85 °C for 1.5 h. During this time, carbon dioxide was evolved and some water-insoluble liquid was formed. The reaction mixture was allowed to cool and was extracted with five 15-mL portions of methylene chloride. The combined dried extracts were distilled to give 9.9 g (90% yield) of fluorodinitromethane.

Dimethyl Dinitromalonate. To a stirred solution of 4 g of 100% nitric acid in 15 mL of concentrated sulfuric acid at room temperature was added 2.7 g of dimethyl nitromalonate.[22] After 30 min the reaction mixture was drowned on ice and an insoluble oil was extracted with 20 mL of methylene chloride. The dried extract was distilled in a microdistillation apparatus to give 0.7 g of a colorless liquid: bp 85–87 °C (0.1 mm); NMR ($CDCl_3$) δ 4.04 (s). Anal. Calcd for $C_5H_6N_2O_8$: C, 27.04; H, 2.72; N, 12.61. Found: C, 27.35; H, 2.75; N, 11.82.

A 2.22-g (0.01 mol) sample of dimethyl dinitromalonate was treated at ambient temperature with an excess of methanolic potassium hydroxide. A yellow potassium salt of methyl dinitroacetate was collected and washed with methanol: 1.8 g (90% yield); mp 216 °C dec (reported[17] mp 213–214 °C).

A suspension of the methyl potassium dinitroacetate above in 5 mL of ice–water was acidified with 2 mL of 20% hydrochloric acid. The water-insoluble liquid which separated on acidification was extracted with 10 mL of methylene chloride. The extract was dried and distilled to give 1.1 g (76% yield) of methyl dinitroacetate.

Fluorodinitroethyl Methyl Carbonate. Methyl cyanodinitroacetate (120 g, 0.635 mol) was stirred with 250 mL of water at 25–30 °C with occasional ice–water cooling until a clear solution resulted (45 min). The acidic solution was neutralized (pH 7–8) with 10% aqueous sodium hydroxide, 400 mL of 1,1,2-trichloro-1,2,2-trifluoroethane was added, and the mixture was fluorinated (5.5 h) with 0.6 mol of elemental fluorine at 5–8 °C. The phases were separated, and the aqueous phase was extracted with three 50-mL portions of methylene chloride. The 1,1,2-trichloro-1,2,2-trifluoroethane solution was combined with the methylene chloride extracts. The combined solutions were dried and concentrated to remove the solvents. The residue, 40 g of a pale yellow liquid, analyzed by fluorine and proton NMR spectroscopy, contained ca. 15% of fluorodinitroacetonitrile, 30% of fluorodinitromethane, and 55% of fluorodinitroethyl methyl carbonate. This mixture was fractionated, and after removal of the two volatile components, 20 g of the carbonate, bp 60 °C (0.5 mm), was obtained: NMR ($CDCl_3$) δ 3.84 (s, CH_3) and 5.18 (d, J_{HF} = 16 Hz, CH_2).[23] Anal. Calcd for $C_4H_5N_2FO_7$: C, 22.65; H, 2.38; N, 13.21. Found: C, 22.41; H, 2.20; N, 12.98.

Registry No.—Dimethyl malonate, 108-59-8; methyl malonate, 16695-14-0; ethyl malonate, 1071-46-1; diethyl malonate, 105-53-3; methyl dinitroacetete, 25160-76-3; 3,4-bis(methoxycarbonyl)furazan 2-oxide, 18322-90-2; potassium dinitromethane, 32617-22-4;

methyl potassium dinitroacetate, 33717-84-9; potassium dinitroacetonitrile, 6928-22-9; ammonium dinitromethane, 12373-04-5; potassium dinitroethanol, 6928-29-6; fluorodinitroethanol, 17003-75-7; fluorodinitromethane, 7182-87-8; fluorodinitroacetonitrile, 15562-09-1; fluorodinitroacetamide, 15562-10-4; dimethyl dinitromalonate, 66901-53-9; dimethyl nitromalonate, 5437-67-2; fluorodinitroethyl methyl carbonate, 66901-54-0; methyl cyanodinitroacetate, 66901-55-1; diethyl nitromalonate, 603-67-8; dinitromethane, 625-76-3.

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(20) L. Herzog, M. H. Gold, and R. D. Geckler, *J. Am. Chem. Soc.*, **73**, 749 (1951).
(21) R. A. Wiesboeck and J. J. Ruff, *J. Org. Chem.*, **33**, 1257 (1968).
(22) Dimethyl nitromalonate, bp 80 °C (0.3 mm), was prepared in 95% yield following the procedure of D. I. Weisblat and D. A. Lyttle, ref 16, used for the synthesis of the diethyl derivative: NMR ($CDCl_3$) δ 3.83 (s, 6 H) and 6.63 (s, 1 H). Anal. Calcd for $C_5H_7NO_2$: C, 33.90; H, 3.98. Found: C, 33.61; H, 3.92.
(23) See V. Grakauskas, *J. Org. Chem.*, **35**, 3030 (1970), for the synthesis and NMR spectrum of fluorodinitroethyl methyl carbonate.

Competitive Processes in the Hydration of Dicarbonyl η^5-(Cyclopentadienyl)alleneiron Cations

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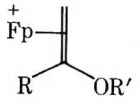
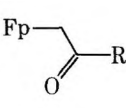
Hydration of the allene complex [**3**, Fp = $CpFe(CO)_2$], under acidic conditions, gives a mixture of ketone and aldehyde complexes (**4** and **5**). The aldehyde complex is shown to be derived by acid catalyzed rearrangement of the allyl alcohol complex (**6**) in a process involving the metal-stabilized cation (**7**). Rearrangement occurs at an appreciable rate even at pH 3.3, reflecting the unusually high stability of **7**. Hydration of *syn*-3-methylallene and *syn*-3-phenylallene complexes (**13a,b**) proceeds in a manner closely paralleling the parent complex, but the isomeric *anti*-3-methylallene and *anti*-3-phenylallene complexes (**14a,b**) behave differently. These undergo hydration principally through the less stable tautomeric 1-methylallene and 1-phenylallene complexes (**15a,b**) due to steric effects associated with the anti substituent.

Recently, our interest in the use of complexes such as **1** as organometallic synthons prompted us to examine the preparation of the precursor ketones (**2**) by routes other than those previously employed[1] [Fp ≡ η^5-$C_5H_5Fe(CO)_2$].



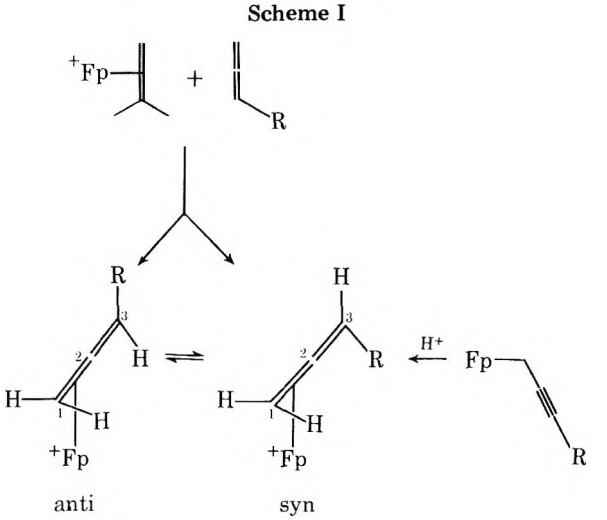
1



2

Since it is well known that coordinated olefins in Fp(olefin) cations readily add a number of carbon and heteronuclear nucleophiles,[2] we considered the prospect that Fp(allene) cations might serve as useful precursors of **2**. The allene complexes are readily available either through an exchange reaction involving the Fp(isobutylene) cation and an allene[3] or by protonation of a (σ-propargyl)Fp complex.[4] The latter are conveniently obtained by metalation with Fp anion of either 1-halo- or 1-tosyloxy-2-alkynes.[5] While the exchange reaction with monosubstituted allenes may be expected to afford mixtures of syn- and anti-3-substituted allene complexes,[3] protonation of (σ-progargyl)Fp complexes has been observed to proceed stereospecifically to give the syn stereoisomers exclusively.[6,7] Furthermore, syn and anti stereoisomers have been shown to be thermally interconvertible through a succession of 1,2 shifts by the Fp group[3] (Scheme I).

Scheme I



Results

Hydration of the Fp(allene) Cation. In general, the addition of nucleophiles, including hydroxide ion, to Fp(allene)

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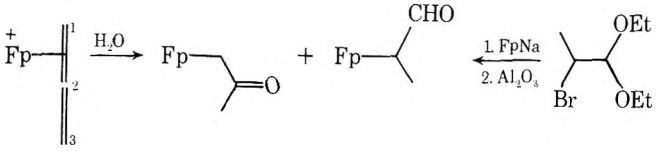
cations has been shown to occur preferentially at C(1).[7] However, hydration in acid media might be expected to yield the desired ketone, since under these conditions addition to C(1) would be expected to be reversible, while reaction at C(2) would not.

In the event, hydrolysis of the parent cation (**3**) in aqueous acetone at room temperature for 10 min gave a 1:2 mixture of the desired ketone (**4**) and a second component in 61% yield. This substance could not be separated chromatographically from the ketone, but an ^1H NMR spectrum of the mixture showed the presence of an aldehyde proton as a doublet signal at δ 9.2, as well as a methyl doublet at δ 1.20, a one proton double quartet at δ 2.3, and a singlet resonance at δ 4.67 for cyclopentadienyl protons. On the basis of these data, the complex was assigned the structure **5**, and this was readily



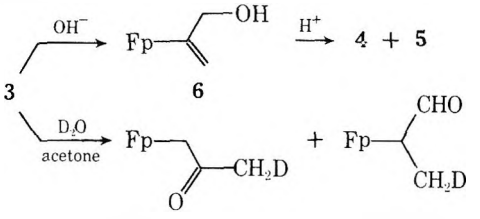
3 **4** **5**

confirmed by its synthesis from α-bromopropionaldehyde diethyl acetal by metalation and hydrolysis.

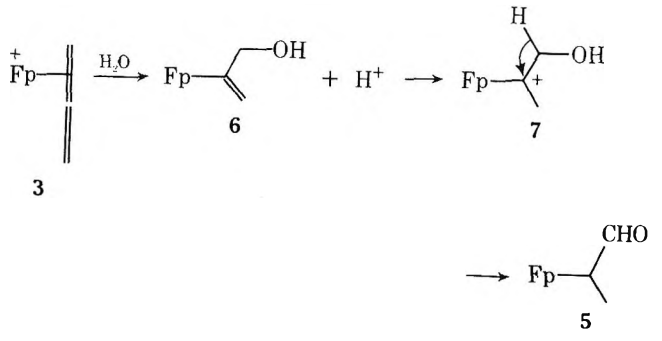
The formation of **4** in this reaction requires no special comment, but the aldehyde (**5**) represents a form of rearrangement product not hitherto observed in the reactions of Fp(allene) cations with nucleophiles.[7]

The allyl alcohol **6**, a likely intermediate in the rearrangement reaction, may be prepared by treatment of **3** with benzyltrimethylammonium acetate, followed by lithium aluminum hydride reduction of the acetate, or more directly by treatment of **3** with excess 0.1 N sodium hydroxide.

Brief exposure of the allyl alcohol (**6**) to 1 equiv of fluoroboric acid in aqueous acetone at room temperature converted it to a 1:2 mixture of **4** and **5** in 70% yield. Significantly, when hydration of **3** was carried out in D_2O–acetone, the propionaldehyde complex obtained was found to be monodeuterated exclusively at C(3).

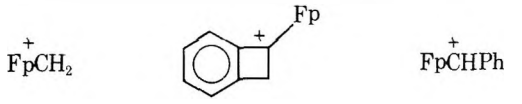


These results are in accord with a mechanism involving intermediacy of the cationic carbene complex (**7**), generated by protonation of the allyl alcohol (**6**). Subsequent hydride



shift within this cation yields the aldehyde (**5**). This latter step requires no special comment, since it is well precedented.[8] However, the formation of the carbene complex (**7**) under comparatively mild acid conditions is remarkable.

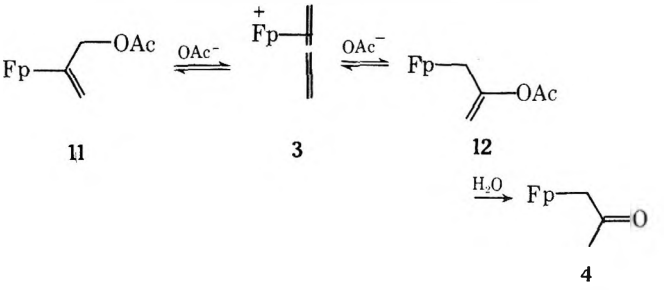
Evidence for the transient existence of the parent cationic carbene complex (**8**) was provided some years ago by Jolly and Pettit,[9] and by Green, Ishaq, and Whiteley.[10] More recently the phenyl-stabilized derivatives **9**[11] and **10**[12] have been isolated. The present results show that these ions may be generated even in relatively weak acid media. Thus, rearrange-



8 **9** **10**

ment of the allyl alcohol (**6**) takes place rapidly in an aqueous–acetone solution 0.2 M in HBF_4, and formation of **4** and **5** from **3** occurs with equal ease in 0.06 M aqueous–acetone solutions of the salt, which therefore cannot be more than 0.06 M in HBF_4. Hydrolytic rearrangement of **3** takes place slowly even when the salt is suspended in an aqueous phosphate solution buffered to pH 3.3.

With these considerations in mind, we undertook an examination of the hydrolysis of **3** in aqueous acetic acid–sodium acetate solutions, under conditions which would preclude the



11 **3** **12** **4**

rapid formation of **7**, but would allow reversible formation of the acetate (**11**) and hydrolysis of the more reactive enol acetate intermediate (**12**). These reactions are summarized below.

We found that aqueous acetic acid–sodium acetate solutions (pH 3.3) were effective in converting the allene complex (**3**) to ketone (**4**). The crude product, obtained in 53% yield, contained <10% of the undesired aldehyde. Similarly, treatment of the allyl acetate (**11**) under these conditions converted it in 73% yield to the ketone (**4**), containing 10% of the isomeric aldehyde.

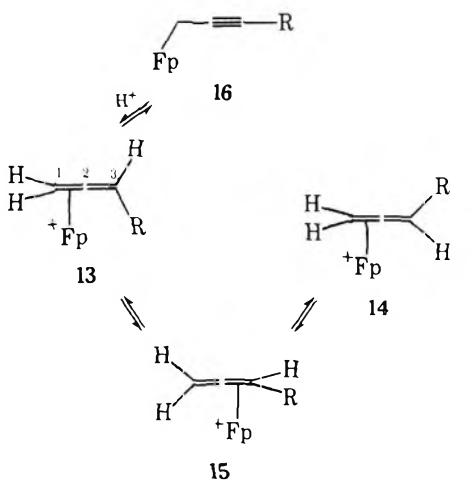
Preparation of Syn- and Anti-Substituted Allene Complexes. The results obtained with the parent allene complex (**3**) prompted us to examine the reactions of the related 3-methyl- and 3-phenylallene complexes. These substances may exist in geometrically isomeric syn and anti forms (**13** and **14**), which may equilibrate with one another through the intermediacy of the 1-substituted allene complex (**15**). The syn complexes (**13a,b**) were readily prepared by low-temperature protonation of the related σ-propargyl complexes (**16a,b**), a process shown earlier[3,6] to proceed with high stereospecificity (Scheme II).

Although the *anti*-3-methylallene complex (**14a**) is thermodynamically more stable than the syn isomer, it cannot be obtained in pure form by thermal isomerization of the latter complex, since equilibration results in a 2:1 mixture of anti and syn isomers. However, good advantage may be taken of the transperiplanar stereospecificity of the protonation reaction, which converts **16** to **13**. The reverse process should be equally stereospecific. In the event, deprotonation of an equilibrium mixture of **13a** and **14a** by treatment with dicyclohexylethylamine at 0 °C for 30 min smoothly deprotonated **13a**, leaving **14a** unchanged. The latter was then isolated by precipitation from methylene chloride solution with ether.

The preparation of the *anti*-3-phenylallene complex (**14b**) was more direct, since the syn complex (**13b**) is completely isomerized to **14b** on heating in methylene chloride solution at 40 °C for 30 min.

Before considering the hydration reactions of substituted Fp(allene) cations it is of interest to digress briefly to note the

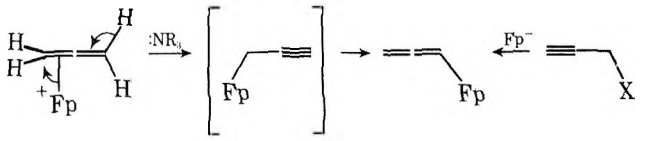
Scheme II



a, R = Me; b, R = Ph

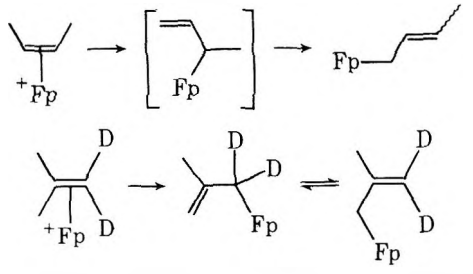
behavior of the parent cation (3) on deprotonation with dicyclohexylethylamine. In contrast to the reaction of **13a**, which is smoothly converted to **16a** on treatment with this amine, similar treatment of **3** yields the σ-allenyl complex (**18**), rather than the anticipated σ-propargyl complex (**17**). We believe that **17** is the initial product of this reaction, but that it undergoes a rapid sigmatropic change to give the more stable allenyl complex (**18**).

The same process may intervene in the metalation of propargyl bromide[5,13] or benzenesulfonate[6] by Fp anion, which yields **18** rather than **17**, although a preference for S_N2' dis-



3 **17** **18**

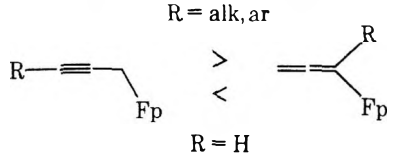
placement in this reaction cannot be excluded. A similar sigmatropic process appears to be involved in the formation of (*cis*- and *trans*-(2-butenyl)Fp on deprotonation of the



Fp(*cis*-2-butene) cation,[14] and in deuterium label scrambling on deprotonation of the Fp(1,1-dideuterioisobutylene) cation at 0 °C.[14]

Merour and Cadiot[15] have also reported that (1,1′-dideuterioallyl)Fp, prepared by metalation of 1,1′-dideuterioallyl tosylate, undergoes facile equilibration at ambient temperature.

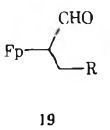
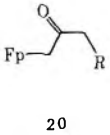
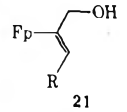
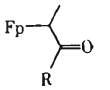
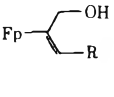
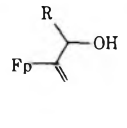
The limited data would suggest that equilibrium between isomeric (η^1-allyl)Fp complexes favors the complex with a primary metal–carbon bond. Analogously, sigmatropic change, which interconverts (η^1-propargyl)Fp and (η^1-allenyl)Fp complexes, suggests the order of stability as:



R = alk, ar

R = H

Table I. Hydration Products of Allene Complexes 13 and 14

allene complex	products and ratio			% yield
				
	19	**20**	**21**	
syn (13)				
a, R = Me[a]	2[e]	1[i]	0	60
b, R = Ph[b]	10[f]	1[j]	0	70
				
	22	**23**	**24**	
anti (14)				
a, R = Me[c]	2[g]	0	1[l]	30
b, R = Ph[d]	2[h]	1[k]	0	10

[a] Registry no.: 59752-01-1. [b] Registry no.: 66807-52-1. [c] Registry no.: 41357-51-1. [d] Registry no.: 66807-54-3. [e] Registry no.: 66769-04-8. [f] Registry no.: 66769-05-9. [g] Registry no.: 66769-15-1. [h] Registry no.: 66769-16-2. [i] Registry no.: 41611-23-8. [j] Registry no.: 41611-24-9. [k] Registry no.: 56810-66-3. [l] Registry no.: 66769-17-3.

The difference in energy between such isomers cannot, however, be great, since when R = CH_2OH[16] or CH_2OMe[3] equilibrium favors the allenyl form, possibly due to attractive interaction between the heteroatom and a carbonyl ligand.

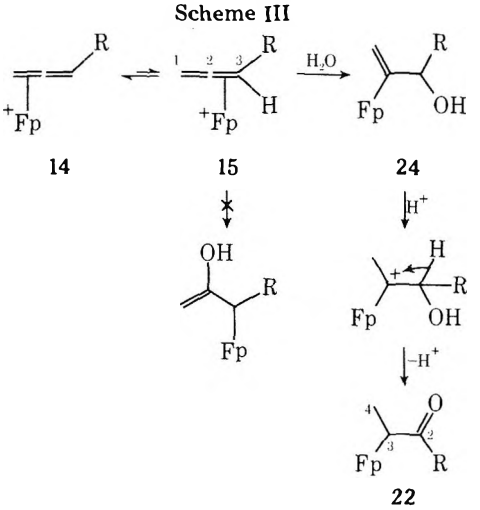
Hydration of Substituted Allene Complexes. With both syn and anti isomers (**13** and **14**) in hand, we proceeded to examine their behavior on hydration. The *syn*-3-methyl- and 3-phenylallene complexes (**13a,b**) behaved like the parent complex, yielding mixtures of ketone and aldehyde complexes (**19** and **20**). These results are summarized in Table I.

The allyl alcohol complexes (**21a,b**) were not isolated in these reactions, but could be prepared independently, as for the parent complex, by quenching the cations (**13a,b**) with hydroxide. As anticipated, treatment of these alcohols with a catalytic amount of HBF_4 in acetone solution converted them to the corresponding aldehydes (**19a,b**).

The corresponding *anti*-3-methyl- and 3-phenylallene complexes (**14a,b**) behaved very differently on hydration. Complex **14a** yielded only the rearranged ketone and allyl alcohol complexes (**22a** and **24a**) in low yield when treated under conditions used in the hydration of **13a** and **13b**. Similarly, **14b** gave only the rearranged ketone complex (**22b**) and a smaller amount of the unrearranged allyl alcohol (**23b**).

The formation of ketones **22a,b** may be depicted as proceeding through hydration of the less stable tautomeric form of the allene complexes (**15a,b**), as shown in Scheme III.

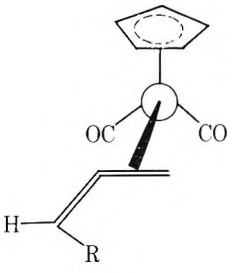
Scheme III



14 **15** **24** **22**

This sequence of steps closely resembles the course of reaction leading to the aldehyde (**5**) from the parent complex (**3**). The formation of the butanone complex (**22a**) does not involve hydration at C-2 of the allene complex (**15a**) rather than at C-3, since when the reaction of **14** is carried out in D_2O, monodeuteration occurs at C-4 in the product in accord with the steps: **14** → **15** → **24** → **22.** The failure of water to add to the internal carbon atom in the reactive intermediate allene complexes (**15a,b**), as it does with **3** and with the isomeric syn complexes (**13a,b**), is noteworthy and may possibly reflect increased charge accumulation at the terminal allene carbon center (C-3) due to substitution at this point. Evidence for the role of allyl alcohols (**24a,b**) as intermediates in the formation of ketone complexes (**22a,b**) is provided by the observation that mixtures of **22a** and **24a** are converted to **22a** on treatment with HBF_4.

The failure of the anti complexes (**14a,b**) to undergo hydration competitive with isomerization to their less stable tautomers (**15a,b**) must be attributed to steric effects associated with the substituent at C-3. Pronounced steric effects are to be expected, since, unlike the uncomplexed ligand, allenes bound to transition metals through π complexation are distorted from linearity.[17] In Fp(tetramethylallene) tetrafluoroborate the allene carbon framework forms an angle of 145.7°, with the uncoordinated carbon atom being bent away from the iron atom, but in the plane defined by this atom and the coordinated carbon atoms.[18] The consequence of this distortion is to greatly increase the steric hindrance of an anti substituent at C-3 for nucleophilic addition to both C-1 and C-2, since such reaction takes place trans to the iron–olefin bond[2a,19] (**25**).



25

Since hydration of the syn complex (**13a**) gives none of the products formed from its anti isomer (**14a**), the activation energy for hydration must be at least 2 kcal/mol less than the energy barrier (23 kcal/mol)[3] separating these isomers, assuming a symmetrical energy barrier between **15a** and both **13a** and **14a.** Furthermore, the activation energy for hydration of **14a** must then be at least 2 kcal/mol higher than the activation energy for conversion of **14a** to **15a.** Thus, steric effects associated with the methyl substituent in **14a** must contribute at least 4 kcal/mol to the activation energy for hydration of this complex compared with its syn isomer **13a.**

Finally, since hydration of **14** proceeds through the less stable isomer (**15**), and hydration of this species competes effectively with its further isomerization to **13,** it follows that the rate-limiting step in the hydration of **14** is its conversion to **15.** It is therefore not surprising that hydration of **14** under conditions similar to those applied to **13** is a much slower process, as is evidenced by the comparative yields of hydration products. This is particularly so for **15b,** where steric effects[18] due to the phenyl group would be expected to appreciably destabilize the complex relative to its isomer **14b** and raise the energy barrier for the exchange of **14b** with **15b.** The formation of a small amount of the unrearranged alcohol (**23b**) in the hydration of this substance no doubt reflects the balance between steric effects which retard rearrangement to **15b** as well as nucleophilic attack at C-1 in complex **14b.**

Experimental Section

Solvents were routinely dried by standard procedures, maintained under nitrogen over molecular sieves, and degassed prior to use.

All reactions, subsequent purification procedures, and spectroscopic examinations were performed under nitrogen. Reactions were conducted in flame-dried apparatus.

Infrared spectra were recorded on Perkin-Elmer Model 137 and 457 spectrophotometers. Nuclear magnetic resonance spectra were recorded on Varian Model A 60-A (NIH GM-13183), Perkin-Elmer R-32 (NSF GU-3852), and Bruker WH-90 (NSF GU-3852, GP-37156) spectrometers.

Melting points were determined in sealed capillaries and are uncorrected.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Hydration of $Fp(CH_2CCH_2)BF_4$ (3). Formation of 4 and 5. The salt (**3;** 0.2 g, 0.7 mmol) was dissolved in 10 mL of acetone at room temperature and to this was added 1 mL of water. An immediate color change from yellow to orange took place. Reaction was allowed to continue for 10 min and the solution was then poured into a mixture of 10 mL each of methylene chloride and water. The organic layer was separated and the aqueous layer was extracted once with 10 mL of methylene chloride. The combined organic extracts were dried, solvent was removed, and the residue was chromatographed on 10 g of activity III neutral alumina. Elution with ether–petroleum ether mixtures of increasing polarity removed the product as a single yellow band (with 70% ether–petroleum ether). The yield of product (**4** and **5**), obtained as a yellow oil, was 0.094 g (61%). **4:** IR (CH_2Cl_2) 1965, 2030, 1640 cm^{-1}; NMR (CS_2) δ 4.76 (s, 5, Cp), 1.92 (s, 3, CH_3CO), 1.60 (s, 2, CH_2CO). **5:** IR (CH_2Cl_2) 1965, 2030, 1640 cm^{-1}; NMR (CS_2) δ 9.2 (d, 1, J = 3 Hz, CHO), 4.67 (s, 5, Cp), 2.3 (dq, 1, J = 3, 6 Hz, FpCH), 1.20 (d, 3, J = 6 Hz, CH_3). Anal. Calcd for $C_{10}H_{10}FeO_3$: C, 51.32; H, 4.30. Found: C, 51.32; H, 4.15.

Preparation of $Fp(CH_3CHCHO)$ (5). A 0.5 M solution of NaFp in THF was prepared from dicarbonyl η^5-cyclopentadienyliron dimer,[20] and this was added (160 mL, 80 mmol) to 2-bromopropionaldehyde diethyl acetal (16.7 g, 80 mmol) at room temperature. After stirring the solution for 3.5 h, solvent was removed in vacuo and the residue was extracted with petroleum ether. The combined extracts were filtered under nitrogen, and the solution was concentrated and then chromatographed on 200 g of activity III neutral alumina. The acetal, which hydrolyzes on the column, was eluted with 60–80% ether–petroleum ether as a yellow band. Removal of the solvent left a yellow solid, which was recrystallized from ether–petroleum ether by blowing a stream of nitrogen through the mixture. The yield of **5,** mp 70–72 dec, was 2 g (11%). Its ^1H NMR spectral properties were identical with the product obtained in the hydration of **3.** Anal. Calcd for $C_{10}H_{10}FeO_3$: C, 51.32; H, 4.30. Found: C, 50.81; H, 4.10.

Deprotonation of $Fp(CH_2CCH_2)BF_4$ (3). Formation of 18. The allene complex (0.15 g, 0.40 mmol) was suspended in 5 mL of methylene chloride and cooled to 0 °C. Dicyclohexylethylamine (0.086 g, 0.4 mmol) was added to the solution. After 30 min reaction was complete. The solution was filtered under nitrogen through a short column of activity III alumina and the solvent was evaporated to give 0.060 (70%) of Fp(allenyl) (**18**).[6]

Synthesis of $Fp(AcOCH_2CCH_2)$ (11). The allene complex (**3**) was added to a methylene chloride solution (5 mL) of benzyltrimethylammonium acetate (0.15 g, 0.70 mmol), prepared from benzyltrimethylammonium tetrafluoroborate by exchange on Dowex 1. After stirring for 30 min, 30 mL of ether was added and the resulting mixture was filtered under nitrogen. Evaporation of solvent left the product (**11**), 0.114 g (83%), as an orange oil, which was used without purification: IR (CH_2Cl_2) 1960, 2030, 1725 cm^{-1}; NMR (CS_2) δ 5.65 (t, 1, J = 1.5 Hz, CH=), 5.0 (t, 1, J = 1.5 Hz, CH=), 4.82 (s, 5, Cp), 4.4 (t, 2, J = 1.5 Hz, CH_2OAc). 1.95 (s, 3, CH_3).

Synthesis of $Fp(HOCH_2CCH_2)$ (6). A. $LiAlH_4$ (0.06 g, 1.5 mmol) was suspended in 50 mL of ether and cooled to 0 °C. The allyl acetate complex (**11;** 0.57 g, 2.0 mmol) was dissolved in 5 mL of ether and added to this by stringe. After 30 min the reaction was quenched successively with 1 mL of H_2O, 1 mL of 15% NaOH, and 3 mL of water. The mixture was filtered under nitrogen and the ether solution was separated and dried. After removal of solvent, the residue was taken up in petroleum ether and chromatographed on 10 g of activity III alumina with 60–80% ether–petroleum ether to give 0.162 g (35%) of allyl alcohol complex (**6**), mp 58–59 °C. The product could be further purified by crystallization as yellow needles from ether–petroleum ether: IR (CH_2Cl_2) 3600, 2020, 1960 cm^{-1}; NMR (CS_2) δ 5.75 (t, 1, J = 1.5 Hz, CH=), 5.0 (br s, 1, CH=), 4.78 (s, 5, Cp), 4.0 (br s, 2, CH_2OH), 1.55 (br s, 1, OH). Anal. Calcd for $C_{10}H_{10}FeO_3$: C, 51.32; H, 4.30. Found: C, 51.20; H, 4.31.

B. The allene complex (**3**; 0.2 g, 0.7 mmol) was dissolved in 20 mL of carefully dried acetone and to this was added 7 mL of a 0.1 N NaOH solution. The reaction mixture turned brown immediately. After 10 min the reaction was worked up and chromatographed on alumina. Elution with ether–petroleum ether gave the alcohol, 0.53 g (35%), identical with the product obtained above.

Rearrangement of Fp($HOCH_2CCH_2$) (6). The allyl alcohol complex (0.02 g, 0.1 mmol) was dissolved in 5 mL of acetone and 1.0 mL of 0.1 M HBF_4 was added. The solution was stirred at room temperature for 10 min and then worked up. Chromatography on 10 g of activity III neutral alumina gave 0.014 g (70%) of product as an amber oil. A ^1H NMR spectrum of the product showed it to be a mixture of **4** and **5** in a ratio of 1:2.

Preparation of Fp(CH_2COCH_3) (4) from 3. The allene complex (**3**; 0.20 g, 0.70 mmol) and potassium acetate (0.070 g, 0.7 mmol) were taken up in a solution of 1.0 mL of acetic acid and 0.1 mL of water. The solution was stirred at room temperature for 0.5 h. At the end of this period, 20 mL of methylene chloride was added, and the organic layer was separated and dried. After removal of solvent, the product was taken up in a small amount of ether and chromatographed on 10 g of activity III neutral alumina. Elution with 60–80% ether–petroleum ether gave 0.073 g (50%) of product shown by its ^1H NMR spectrum to be **4**. A small amount, estimated to be <10%, of the aldehyde (**5**) was also present.

Hydrolysis of Fp(CH_2CCH_2)BF_4 with D_2O. The allene complex (0.2 g, 0.7 mmol) was dissolved in 10 mL of carefully dried acetone and 1.0 mL of D_2O (99.8%) was added. The solution was stirred for 10 min, acetone was then evaporated, and the product was worked up as described in the hydrolysis of **3**. The yield of product was 0.080 g (52%). A NMR spectrum of the product showed the aldehyde component to have resonances at δ 9.2 (CHO), 4.67 (Cp), 2.3 (FpCH), and 1.2 (CH_3) in ratios of 0.9:4.6:1.0:2.2 (average of three integrations). The ketone component similarly showed resonances at δ 4.76 (Cp), 1.92 (CH_3CO), and 1.60 (CH_2CO) in a ratio of 5.0:1.9:1.9.

Conversion of Fp($AcOCH_2CCH_2$) (11) to FpCH_2COCH_3 (4). The acetate (0.050 g, 0.2 mmol) was taken up in 1 mL of acetic acid containing 0.1 mL of water and 0.1 g of potassium acetate. After stirring at room temperature for 0.5 h, methylene chloride and water were added and the organic layer was separated and dried. Solvent was removed in vacuo and the residue was taken up in petroleum ether and chromatographed on activity III alumina. Elution with 60–80% ether–petroleum ether gave the product as a 10:1 mixture of **4** and **5** in 73% yield.

Hydration of Fp(CH_2CCH_2)BF_4^- at pH 3.3. The allene salt (**3**; 0.30 g, 1.0 mmol) was suspended in 1.5 mL of a phosphate buffer solution (pH 3.3) and stirred at room temperature for 15 min. The resulting gummy material was added to 5 mL of methylene chloride, and the organic phase was separated. After extraction of the aqueous phase with methylene chloride, the combined organic solutions were dried, solvent was removed, and the residue was chromatographed on 10 g of activity III alumina. Elution gave 55 mg of product (25%), shown by NMR spectral analysis to be a 3:2 mixture of Fp(CH_2COCH_3) and Fp(CH_2CHCHO).

Preparation of Fp(*anti*-CH_2CCHCH_3)BF_4 (14a). The *syn*-3-methylallene complex (**13a**), prepared by protonation of **12**,[3] was allowed to equilibrate in refluxing methylene chloride solution. A solution of this mixture (0.50 g, 1.6 mmol) in 10 mL of methylene chloride was cooled to 0 °C and was then treated with 0.63 mmol of dicyclohexylethylamine for 30 min. At the end of this time 50 mL of ether was added and the precipitate was collected under nitrogen in a Schlenk tube and washed with 100 mL of 1:1 methylene chloride–ether mixtures. The residue was dissolved in 10 mL of methylene chloride and filtered. Addition of ether to this solution gave 0.14 g of **14a** (41% based on the presence of 0.33 g of this isomer in the initial mixture). An NMR spectrum taken in CD_3NO_2 did not indicate the presence of syn isomer in the product: NMR (CD_3NO_2) δ 6.4 (m, 1, =CH), 5.7 (s, 5, Cp), 3.2 (m, 2, $=CH_2$), 2.1 (m, 3, CH_3).

Preparation of Fp(*syn*-CH_2CCHPh)BF_4 (13b) and of Fp(*anti*-CH_2CCHPh)BF_4 (14b). The *syn*-3-phenylallene complex (**13b**; 0.5 g, 1.3 mmol) was prepared by protonation of **16**,[5] following the procedure employed in the preparation of **13a**: NMR (acetone-d_6, 0 °C) δ 8.2 (s, 1, =CH), 7.3–7.9 (m, 5, Ph), 6.1 (s, 5, Cp), 3.6 (d, 2, J = 4 Hz, $=CH_2$). This product was suspended in 10 mL of methylene chloride and the solvent was brought to reflux for 30 min. Ether (30 mL) was then added to ensure complete precipitation of product, which was collected in a Schlenk tube and washed with methylene chloride–ether (1:1). The product (**14b**) was dried in vacuo: yield 0.43 g (86%); NMR (acetone-d_6) δ 7.3–7.9 (m, 6, Ph, =CH), 6.05 (s, 5, Cp), 3.9 (d, 2, J = 4 Hz, $=CH_2$); NMR (CD_3NO_2) δ 7.3–7.7 (m, 6, Ph, =CH), 5.85 (s, 5, Cp), 3.7 (d, 2, J = 4 Hz, $=CH_2$).

Hydration of Fp(*syn*-CH_2CCHCH_3) (13a). Formation of 19a and 20a. The procedure employed for the hydration of **3** was followed. From 0.21 g of **13a**, 0.09 g (60%) of a 2:1 mixture of **19a** and **20a** was obtained after chromatographic purification on alumina. The mixture, which could not be separated, showed: IR (CH_2Cl_2) 2030, 1965, 1640 cm^{-1}; NMR (CS_2) δ 9.2 (d, 1, J = 3 Hz, CHO), 4.78 (s, 5, Cp), 4.68 (s, 5, Cp), 0.6–2.4 (m, CH, CH_2, CH_3). Anal. Calcd for $C_{11}H_{12}FeO_3$: C, 53.26; H, 4.84. Found: C, 53.58; H, 5.01.

Hydration of Fp(*syn*-CH_2CCHPh) (13b). Formation of 19b and 20b. Hydration of 1.0 g of **13b**, following standard conditions, except that reaction time was 1 h, gave 0.38 g (47%) of a 10:1 mixture of **19b** and **20b** after purification of the crude product on alumina. The mixture showed: IR (CH_2Cl_2) 2030, 1965, 1640 cm^{-1}; NMR (CS_2) of **19b** δ 9.15 (s, 1 CHO), 7.05 (s, 5, Ph), 4.72 (s, 5, Cp), 3.33 (m, 1, FpCH), 2.5 (m, 2, CH_2); NMR of **20b** δ 7.15 (s, 5, Ph), 4.46 (s, 5, Cp), 3.28 (s, 2, $PhCH_2$), 1.76 (s, 2, $FpCH_2$).

Preparation of Fp(*cis*-$HOCH_2CCHCH_3$) (21a). Fp(*syn*-3-methylallene) tetrafluoroborate (**13a**; 0.21 g, 0.7 mmol) was taken up in a small volume of carefully dried acetone and treated with 7 mL of 0.1 N NaOH. After stirring for 10 min, the solution was extracted with methylene chloride and finally chromatographed on 10 g of alumina. Recrystallization from ether–petroleum ether gave 0.05 g (30%) of **21a**; IR (CH_2Cl_2) 3590, 2020, 1955 cm^{-1}; NMR (CS_2) δ 6.22 (q, 1, J = 7 Hz, CH=) 4.8 (s, 5, Cp), 4.0 (br s, 2, CH_2), 1.74 (d, 3, J = 7 Hz, CH_3), 1.18 (br s, 1, OH). Anal. Calcd for $C_{11}H_{12}O_3Fe$: C, 53.26; H, 4.84. Found: C, 53.10; H, 5.02.

Preparation of Fp(*cis*-$HOCH_2CCHPh$) (21b). Treatment of Fp(*syn*-3-phenylallene) tetrafluoroborate (**13b**; 0.25 g, 0.7 mmol) with 8 mL of 0.1 N NaOH as with **13a** above gave 0.05 g (25%) of the alcohol (**21b**): mp 109–110 °C; IR (CH_2Cl_2) 3590, 2030, 1960 cm^{-1}; NMR (acetone-d_6) δ 7.66 (br s, 1, =CH), 7.29 (m, 5, Ph), 4.88 (s, 5, Cp), 4.28 (d, 2, J = 6 Hz, CH_2), 3.8 (t, 1, J = 6 Hz, OH). Anal. Calcd for $C_{16}H_{14}FeO_3$: C, 61.97; H, 4.55. Found: C, 61.21; H, 4.31.

Rearrangement of 21b to 19b. The allylic alcohol (**21b**; 0.06 g, 0.2 mmol) was dissolved in 5 mL of acetone and 0.2 mL of 0.1 M HBF_4 (48%) was added at room temperature. After 90 min of reaction, 30 mL of CH_2Cl_2 was added, the solution was dried, and solvent was removed. An NMR spectrum of the product revealed it to be 3:1 mixture of **21b** and **19b**.

Hydration of Fp(*anti*-CH_2CCHCH_3)BF_4 (14a). Preparation of 22a. The salt (**14a**; 0.064 g, 0.2 mmol) was taken up in 5 mL of acetone and 0.2 mL of water was added. After stirring at room temperature for 10 min, 20 mL of CH_2Cl_2 was added and the solution was dried and filtered. Chromatography of the product on 10 g of activity III neutral alumina with ether–petroleum ether gave **22a** as a yellow solid (0.015 g, 30%); IR (CH_2Cl_2) 2030, 1960, 1635; NMR (CS_2) δ 4.66 (s, 5, Cp), 2.40 (q, 1, J = 7 Hz, FpCH), 1.98 (s, 3, CH_3CO), 1.18 (d, 3, J = 7 Hz, CH_3). Anal. Calcd for $C_{11}H_{12}O_3Fe$: C, 53.26; H, 4.84. Found: C, 53.10; H, 4.86.

Treatment of 14a with D_2O. Formation of 22a and 24a. When the reaction was carried out on a larger scale (0.2 g of **14a**) in D_2O, the product, obtained as a yellow oil (0.050 g, 30%) after chromatography on alumina, exhibited NMR absorption (CS_2) at δ 5.76 (br s, =CH), 4.94 (br s, =CH), 4.8 (s, Cp), 4.15 (m, CHOH), and 1.14 (d, CH_3), in addition to resonances assigned to the major product (**22a**). The ratio of major to minor products (**22a**/**24a**) estimated from the relative intensities of cyclopentadienyl resonances was 2:1.

The product obtained above was taken up in 10 mL of THF and 0.5 mL of CF_3COOD was added at room temperature. Reaction was allowed to continue at room temperature for 30 min. Solvent was then removed in vacuo and the crude product was chromatographed on 10 g of alumina. Elution with ether–petroleum ether gave 0.036 g of product identified as the monodeuterated complex (**22a**).

Hydration of Fp(*anti*-CH_2CCHPh)BF_4 (14b). Formation of 22b and 23b. The hydration of 0.31 g (0.8 mmol) of **14b** following reaction and workup conditions for **3** gave 0.025 g (10%) of a mixture of **22b** [IR (CH_2Cl_2) 2030, 1965, 1640 cm^{-1}; NMR (CS_2) 6.9–7.8 (m, Ph), 4.58 (s, 5, Cp), 3.3 (q, 1, J = 7 Hz, FpCH), 1.4 (d, 3, J = 7 Hz, CH_3)] and **23b** [IR (CH_2Cl_2) 2030, 1965 cm^{-1}; NMR (CS_2) δ 6.9–7.1 (m, Ph), 5.93 (s, 1, =CH), 5.1 (s, 2, CH_2OH), 4.4 (s, 5, Cp), 2.05 (br s, 1, OH)]. A third singlet resonance at δ 4.87 about half the intensity of the resonance assigned to cyclopentadienyl protons may indicate the presence of the isomeric allyl alcohol **24b**.

Preparation of the Allyl Alcohol (24a). Treatment of Fp(*anti*-3-methylallene) tetrafluoroborate (0.2 g, 0.6 mmol) in acetone solution with 7 mL of 0.1 N NaOH solution at room temperature for 10 min gave 0.013 g (10%) of the allyl alcohol (**24a**), after chromatography on alumina; IR (CH_2Cl_2) 3590, 2020, 1950 cm^{-1}; NMR (CS_2) δ 5.47 (q, 1, J = 7 Hz, =CH), 4.8 (s, 5, Cp), 4.15 (br s, 2, CH_2), 4.1 (br s, 1, OH) 1.75 (d, 3, J = 7 Hz, CH_3).

Preparation of the Allyl Alcohol (24b). Treatment of Fp(*anti*-3-phenylallene) tetrafluoroborate (0.76 g, 2 mmol) as above with 21 mL of 0.1 N NaOH in acetone gave 0.10 g (16%) of the allyl alcohol (**24b**): IR (CH_2Cl_2) 3590, 2030, 1960 cm^{-1}; NMR (CS_2) δ 7.1–7.4 (m, 5, Ph), 5.94 (s, 1, =CH), 5.1 (s, 2, CH_2), 4.4 (s, 5, Cp). 1.65 (d, 1, J = 4 Hz, OH).

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Registry No.—**3**, 62685-81-8; **4**, 42065-40-7; **4** deuterium derivative, 66769-18-4; **5**, 66769-19-5; **5** deuterium derivative, 66769-20-8; **6**, 65097-84-9; **11**, 66769-21-9; **18**, 42043-77-6; **21a**, 66791-89-7; **21b**, 66791-90-0; **22a** deuterium derivative, 66769-22-0; **24b**, 66769-23-1; NaFp, 12152-20-4; 2-bromopropionaldehyde diethyl acetal, 3400-55-3; benzyltrimethylammonium acetate, 16969-11-2.

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Specific Ortho Bromination of Substituted Benzenes. 3.[1a] Gas-Phase Dealkylation of the *tert*-Butyl Group from 4-*t*-Bu-2-BrC_6H_3X

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The use of solid acid catalyst for the gas-phase dealkylation of a *tert*-butyl group from 4-*t*-Bu-2-BrC_6H_3X was studied. Reactions were carried out in a flow system in the temperature range of 250–400 °C at atmospheric pressure. The tendency of the bromine atom to cleave under the experimental conditions was followed. The lifetime of the catalyst was limited, but it could be reactivated easily. The advantages and limitations of the process are discussed.

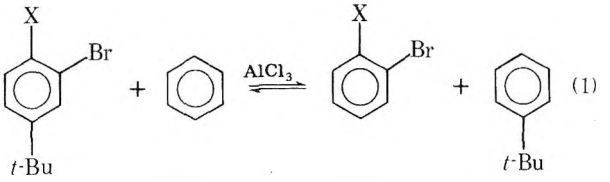
Introduction

Electrophilic aromatic substitution has been and still is being investigated, offering a large body of data including information on isomer distribution in the electrophilic substitution of substituted benzenes.[2] However, only a limited number of procedures for the selective introduction of a functional group into a substituted benzene using bulky positional protecting groups have been described earlier.[1,3–12] One of the bulk groups more frequently used as a positional protecting group is the *tert*-butyl group. In order to recover the final product, i.e., the 1,2-disubstituted aromatic compound, the *tert*-butyl group is usually removed by transfering it to another aromatic nucleus via a Friedel–Crafts type transalkylation reaction.[1,3–5,12] Catalysts for this reaction are generally based on aluminum chloride and related Lewis acid halides. However, this procedure requires an extensive separation technique due to the formation of a complex between the reactants and products with the catalyst as well as the formation of by-products.[12]

We now wish to report the easy and fast dealkylation of the *tert*-butyl group from 4-*t*-Bu-2-BrC_6H_3X over an acidic solid catalyst in a continuous process.

Results and Discussion

In the course of our studies on the specific ortho bromination of substituted benzenes,[1,3,4] we found that the removal of the *tert*-butyl group from 4-*t*-Bu-2-BrC_6H_3X to yield 2-BrC_6H_3X is achieved in the liquid phase by transalkylation reaction (eq 1), using $AlCl_3$ as catalyst, and excess benzene as



(1)

X = CH_3, C_2H_5, Cl, Br

solvent to shift the equilibrium composition to the right-hand side of eq 1.

Although resulting in high yields and high isomer purity, the batch reaction is not convenient for preparation on a large scale. Since it is known that the *tert*-butyl group attached to an aromatic ring has a great tendency to cleave over solid acidic catalysts at elevated temperatures,[13] we investigated

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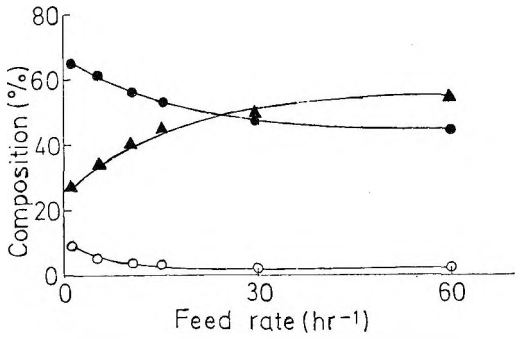
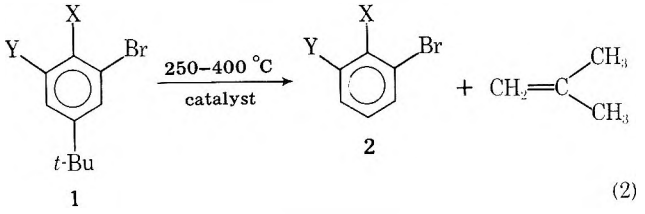


Figure 1. Composition of the reaction mixture after passing **1a** over SiO_2–Al_2O_3 at T = 350 °C at various feed rates (N_2 flow rate = 50 mL/min.): ●, *o*-bromotoluene; ▲, **1a**; O, byproducts.

the cleavage of the *tert*-butyl group from 4-*t*-Bu-2-BrC_6H_3X in the gas phase over solid acid catalyst (eq 2).



(2)

a, X = CH_3; Y = H
b, X = Cl; Y = H
c, X = Br; Y = H
d, X = C_2H_5; Y = H
e, X = CH_3; Y = CH_3

This process has the advantage of a flow system in which the used catalyst can be regenerated and no byproducts, except for isobutylene, are formed in the process. Thus, separation of the product from the unreacted precursor is very simple since the difference in boiling points of ArH and *t*-BuAr is in the range of 80 °C at atmospheric pressure. The recovered precursor can be recycled. Further, in liquid-phase transalkylation reactions, the Lewis acid catalyst must be quenched prior to distillation. The present process does not require any washing of the products, and the product mixture can be directly distilled.

As expected,[14] no dealkylation reactions took place when silica or alumina were used as the catalysts even at 450 °C. We did not use graphite-intercalated metal halides, which are known to rapidly decrease their activity during the process since active Lewis acid is leached out from the graphite.[15] On the other hand, an acid washed silica–alumina (7:1) catalyzed the gas-phase de-*tert*-butylation of **1a** to give **2a** in good conversions and excellent yields. The degree of conversion is dependent upon both the reaction time (Figure 1) and the temperature (Figure 2). Increasing both the temperature and the reaction time increases the degree of conversion.

Olah and Meyer investigated the effect of $AlCl_3$ on the isomerization of halotoluenes.[16] They found that fluorotoluenes and chlorotoluenes isomerize predominantly through intramolecular 1,2 shift. The observation of rearranged products containing as much as 20% chlorobenzene formed by disproportionation points to the methyl group as the migrating entity. In general, the isomerization rate was low at 100 °C, and increased in the order F > Cl. However, isomerization of bromotoluene was completed in ca. 30 min at ambient temperatures, giving the equilibrium isomers mixture. However, based on the data presented,[16] it could not be concluded whether the isomerization of *o*-, *m*-, and *p*-bromotoluenes proceeds through an intermolecular or an intramolecular mechanism.

Although silica–alumina is a much weaker acid than $AlCl_3$, we used elevated temperatures in which cleavage of the C–Br bond may occur even by the catalysis of an acid as weak as silica–alumina. Indeed, C–Br cleavage was observed yielding dibromotoluenes and toluene (eq 3) as well as *m*- and *p*-bromotoluene (eq 4).

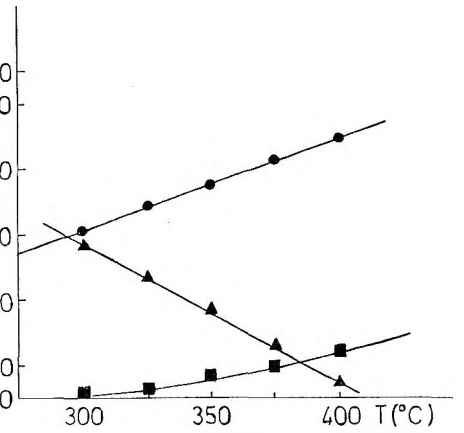
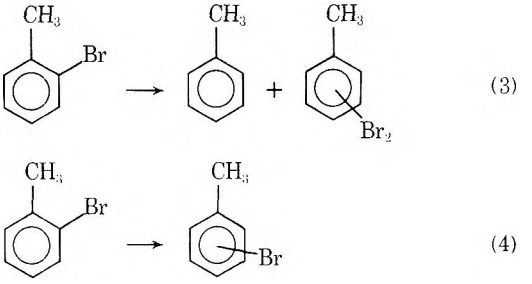


Figure 2. Composition of the reaction mixture after passing 1a over SiO_2–Al_2O_3 at various temperatures (contact time = 1 s): ●, *o*-bromotoluene; ▲, **1a**; ■, byproducts.



(3)

(4)

While the intermolecular isomerization (eq 3) results in easily separated products, the intramolecular isomerization yields isomers which are difficult to separate. It has been observed that the extent of isomerization reactions increases when both the reaction time and temperature are increased. Table I summarizes selected de-*tert*-butylation data of **1a** to give **2a**. The data suggest that while the conversion and isomerization have the same qualitative dependence upon the temperature and the reaction time, the yield is scarcely affected by these parameters.

When transalkylation reactions were carried out in the liquid phase, and catalyzed by water-promoted Lewis acids, it was shown[17] that the reaction rate was dependent upon the basicity of **1**. The more basic **1** is, the higher the reaction rate. Moreover, measurement of $\Delta H^{\ddagger}$ revealed that the more basic **1** is, the lower $\Delta H^{\ddagger}$, i.e., the less temperature dependent is the reaction rate.

Since both the liquid-phase transalkylation and the gas-phase dealkylation are catalyzed by the same species, i.e., the proton, the behavior of **1** over silica–alumina was expected to be similar to that of **1** in a liquid-phase system containing water-promoted Lewis acids. Figure 3 shows good agreement with this expectation. The most basic, **1e**, gives the highest conversion with the least dependence upon temperature while the least basic, **1c**, gives the lowest conversion with the highest temperature dependence.

Alkenes are well known poisons for many solid catalysts as they tend to polymerize on the catalyst surface. In the present experiments, measurements show a gradual decrease of the conversion as the onstream time increased (Figure 4). This decrease in the catalyst activity is attributed to polymerization of the isobutylene formed in the process. The extent of decrease in activity varies, depending upon the temperature and the reaction time. However, the catalyst can be regenerated

Table I. Yields and Purities of *o*-Bromotoluene Obtained by the Dealkylation of 1a over SiO_2–Al_2O_3 at Various Reaction Conditions

T, °C	contact time, s	feed rate, h^{-1}	% conversion	% recovery of precursor	% purity of ortho isomer
350	0.2[a]	60	45	53	>99.5
300	1.0[b]	1.1	51	48	99.5
325	1.0[b]	1.1	60	35	99.0
350	0.4[a]	30	48	50	99.0
350	0.8[a]	15	53	43	98.7
400	0.2[a]	60	51	46	98.5
350	1.2[a]	10	56	40	98.2
400	0.4[a]	30	54	42	98.2
350	1.0[b]	1.1	65	28	98.0
350	2.5[a]	5	60	35	97.5
375	1.0[b]	1.1	73	17	97.0
400	1.0[b]	1.1	80	5	96.5

[a] Nitrogen flow rate = 50 mL/min. [b] Nitrogen flow rate = 400 mL/min.

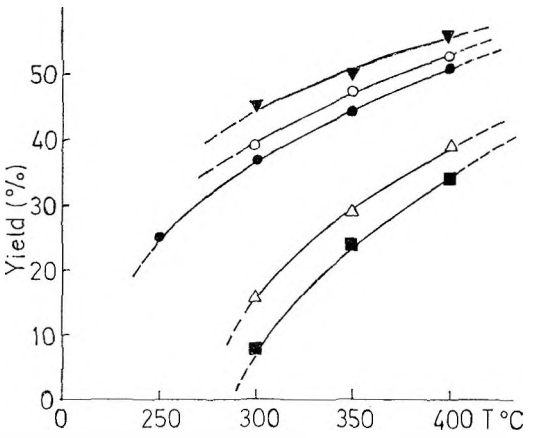


Figure 3. Percent conversion of ortho bromo-substituted benzenes on passing 1a–1e over SiO_2–Al_2O_3 at various temperatures (contact time = 0.2 s): ●, 1a; Δ, 1b; ■, 1c; ○, 1d; ▼, 1e.

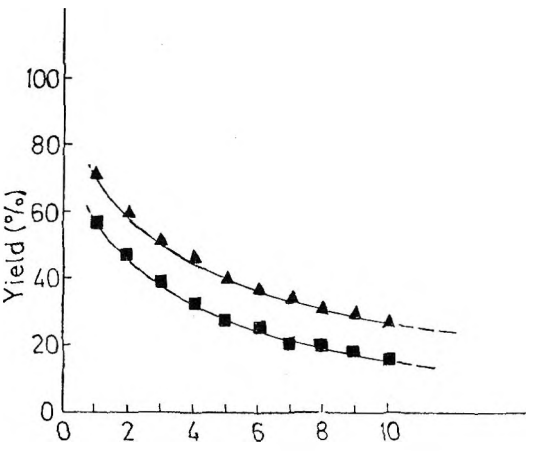


Figure 4. Catalytic activity (% conversion) of SiO_2-Al_2O_3 as a function of the onstream time. T = 350 °C; contact time = 0.2 s: ▲, over fresh catalyst; ■, over reactivated catalyst.

to ca. 80% of its original reactivity by heating it to 500 °C in an air stream.

Conclusion

The present process provides a simple method for the removal of the blocking group, namely, the *tert*-butyl group. Yield is excellent in this process with ca. 50% conversion. Workup requires only separation by distillation after which the unreacted precursor can be recycled.

Experimental Section

Reagents. All starting materials were prepared as described previously.[3]

Experimental Procedure. Gas-phase reactions over SiO_2–Al_2O_3 (7:1) were carried out in a 210 × 11.3 mm glass tube reactor in which the catalyst was supported by glass wool. The reactor was charged with 8.6 g (15 mL) of the solid catalyst, while dry N_2 was passed through at rates of 50 and 400 mL/min. The reactor was electrically heated to a predetermined temperature (temperature deviation was ±2 °C). Products emerging from the catalytic reactor were condensed and analyzed by gas–liquid chromatography. Under the experimental conditions used, the space velocity was in the range of 9.2×10^{-5} to 1.7×10^{-6} mol/s g of catalyst, and the contact time over the catalyst was 0.2–2.5 s.

Analysis of Products. Products were analyzed by gas–liquid chromatography using a Varian gas chromatograph Model 2800 equipped with thermal conductivity detector. A 3 ft × ⅛ in. 10% SE-30 on gas Chromosorb P column was used to analyze reaction mixtures. For isomer analysis a 10 ft × ⅛ in. 3% XE-60 on gas Chromosorb P column separated ortho isomer from meta and para isomers. Peak areas were integrated using an Autolab digital integrator Model 6300.

Acknowledgment. The authors wish to thank Professor George A. Olah of the University of Southern California for his helpful remarks.

Registry No.—1a, 61024-94-0; 1b, 61024-95-1; 1c, 6683-75-6; 1d, 57190-08-6; 1e, 61024-97-3; 2a, 95-46-5.

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Cyclopropanation of Some Simple Olefinic Compounds. Byproduct Formation in Excess Simmons–Smith Reagent

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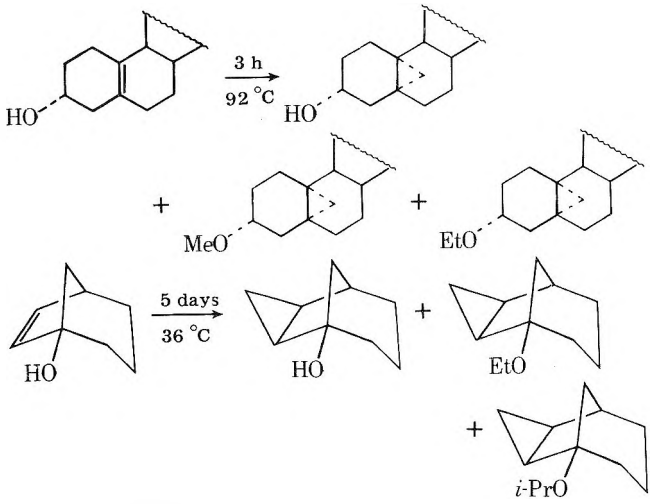
The Simmons–Smith reaction of certain unreactive alkenes of the types CH_2=$CHCH_2CO_2R$ (R = H, **1**; CH_3, **2**; CD_3, **3**) and CH_2=$CHCH_2CH_2OR'$ (R' = $COCH_3$, **4**; CH_3, **5**; H, **6**) has been studied in excess diiodomethane and zinc–copper couple or zinc–mercury couple. In some cases the initially formed cyclopropane adducts reacted further to furnish ethers, formals, and transesterification byproducts. Ester **2** gave **10** and **11**; alcohol **6** afforded **12**, **9**, **14**, and **15**. Qualitatively, the order of reactivity of these compounds appears to follow the trend **6** ≥ **5** > **2** > **4** > **1**. A convenient procedure for the preparation of symmetrical formals is reported.

The reaction of alkenes with methylene iodide and zinc–copper couple, the Simmons–Smith reaction, has long been a useful synthetic tool for the preparation of cyclopropane compounds.[1] Vinylic alkyl substituents enhance the reaction rate, but excessive substitution brings about rate retardation.[1,2] Oxygen functions, particularly hydroxyl, in the vicinity of the double bond may enhance the reaction rate and direct the attack cis stereospecifically.[1,3] The nature of the "methylene transfer" intermediate has been discussed.[1]

Previous reports indicate that Simmons–Smith reactions of relatively unreactive alcohols furnish cyclopropyl alcohols, and in addition, ethers and formals when carried out under forcing conditions. For example, estr-5(10)-ene-3α,17β-diol gave not only the alcohol that results from direct cyclopropanation of the double bond but also the corresponding methyl and ethyl ethers.[4] Similarly, bicyclo[3.2.1]oct-6-en-1-ol afforded exo-tricylo[3.3.1.$0^{2,4}$]nonan-1-ol and the corresponding ethyl and isopropyl ethers.[5] In another work, Majerski and Schleyer[6] obtained symmetrical formals as side products during cyclopropanation reactions of allyl alcohols. In fact, depending upon reaction conditions, some of these alcohols furnished the corresponding formals predominantly.

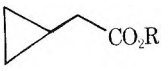


The above results prompted an investigation of terminal, unsubstituted alkenes **1**–**6**. These were prepared by standard methods and identified spectroscopically. All reactions were carried out in anhydrous ethyl ether using a large excess of diiodomethane and zinc–copper couple. Replacement of zinc–copper with amalgamated zinc (the use of which is unprecedented in Simmons–Smith reactions) afforded the same products, albeit in lower yields (Table I). Variation in the couple has also been reported by Conia,[7] who obtained higher yields with zinc–silver in lieu of zinc–copper couple. In this work, the use of zinc–mercury as a substitute for zinc–copper was not thoroughly explored.

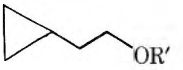
CH_2=$CHCH_2CO_2R$
1, R = H
2, R = CH_3
3, R = CD_3

CH_2=$CHCH_2CH_2OR'$
4, R' = $COCH_3$
5, R' = CH_3
6, R' = H
16, R' = $CH_2OCH_2CH_2CH$=CH_2

Cyclopropanation of **1**, **4**, and **5** gave the corresponding cyclopropane adducts **7**, **8**, and **9**, respectively. Similar treatment of **2**, prepared from **1** and diazomethane and uncontaminated by ethyl ester, yielded **10** as the major product contaminated by ethyl ester **11**. When **10** was subjected to the reaction conditions for 5 days, the crude mixture consisted of unreacted **10** (47%), ethyl ester **11** (40%), and two unidentified products (13%) of greater VPC retention times. Reduction of the mixture with lithium aluminum hydride afforded **12** as the only isolable product. These results might suggest C–H

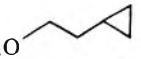


7, R = H
10, R = CH_3
13, R = CD_3
11, R = C_2H_5



8, R' = $COCH_3$
9, R' = CH_3
12, R' = H

14, R' = $CH_2OC_2H_5$

15, R' = CH_2O 

17, R' = $CH_2OCH_2CH_2CH$=CH_2

insertion; however, analogous reaction of the trideuterated methyl ester **3** yielded the corresponding methyl ester **13** as well as the nondeuterated ethyl ester **11**, thus excluding a possible C–H insertion mechanism. It has been shown by Blanchard and Simmons[1] that if the reaction is carried out in ethyl ether, side products such as methyl iodide, ethoxyzinc iodide, and others are formed. Generation of these species is particularly favored here since excess reagent and longer reaction periods were employed. Therefore, it is conceivable that **11** may be formed via transesterification of **10** or **13** by ethoxyzinc iodide.

Cyclopropanation of **6** has been reported[8] as yielding only 25–26% of **12**. In this work, two additional products were obtained under various conditions and identified as **14** and **15** (Table I). Formal **15** was the major product in several runs, as suggested by Majerski and Schleyer,[6] who incidently were the first to obtain symmetrical formals in Simmons–Smith reactions (see above). On accasion, a third byproduct was obtained and identified as **9**. Structural elucidation of **14** presented initial difficulty due to the absence of the molecular ion in the mass spectrum and the superposition of the oxy-

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Table I. Cyclopropanation of Various Alkenes

Alkene	Alkene/CH_2I_2/Zn–Cu[a] (molar ratio)	Reaction period, h	% relative composition[b]			
			1	**7**	Unidentified	
1	1:3:5.4	84	72	12	16	
			6	**10**	**11**	
2	1:3:5.4	48	37	57	6	
	1:3:5.4[c]	48	63	35	2	
	1:3:6	24	19	78	3[d]	
	1:6:12	37	6	81[e]	13[e]	
			4	**8**		
4	1:3:5.4	48	50	50		
	1:3:5.4[c]	48	87	13		
	1:3:6	24	38	62[d]		
	1:2:2.5	60		23[f,g]		
			5	**9**		
5	1:3:3	48	3	97		
				87[f]		
	1:3:3[c]	48	16	84		
				77[f]		
			6	**12**	**14**	**15**
6	1:3:5.4	48	0	46	17	37
	1:3:5.4[c]	48	0	43	25	32
	1:2:2	48	23	71	4	3
	1:3:6	2	0	57	12	31
	1:3:6	24	0	46	11	43[d]

[a] A 0.05-mol amount of alkene was used in most experiments. [b] Determined from VPC peak areas. [c] Zinc–mercury was used instead of zinc–copper couple. [d] Percent relative yields were determined by use of cylooctane as an internal area standard. [e] Isolated yield of **10** and **11** combined is 50%. [f] Isolated yield. [g] Reference 10.

Table II. Product Analysis of 6 as a Function of Time

Time, h	% relative VPC area			
	6	**12**	**14**	**15**
1.00	100			
1.33	98	2		
1.83	79	19	3	
2.50	42	55	3	
3.00	30	63	7	
4.00	13	75	10	3
5.00	5	76	14	6
7.00		72	15	14
9.00		67	17	16
11.00		58	19	23
19.00		56	19	25
29.00		54	19	27
45.75		50	20	30
72.00		49	21	30
120.00		46	21	33

methylene protons of the two alkyl groups in the NMR spectrum. This accidental degeneracy resulted in a symmetrical heptet centered at δ 3.47 and was not removed by changing the solvent to benzene. Finally, elemental analysis and spin decoupling revealed the structure. Irradiation of the methyl protons (δ 1.13) caused the collapse of the heptet to a triplet ($C_3H_5CH_2CH_2O$–) and a broad singlet (–OCH_2CH_3). The structural assignments were confirmed by spectroscopic comparison with authentic samples.

The independent synthesis of **15** and **16** as well as the unsymmetrical **14** is worthy of mention as it provides a simple, convenient procedure for symmetrical formals. As a typical example, **6** was sealed in a tube with anhydrous calcium chloride powder and paraformaldehyde and heated at 98–100 °C for 3 days. Distillation gave starting **6** and **16** (56%). This eliminates the inconvenience associated with depolymerizing paraformaldehyde. Although there is an equilibrium involved between the alcohol and the formal, the large difference in boiling points affords a convenient separation by simple distillation. Authentic samples of **14** and **15** were prepared in the same manner from **12** and ethanol.

In an attempt to find optimum conditions for the formation of alcohol **12**, cyclopropanation of **6** was repeated and samples were withdrawn periodically and analyzed by VPC (Table II). A plot of the time course of the reaction (Figure 1) reveals the initial formation of **12**, which, being unstable under the reaction conditions, reacts further to yield formals **14** and **15** either directly or indirectly. Hydrolysis of **15** was carried out with an equivolume solution of 10% aqueous sulfuric acid and THF. Analysis of the mixture by VPC indicated starting **15** (4%) and **12** (96%). Thus, aqueous mineral acid hydrolysis of the reaction mixture of **6** could provide **12** in high yield. Partial cleavage of **15** was also effected by refluxing with zinc iodide, a strong Lewis acid byproduct in Simmons–Smith reactions, in anhydrous ethyl ether. VPC analysis revealed starting **15** (52%) and **12** (48%). Reaction of **12** alone with the Simmons–Smith reagent furnished starting **12** (27%), **9** (6%), **14** (19%), and **15** (48%). Under more vigorous conditions, it gave **12** (12%), **14** (68%), and **15** (20%). Interestingly, when **15** was subjected to the reaction conditions, it afforded **14** (48%) with the remainder being starting material. Reaction of **15** with diiodomethane in ethyl ether at the exclusion of zinc–copper couple failed, as analysis of the mixture revealed starting material only. Another interesting result was obtained during cyclopropanation of **16**, which also gave product **14** (29%) in addition to **17** (35%) and **15** (36%). These control reactions in conjunction with the results of Figure 1 suggest the following: (a) cyclopropanation of **6** occurs faster than formal generation; (b) alcohol **12** furnishes **14** and **15**; (c) symmetrical formal **15** is cleaved slowly under the reaction conditions to give unsymmetrical formal **14** via subsequent reactions; and (d) **14** seems to be the thermodynamically most stable product.

It should be emphasized that the various byproducts discussed above were obtained as a result of strenuous reaction conditions in an effort to increase the cyclopropane yields of unreactive olefinic compounds.

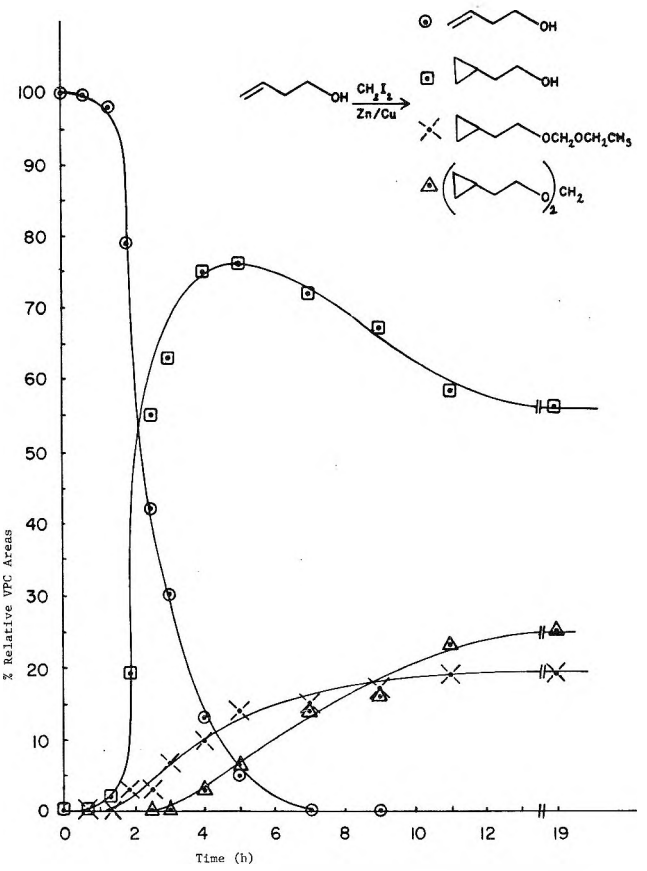

Figure 1. Product composition in the Simmons–Smith reaction of 3-buten-1-ol as a function of time.

Finally, a qualitative order of reactivity of the five compounds studied here may be inferred from the unreacted starting material obtained under similar reaction conditions (Table I). Thus, **6** ≥ **5** > **2** > **4** > **1**. Since these substrates are not activated (inductive effect) or deactivated (steric effect) by alkyl substitution at the vinyl locants, the above order of reactivity may reflect the ability of the methylene transfer reagent to coordinate with the oxygen functional groups at the homoallylic positions.

Experimental Section

Materials and Equipment. Analytical VPC separations were carried out on an F and M Model 5750 gas chromatograph equipped with a flame ionization detector and a mechanical integrator using a 12 ft × ⅛ in stainless steel column packed with 7 g of 20% Carbowax 20M on 60–80 mesh Chromosorb P. Preparative VPC separations were performed on an F and M Model 700 gas chromatograph equipped with a thermal conductivity detector. An aluminum column packed with 40 g of 20% Carbowax 20M on 60–80 mesh Chromosorb P was employed. NMR spectra were obtained on Hitachi Perkin-Elmer R-20 and Varian Model A-60 spectrometers (60 MHz) in CCl_4 solution and are reported in units of δ (ppm) downfield from a Me_4Si in CCl_4 external reference. Infrared spectra (~5% CCl_4 solution) were recorded on a Perkin-Elmer Model 337 infrared spectrophotometer. Boiling points are uncorrected. Microanalyses were carried out by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. All solutions were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4.

The ethyl ether used for Simmons–Smith reactions was distilled over lithium aluminum hydride. Freshly opened cans (Mallinckrodt) were also satisfactory. Commercial samples of diiodomethane and zinc–copper couple were used without further purification. 3-Buten-1-ol (**6**) was prepared by reduction of 3-butenoic acid (**1**) with lithium aluminum hydride: bp 28 °C (12 mm); n^{23}_D 1.4197 [lit.[9] bp 115 °C (770 mm), n^{25}_D 1.4182]. Treatment of **6** with acetic anhydride in pyridine gave 3-butenyl acetate (**4**): bp 120–123 °C; n^{23}_D 1.4240 [lit.[10] bp 121–123 and 126 °C, n^{25}_D 1.4104 and n^{20}_D 1.4105]. Reaction of **6** with diazomethane (prepared from *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide)[11] and a catalytic amount of boron trifluoride etherate in ethyl ether[12] afforded 4-methoxy-1-butene (**5**): bp 70–72 °C; n^{22}_D 1.3910 [lit.[13] bp 68–69 °C (750 mm), n^{20}_D 1.3976]. Methyl 3-butenoate (**2**) was obtained from **1** and diazomethane: bp 104–106 °C; n^{23}_D 1.4070 [lit.[13] bp 106 °C (745 mm)]. The compounds described above were at least 97% pure by VPC. Structural assignments were confirmed by IR and NMR spectroscopy.

Zinc–Mercury Couple for Simmons–Smith Reactions. Amalgamated zinc was prepared according to a procedure described in the literature[14a] except that zinc dust was used instead of mossy zinc. The couple was washed thoroughly first with water and then with ether. It was dried in a desiccator under vacuum.

Trideuteriomethyl 3-Butenoate (3). The trideuterated methyl ester was prepared according to the procedure of Sarett.[14b] A 250-mL round-bottom flask equipped with a condenser and drying tube was charged with anhydrous potassium carbonate (17.3 g, 0.151 mol) and purified acetone (80 mL). The mixture was heated at reflux for 3 h, at the end of which the heating source was removed and 3-butenoic acid (10.8 g, 0.125 mol) in dry acetone (25 mL) was added dropwise. Foaming occurred and a white slurry resulted. After heating for an additional 0.5 h, trideuteriomethyl iodide (15.5 g, 0.107 mol) in dry acetone (45 mL) was added dropwise, and the flask was heated at reflux for 20 h. The mixture was diluted with ethyl ether until potassium iodide precipitated out of solution. Filtration, drying, and removal of the solvents by distillation at atmospheric pressure gave a crude product which was purified by distillation to give 6.0 g (47%) of a colorless liquid: bp 107 °C; n^{28}_D 1.4050. The NMR spectrum is identical with that of the protio ester except that the singlet due to the methoxy protons at δ 3.52 is absent (0.0 H); IR 3095, 2990, 2260, 2200, 2125, 2080, 1745, 1645, 1420, 1410, 1335, 1292, 1270, 1192, 1093, 992, 922 cm^{-1}.

1,1-Di(3-butenoxy)methane (16). 3-Buten-1-ol (8.64 g, 0.120 mol), paraformaldehyde (1.80 g, 0.0599 mol), and powdered calcium chloride (3.33 g, 0.0300 mol), which was predried in an oven at 150 °C, were sealed in a tube and heated in an oil bath at 100 °C for 3 days. The mixture was diluted with ether (50 mL) and filtered. After drying and concentration, the residue was distilled to give starting material and 5.2 g (56%) of a colorless liquid: bp 65–68 °C (9 mm); NMR δ 2.27 (q, 4 H, allylic methylene), 3.49 (t, 4 H, oxymethylene), 4.54 (s, 2 H, methylenedioxy), 4.79–5.22 (m, 4 H, C-4 vinyl), 5.44–6.14 (m, 2 H, C-3 vinyl); IR 3080, 2985, 2930, 2875, 1740, 1640, 1425, 1375, 1180, 1124, 1078, 1040, 1000, 965, 921 cm^{-1}. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C,69.15; H, 10.25.

1-(2-Cyclopropylethoxy)-1-ethoxymethane (14) and 1,1-Di-(2-cyclopropylethoxy)methane (15). 2-Cyclopropylethanol (**12**; 0.860 g, 0.0100 mol), absolute ethanol (0.460 g, 0.0100 mol), paraformaldehyde (0.300 g, 0.0100 mol), and anhydrous calcium chloride (0.555 g. 0.00500 mol) were sealed in a tube and heated as above. After workup of the reaction mixture and removal of ether, the crude product was separated by VPC (at 170 °C) to give four fractions with retention times of 1.7 (5%), 5.3 (55%), 6.5 (12%), and 19.8 (28%) min. The first fraction (5%) was not identified. The second fraction (55%) was shown to be **14**: n^{27}_D 1.4520; NMR δ −0.1 to 1.3 (cyclopropane), 1.13 (t, methyl), 1.39 (q, methylene at C-2; total measured area between δ −0.1 and 1.7 is 10 H), 3.47 (heptet, 4 H, $-CH_2OCH_2OCH_2-$), 4.51 (s, 2 H, methylenedioxy); IR 3070, 2975, 2870, 1375, 1192, 1122, 1103, 1087, 1053, 1041, 1021, 951 cm^{-1}. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.51; H, 11.02. The third fraction (12%) was identified as **12**. The fourth fraction (28%) was identified as **15**: n^{27}_D 1.4390; NMR δ −0.16 to 1.2 (m, 10 H, cyclopropane), 1.43 (q, 4 H, methylene at C-2), 3.53 (t, 4 H, methylene at C-1), 4.57 (s, 2 H, methylenedioxy); IR 3070, 3000, 2925, 2870, 1455, 1415, 1370, 1190, 1123, 1092, 1065, 1045, 1023, 963, 930, 885 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.56; H, 10.86.

General Cyclopropanation Procedure. To a 250-mL round-bottom flask equipped with a condenser, drying tube, and dropping funnel was added zinc–copper couple (0.10–0.60 mol) or zinc–mercury couple (0.15–0.27 mol), a few crystals of iodine, and anhydrous ethyl ether (50–75 mL). The stirred mixture was heated at reflux for 0.5 h. A solution of methylene iodide (0.10–0.30 mol) and the olefinic compound (ca. 0.05 mol) in anhydrous ethyl ether was added dropwise, and the mixture was refluxed for the specified time. The flask was cooled in an ice–water bath, and the mixture was hydrolyzed by the dropwise addition of a saturated ammonium chloride solution (100 mL). The aqueous layer was extracted several times with ether, and the combined ether extracts were washed with saturated potassium carbonate (100 mL) and then with brine (100 mL). The ether layer was dried, filtered, and concentrated at atmospheric pressure to give an oily mixture which was analyzed by VPC and purified either by preparative VPC or by distillation. Specific examples are given below, and repeated experiments using modifications of reagent ratios or reaction conditions are shown in Table I.

Cyclopropanation of 3-Butenoic Acid (1). Reaction of 5.4 g (0.05 mol) of **1** afforded 12% (by VPC) of cyclopropylacetic acid and 16% of an unidentified compound. The former was identified by comparison with an authentic sample.[15]

Cyclopropanation of 3-Buten-1-yl Acetate (4). Using the above procedure, 5.7 g (0.050 mol) of **4** afforded an oily mixture which upon VPC analysis gave two fractions. The first fraction (38%) was identified as **4** by coinjection with an authentic sample. The second fraction (62%) had bp 77 °C (56 mm), n^{23}_D 1.4220 [lit.[10a] n^{25}_D 1.4200]. Its NMR and IR spectra were identical with those reported for 2-cyclopropylethyl acetate.[16,17]

Cyclopropanation of 3-Buten-1-yl Methyl Ether (5). 3-Buten-1-yl methyl ether (4.30 g, 0.050 mol) was treated with the Simmons–Smith reagent, and the crude product was distilled and identified as 2-cyclopropylethyl methyl ether (**9**; 4.36 g, 87%): bp 97 °C (micro bp[18] 106 °C); n^{26}_D 1.4002; NMR δ −0.11 to 1.24 (m, 5 H, cyclopropane), 1.45 (q, 2 H, methylene at C-2), 3.28 [s, methoxy protons; overlapping with δ 3.37 (t, methylene at C-1); total area 5 H]; IR 3080, 3005, 2985, 2925, 2870, 2730, 1445, 1375, 1320, 1267, 1233, 1201, 1171, 1120, 1045, 1016, 997, 966, 926, 885, 820 cm^{-1}. Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.22; H, 11.82.

Cyclopropanation of Methyl 3-Butenoate (2). Cyclopropanation of **2** (5.0 g, 0.050 mol) followed by VPC (column temperature, 145 °C) yielded three fractions. The first fraction (retention time of 4.8 min; 19%) was identical with **2** by coinjection. The second fraction (retention time of 8.6 min; 78%) had identical NMR and IR spectra with those of methyl cyclopropylacetate[19] (**10**). The third fraction (retention time of 10.2 min; 3%) was identified as ethyl cyclopropylacetate (**11**): n^{22}_D 1.4205; NMR, the complex multiplet due to the five cyclopropane protons had a chemical shift between δ −0.05 and 1.3 and overlapped with the triplet due to the methyl protons between δ 1.0–1.4 (total area 8 H), δ 2.04 (d, 2 H, methylene at C-2), 4.02 (q, 2 H, ethoxy methylene); IR 3080, 2980, 1735, 1320, 1259, 1208, 1185, 1118, 1102, 1038, 1023, 989, 955, 912, 828 cm^{-1}. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.73; H, 9.67.

A mixture of the second and the third fractions was isolated by preparative VPC and reduced with lithium aluminum hydride. Only one product was obtained which had identical NMR and IR spectra with an authentic sample of 2-cyclopropylethanol (**12**).

Simmons–Smith Reaction of Methyl Cyclopropylacetate (10). Using the standard cyclopropanation procedure, a mixture of **10** (2.89 g, 0.0253 mol), diiodomethane (40.2 g, 0.150 mol), zinc–copper couple (20.0 g), and a catalytic amount of iodine in ethyl ether (100 mL) was heated at reflux for 5 days. After the usual workup procedure, the sample was analyzed by VPC and found to consist of starting **10** (47%), ethyl ester **11** (40%), and two unidentified, longer retention time products (13%). Other products of extremely short retention times were also observed and are probably the same as those observed and accounted for elsewhere.[1]

Cyclopropanation of Trideuteriomethyl 3-Butenoate (3). The Simmons–Smith reaction of the deuterated ester (same condition as for **2**) gave starting material and two other fractions which were isolated by preparative VPC and analyzed. The second fraction had n^{28}_D 1.4195. The NMR spectrum was similar to that of **10** as reported,[19] except that the singlet due to the methoxy groups at δ 3.6 was absent: NMR δ −0.3 to 1.4 (m, 5 H, cyclopropane), 2.10 (br d, 2 H, methylene at C-2); IR 3085, 3015, 2920, 2255, 2190, 2120, 2080, 1740, 1320, 1270, 1194, 1121, 1090, 1050, 1023, 998, 967, 938, 835 cm^{-1}. The NMR and IR spectra of the third VPC fraction were identical with those of **11**, indicating the complete absence of deuterium.

Cyclopropanation of 3-Buten-1-ol (6). A. Under Various Conditions. The Simmons–Smith reaction of **6** (10.8 g, 0.150 mol), when carried out under various conditions (Table I), furnished four fractions. The first fraction was observed in small amount after several repetitions of the reaction. It was tentatively identified as 2-cyclopropylethyl methyl ether (**9**) by comparison of its VPC retention time with that of the sample isolated from cyclopropanation of **5**. The second fraction (retention time of 8.4 min at 158 °C; 11%), n^{27}_D 1.4520, was identified as **14** by comparison of its spectral properties with those of the authentic sample prepared above. The third fraction (retention time of 10.8 min at 158 °C; 46%) had NMR and IR spectra identical with those of 2-cyclopropylethanol (**12**). The fourth fraction (retention time of 38.2 min at 158 °C; 43%), n^{27}_D 1.4390, was identified as **15** by spectroscopic comparison with an authentic sample.

B. Product Analysis as a Function of Time. Using the general procedure, a mixture of **6** (7.2 g, 0.10 mol), diiodomethane (80.4 g, 0.30 mol), and zinc–copper couple (22.2 g, 0.30 mol) in anhydrous ethyl ether (100 mL) was heated at reflux. Samples (1 mL) were withdrawn with a syringe at appropriate intervals and analyzed by VPC. Weight percent relative amounts of products calculated from VPC areas are given in Table II. Molar response corrections were not made (see Figure 1).

Cleavage of 1,1-Di(2-cyclopropylethoxy)methane (15). A. With Mineral Acid. Ketal **15** (1.0 g, 0.0054 mol) was dissolved in tetrahydrofuran (30 mL). A 10% aqueous sulfuric acid solution (30 mL) was added, and the heterogeneous solution was heated with vigorous stirring for 21 h. The solution was extracted several times with 50 mL portions of ether, and the combined ether extracts were washed successively with water, potassium carbonate, and brine. Drying, filtration, and removal of ether gave a crude product which on VPC analysis showed starting formal (4%) and **12** (96%).

B. With Zinc Iodide. A mixture of **15** (1.84 g, 0.010 mol), zinc iodide (6.38 g, 0.202 mol), and a few crystals of iodine in anhydrous ether (30 mL) was heated at reflux for 48 h. Analysis by VPC indicated starting **15** (52%) and **12** (48%).

Simmons–Smith Reaction of 2-Cyclopropylethanol (12). 2-Cyclopropylethanol (2.15 g, 0.025 mol), methylene iodide (6.70 g, 0.025 mol), zinc–copper couple (3.7 g, 0.05 mol), and a few crystals of iodine were dissolved in ether (25 mL), and the mixture was heated at reflux for 24 h. VPC of the crude mixture revealed the following composition: **12** (27%), **9** (6%), **14** (19%), and **15** (48%). In a second reaction, a mixture of **12** (1.00 g, 0.012 mol), methylene iodide (20.1 g, 0.075 mol), zinc–copper couple (10.0 g, 0.135 mol), and a few crystals of iodine in ether (100 mL) was heated at reflux for 84 h. The following compounds were observed upon VPC analysis: **12** (12%), **14** (68%), and **15** (20%). Other shorter retention time peaks were also observed in small amounts but were not identified.

Simmons–Smith Reaction of 1,1-Di(2-cyclopropylethoxy)-methane (15). Using the general procedure, a mixture of **15** (1.84 g, 0.010 mol), methylene iodide (8.04 g, 0.030 mol), zinc–copper couple (4.44 g, 0.061 mol), and a catalytic amount of iodine in ether (30 mL) was heated at reflux for 48 h. Analysis by VPC gave starting **15** (52%) and **14** (48%). When the reaction was repeated using the same materials as above, but not using zinc–copper couple, **15** was recovered unreacted.

Cyclopropanation of 1,1-Di-(3-butenoxy)methane (16). Using the general procedure, a mixture of **16** (3.9 g, 0.025 mol), diiodomethane (40.2 g, 0.15 mol), zinc–copper couple (20.0 g, 0.27 mol), and a catalytic amount of iodine in ether (100 mL) was heated at reflux for 5 days. Analysis of the crude product mixture by VPC revealed three fractions. The first fraction (29%) had an identical NMR spectrum with that of **14**. The second fraction (35%), n^{26}_D 1.4278, was identified as 1-(3-butenoxy)-1-(2-cyclopropylethoxy)methane (**17**) on the basis of the following data: NMR δ −0.2 to 1.2 (m, 5 H, cyclopropane), 1.36 (q, 2 H, cyclopropylcarbinyl protons), 2.24 (q, 2 H, allylic protons), 3.46 (t, 4 H, $-CH_2OCH_2OCH_2-$), 4.50 (s, 2 H, methylenedioxy), 4.73–5.22 (br d, 2 H, terminal vinyl protons), 5.27–5.98 (m, 1 H, internal vinyl proton); IR 3075, 3005, 2930, 2870, 1640, 1460, 1420, 1370, 1178, 1115, 1083, 1037, 1017, 950, 914, 882 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.39; H, 10.47. The third fraction (36%) had an NMR spectrum identical with that of **15**.

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Registry No.—**1**, 625-38-7; **2**, 3724-55-8; **3**, 66688-09-3; **4**, 1576-84-7; **5**, 4696-30-4; **6**, 627-27-0; **7**, 5239-82-7; **8**, 66688-05-9; **9**, 66688-06-0; **10**, 34108-21-9; **11**, 53432-87-4; **12**, 2566-44-1; **13**, 66688-11-7; **14**, 66688-07-1; **15**, 66688-08-2; **16**, 48057-46-1; **17**, 66688-10-6; trideuteriomethyl iodide, 865-50-9.

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Reduction of *gem*-Dihalocyclopropanes with Zinc. Monoreductive Dehalogenation of *gem*-Dihalocyclopropyl Methyl Ketones and Dioxolanes

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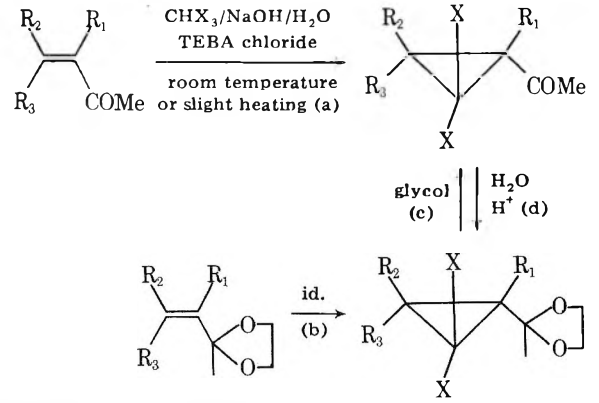
The monoreduction, by means of zinc powder in alcoholic potassium hydroxide, of 11 *gem*-dihalocyclopropyl methyl ketones and six *gem*-dihalocyclopropylmethyldioxolanes was reported and gave satisfactory yields. With ketones, contrary to dioxolanes, the monoreduction occurred without general stereoselectivity, but required critical temperature control and precise reaction times to prevent total reduction. α-Alkylated ketones ($R_2 = R_3 = H$; R_1 = Me, *i*-Pr, or *t*-Bu) led predominantly to cis isomers, especially with bulky R_1, while α,β- ($R_3 = H$; R_1 = Me; R_2 = Me or *i*-Pr) and β,β′-dialkylated ketones ($R_1 = H$; $R_2 = R_3$ = Me) gave steric preference depending on the nature of the halogen. In all cases, dioxolanes gave a stereoselective formation of the trans isomers. These results were rationalized by postulating a predominant initial zinc attack at the less hindered C–X bond. With dioxolanes, the second step would be a high inversion of the resulting α-halocyclopropyl radicals. With ketones, intermediates could be carbanions and results explained by an easier inversion of the α-chlorocyclopropyl carbanions relative to the α-bromocyclopropyl carbanions.

A large variety of reagents can bring about reductive monodehalogenation of *gem*-dihalocyclopropanes.[1,2] Furthermore, recent studies examined the stereoselectivity of such a monoreduction with organotin hydride,[3-5] lithium aluminum hydride ($LiAlH_4$),[6,7] or related hydrides.[8,9] Moreover,



zinc powder in acetic acid[10] or ethanol–acetic acid[11] was revealed as an efficient and cheap means for reducing dihalocyclopropanes. The recent reduction with zinc in alcoholic potassium hydroxide appeared particularly attractive as a stereoselective and easy method.[2]

We wish now to report the monoreduction of *gem*-dihalocyclopropyl methyl ketones and their corresponding dioxolanes with this latter reagent. It was of interest to test the generality of the monoreduction, with a free or a protected carbonyl group as ring substituent, and to check its stereoselectivity especially with a crowded group such as a dioxolane.

The substrates were easily available by dihalocarbenic addition to olefinic ketones (a) or to dioxolanes (b) with subsequent ketalization (c) or hydrolysis (d) if needed.[12] The two-step procedure (a + c) for dioxolane synthesis was preferred to the direct addition (b). Conversely, for ketones, the direct method (a) was better except for compounds with $R_1 = H$, which required steps b and d.

Results

Results are summarized in Tables I and II. Our experimental conditions (method m_1) gave monoreduced rings as major products with satisfactory yields.

Ketones A–K (Table I) underwent reduction more easily than dioxolanes L–Q (Table II) with the exception of the dichloro ketone F, which was not reduced in boiling ethanol but required boiling propanol or butanol. It is also noteworthy that dibromo ketones underwent monoreduction more readily than dichloro ketones. In both cases formation of fully reduced cyclopropanes was difficult to avoid.

For ketones the extent of the reduction was greatly dependent on the temperature. In order to limit the reduction and to obtain preferably monoreduced ketones each substrate required specific temperature conditions and reaction time. Furthermore, for a few ketones we determined a critical temperature below which the extent of the reduction was considerably reduced and above which the complete reduction occurred rapidly. In all cases stereoisomeric pairs of cis and trans monoreduced compounds (cis and trans refer to the position of the halogen relative to the acetyl group) were obtained without general selection.

For dioxolanes, with careful temperature and reaction time controls we obtained a stereoselective monoreduction, giving predominantly the trans isomer.

Identification and Characterization

Identification and configurational assignments of the reduced compounds were easily achieved by comparison with halocarbenoid adducts of olefinic dioxolanes previously prepared.[13] Halocyclopropanation by halogen exchange gave both chloro- and bromodioxolanes which were converted, when

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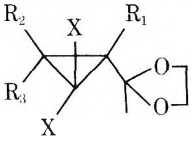
Table I. Monoreduction of *gem*-Dihalocyclopropyl Methyl Ketones

substrate					registry	temp,	time,	% yield		trans isomer			cis isomer			trans/
								mono-	full		registry			registry		
no.	R_1	R_2	R_3	X	no.	°C	h	redn	redn	no.	no.	%	no.	no.	%	cis (*t*/*c*)
A	Me	H	H	Cl	2568-72-1	60	20	90	0	**1t**	66793-70-2	35	**1c**	66788-39-4	65	0.53
B	Me	H	H	Br	2568-73-2	60	17	95	5	**2t**	52034-84-1	37	**2c**	64731-69-7	63	0.58
C	*i*-Pr	H	H	Cl	52100-72-8	60	30	80	0	**3t**	66788-35-0	30	**3c**	66788-40-7	70	0.43
D	*i*-Pr	H	H	Br	52100-82-0	40	25	75	0	**4t**	66788-36-1	20	**4c**	66788-27-0	80	0.25
						80	20	0	100							
E	*t*-Bu	H	H	Cl	52100-73-9	50	50[a]	40	15	**5t**[b]	66788-37-2	10	**5c**[b]	66788-28-1	90	0.11
F	Me	Me	H	Cl	52100-74-0	97	5	70	5	**6t**	66808-14-8	35	**6c**	66788-29-2	65	0.54
						110	5	50	25			50			50	
G	Me	Me	H	Br	52100-83-1	50	24	30	0	**7t**	62234-89-3	58	**7c**	66101-85-7	42	1.38
						53	18	70	30							
						60	18		100							
H	Me	*i*-Pr	H	Cl	52100-76-2	50	48	70	10	**8t**	66808-15-9	13	**8c**	66788-30-5	87	0.15
I	Me	*i*-Pr	H	Br	52100-85-3	50	15	50	50	**9t**	62234-90-6	55	**9c**	66808-13-7	45	1.22
J	H	Me	Me	Cl	3591-54-6	20	45	85	0	**10t**	66788-38-3	90	**10c**	66788-31-6	10	9.00
K	H	Me	Me	Br	52100-90-0	20	40	90	0	**11t**	66236-48-4	20	**11c**	66788-32-7	80	0.25
						45	6	75	0			50			50	1.00

[a] An increased reaction time did not give higher yields of monoreduced compounds. [b] **5t** and **5c** were not isolated and were identified by chromatographic analogy with other stereoisomer pairs.

Table II. Monoreduction of *gem*-Dihalocyclopropylmethyldioxolanes



substrate					registry	meth-	temp,	time,	% yield		trans isomer			cis isomer			trans/
									mono-	full		registry			registry		
no.	R_1	R_2	R_3	X	no.	od[a]	°C	h	redn	redn	no.	no.	%	no.	no.	%	cis (*t*/*c*)
L	Me	H	H	Cl	66788-33-8	m_1	60	15	75	0	**12t**	64731-81-3	62	**12c**	64731-82-4	38	1.63
						m_2	84	18	95	0			57			43	1.33
M	Me	H	H	Br	66788-34-9	m_1	80	90	90	10	**13t**	64731-53-9	65	**13c**	64731-54-0	35	1.85
N	H	Me	H	Cl	52100-78-4	m_1	80	6	95	5	**14t**	64731-55-1	72	**14c**	64753-84-0	28	2.57
O	H	Me	H	Br	52100-87-5	m_1	45	72	70	15	**15t**	64731-56-2	79	**15c**	64753-85-1	21	3.76
P	H	Me	Me	Cl	52100-80-8	m_1	80	15	100	0	**16t**	59083-00-0	64	**16c**	59082-99-4	36	1.77
						m_2	84	15	90	5			90			10	9.00
						m_3	65	15	30	7			75			25	3.00
						m_3	65	40	60	10			75			25	3.00
Q	H	Me	Me	Br	52100-89-7	m_1	45	50	85	15	**17t**	59083-02-2	77	**17c**	59083-01-1	23	3.35
						m_2	84	14	0	100							

[a] m_1 = Zn/EtOH/KOH; m_2 = $LiAlH_4$/DME; m_3 = $LiAlH_4$/THF.

needed, into corresponding ketones by final acid hydrolysis. (An example can be found in Scheme I.) Halocarbene addition on this starting olefinic dioxolane gave isomeric ratios similar to those obtained by reduction of L and M (**12t/12c** = 72:28 for halocarbene addition; **12t/12c** = 62:38, **13t/13c** = 57:43 for monoreduction). Conversely, reduction of A and B gave reversed ratios (**1t/1c** = 35:65, **2t/2c** = 37:63).

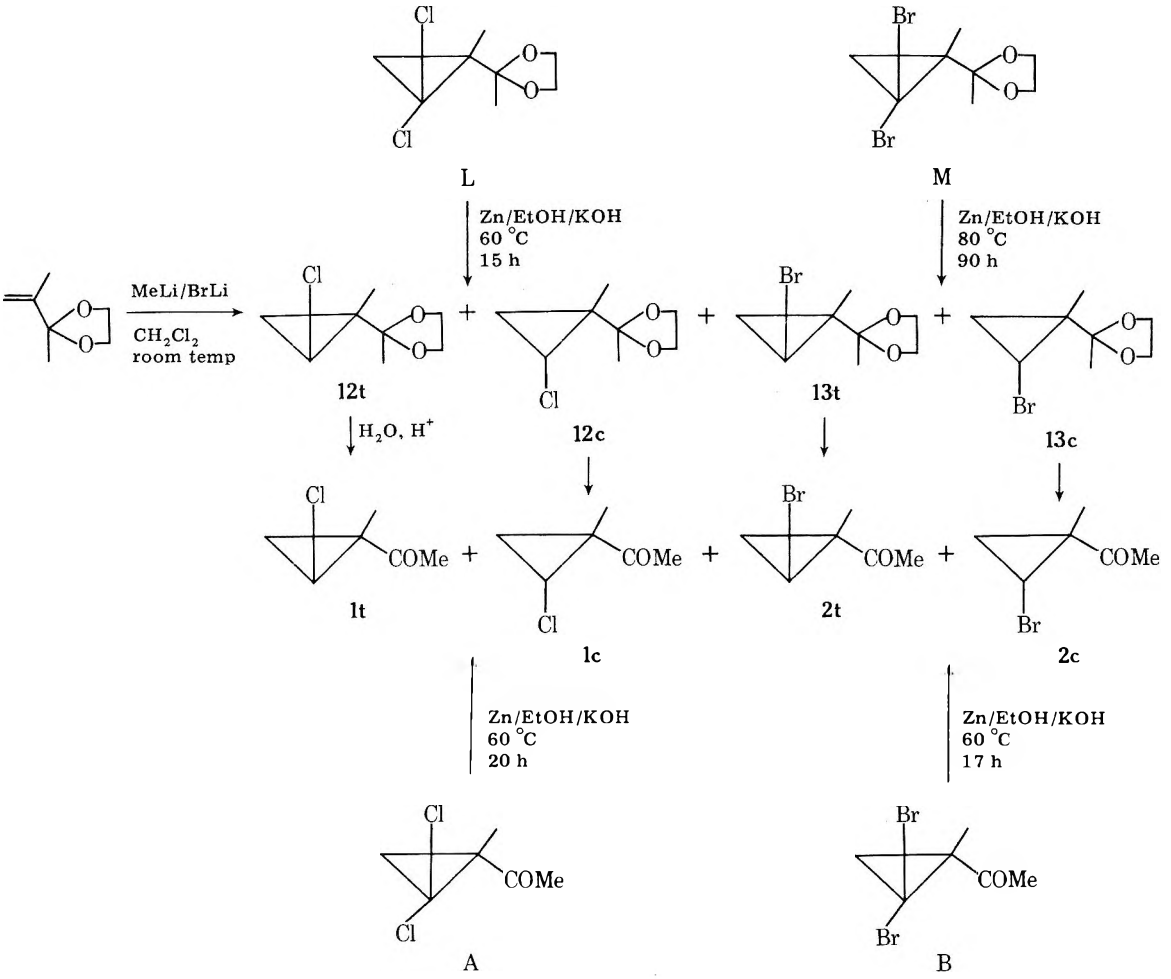
The isomeric ratios were estimated by gas chromatography, taking into account the molecular response factor of each stereoisomer.

2t, **7t**, and **9t** were recently described.[14] The other ketones are new compounds which gave satisfactory elemental analysis (Cl ± 0.3%, Br ± 0.5%).

The configurational assignments of the above compounds are supported by their NMR and IR spectral characterization (Table III): the values of the coupling constants $^3J_{vic}$ ($^3J_{trans}$ ~ 5 Hz, $^3J_{cis}$ ~ 8 Hz) for the two vicinal cyclopropyl protons with isomers **6t** to **11t** and **6c** to **11c**; the induced shifts by $Eu(dpm)_3$, higher for H_3 than for H_2 and H_4 with isomers **1c** to **4c** and lower for h_2 than for H_3 and H_4 with isomers **1t** to **4t**; the greater deshielding of the H_4 proton in trans isomers (diamagnetic anisotropy of the carbonyl group affecting the proton in the cis position more); the lower ν_{CO} absorptions for the trans isomers relative to the cis isomers (important halogen field effect when the halogen and the carbonyl are in cis position).[13]

The trans and cis configurations of the dioxolanes were also determined by the ^1H NMR chemical shift of the H_4 proton which showed, as in ketones, a greater deshielding and a lower $^3J_{vic}$ for the trans stereoisomer. However, the best distinction occurred again with corresponding methyl ketones (Table IV). The monoreduced stereoisomers **12** to **15** showed two $^3J_{vic}$ and the determination of configurations required the LIS effect, with $Eu(dpm)_3$, on the corresponding ketones.

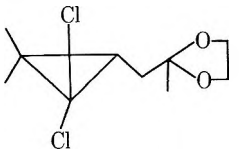
Scheme I



Discussion

The stereoselective reduction of dioxolanes appears easy to rationalize, but in the reduction of ketones the results cannot be explained as easily.

With dioxolanes the predominant formation of the trans isomer (t/c between 1.63 and 3.76) seems strongly dependent on steric factors. For instance, in comparative monoreduction of dichloro and dibromo compounds the stereoselectivity was larger with bromo compounds. On the other hand, when the buttressing dioxolane group is more distant from the halogens the stereoselectivity was reversed (t/c = 1.77 with P, 0.5 with R).



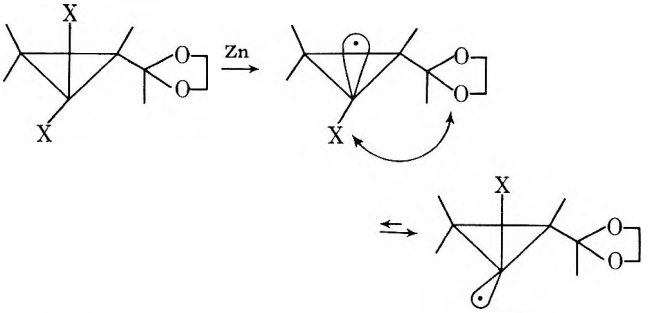
R

m_1, 80 °C, 26 h → trans isomer + cis isomer.

yield of monoreduction 100%: 33% 66%

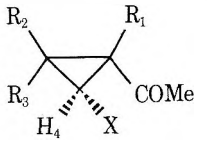
Previous zinc monoreductions of *gem*-bromofluorocyclopropanes proceeded with complete retention of configuration at low temperature and slight inversion at high temperature. Moreover, *gem*-dibromocyclopropanes gave the more hindered monoreduced cyclopropanes (syn stereoselection). To explain these results a three-step mechanism has been postulated:[2] (a) formation of interconvertible radicals with major retention of configuration (slow conversion occurring only at high temperature with α-fluorocyclopropyl radicals and possibly at lower temperature with more easily convertible α-bromocyclopropyl radicals); (b) further reduction of radicals toward unconvertible anion with retention of configuration (direct formation of anion being ruled out because such an intermediate would be rapidly protonated, due to the protic solvent used, before any inversion could occur); and (c) final protonation with solvent.

On the contrary, with our substrates, the less hindered monoreduced compounds were preferentially obtained. With respect to the preceding mechanism *our own results can be interpreted as a predominant attack of zinc metal at the less hindered C–Br bond followed by a high inversion of the resulting α-bromocyclopropyl radical.* The increased inversion of α-bromocyclopropyl radicals β-substituted with a dioxolane group as compared to the unsubstituted radicals would be ascribed to the effect of oxygens as previously suggested[15] and to the steric crowding between the dioxolane group and the cis halogen atom.



Using methods m_2 and m_3 we observed, with the exception of the ambiguous case of L, an increased trans preference (see

Table III. Spectroscopic Identification of Monohalocyclopropyl Methyl Ketones



chloro compd	bromo compd	chemical shifts, δ, ppm R1 (H_1, Me, *i*-Pr)	R2 (H_2, Me, *i*-Pr)	R3 (H_3, Me)	H_4CX trans	H_4CX cis	coupling constants, *J*, Hz $J_{H_1H_4}$	$J_{H_2H_4}$	$J_{H_3H_4}$	$J_{H_2H_3}$	IR absorption ν_{CO}, cm^{-1} trans	IR absorption ν_{CO}, cm^{-1} cis
1t		1.38	0.66	1.60	3.38			5	7.5	5.6	1694	
1c		1.40	1.01	1.73		2.94		7.8	5.5	6.2		1706
	2t	1.55	0.89	1.82	3.33			5.3	8.2	5	1693	
	2c	1.43	1.09	1.75		2.85		7.7	5.7	6.6		1704
3t		1.00, 0.85	0.75	1.50	3.42			5	7.5	5.8	1694	
3c		0.96, 0.82	0.90	1.52		2.97		8	4.8	6.8		1705
	4t	1.05, 0.87	0.82	1.65	3.40			5.2	8	5.5	1692	
	4c	0.98, 0.80	0.93	1.54		2.93		7.8	4.8	7		1704
6t		1.34	1.09	1.65	3.52				7.8		1691	
6c		1.35	1.14	1.97		2.63			5.2			1703
	7t	1.37	1.09	1.62	3.52				7.5		1689	
	7c	1.37	1.15	2.00		2.55			5.2			1703
8t		1.41	1.05, 0.97	1.65	3.48				8		1692	
8c		1.37	1.07, 0.97	1.70		2.66			4.5			1703
	9t	1.45	1.08, 1.02	1.65	3.49				7.3		1690	
	9c	1.38	1.09, 1.02	1.70		2.59			5.5			1703
10t		1.95	1.11	1.33	3.42		5				1697	
10c		1.85	1.18	1.29		3.12	8.2					1703.5
	11t	1.99	1.14	1.35	3.41		4.8				1696	
	11c	1.94	1.21	1.29		3.12	8					1703

Table IV. Spectroscopic Identification of Monohalocyclopropylmethyldioxolanes

dioxolane	δ_{H_4}, ppm	$^3J_{trans}$, Hz	$^3J_{cis}$, Hz	corresponding ketone δ_{H_4}, ppm	corresponding ketone $^3J_{trans}$, Hz	corresponding ketone $^3J_{cis}$, Hz	ν_{CO}, cm^{-1}
12c	2.95	5	8	2.94	5.5	7.8	1706
12t	3.10	4.5	7.8	3.38	5	7.5	1694
13c	2.96	5	8.2	2.85	5.7	7.7	1704
13t	3.14	4.5	8	3.33	5.3	8.2	1693
14c	2.78	5	8	3.00	5	8.2	1705.5
14t	2.98	4.5	7.8	3.42	4.5	7.5	1697
15c	2.80	4.8	8	3.02	5.2	8	1704.5
15t	3.03	4.5	7.8	3.36	5	7.8	1695.5
16c	2.77		8.5	3.12		8.2	1703.5
16t	2.90	4.8		3.42	5		1697
17c	2.78		8.3	3.12		8	1703
17t	2.92	4.6		3.41	4.8		1696

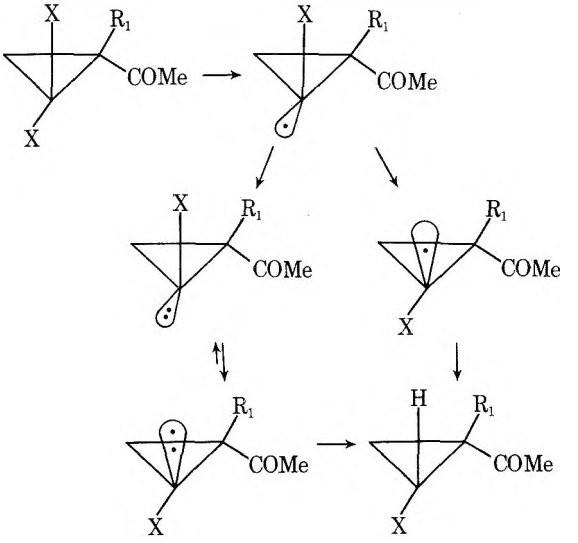
P in Table I and R below). The attack of the reagent at the less-hindered position remains, but it is probable that the direct intermediate is the carbanion[6] and that its inversion can take place in the absence of protic solvent and occurs more rapidly than with corresponding radicals.

$$R \xrightarrow[\substack{m_2,\ 14\ h,\ 84\ °C \\ m_3,\ 40\ h,\ 65\ °C}]{m_1,\ 67\ h,\ 80\ °C} \mathbf{18t} + \mathbf{18c}$$

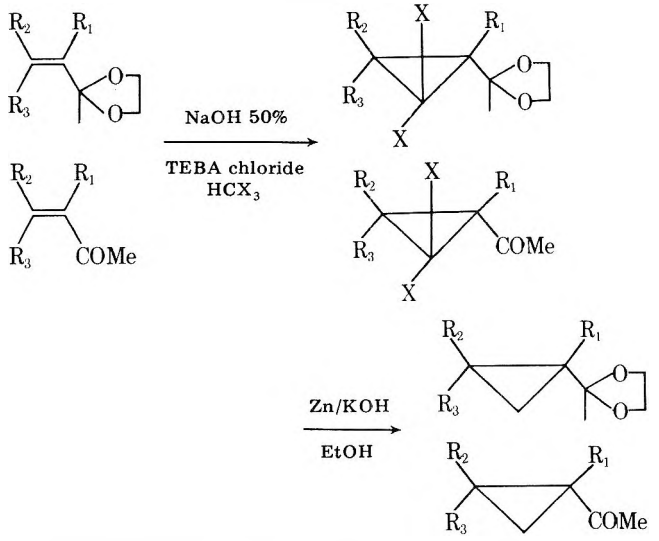
(t/c = 32:48 with method m_1, 48:52 with methods m_2 and m_3)

With ketones, the monoreduction results are very dependent on the ring alkylation and can again be rationalizated by postulating a predominant zinc attack at the less-hindered C–X and a possible inversion involving not only the ketonic radicals but also the ketonic carbanions. Indeed, the ketonic radicals, less strained than the dioxolane radicals, are stabilized and can undergo carbanions before inversion. We observed three different cases.

(1) With the α-alkylated dihalo ketones A–E the monoreduction occurred with an opposite stereoselectivity relative to dihalodioxolanes. Moreover, the increasing steric effect led to increased stereoselectivity (see the decrease of t/c with the increase of the size of R from Me to *t*-Bu). Attack by zinc



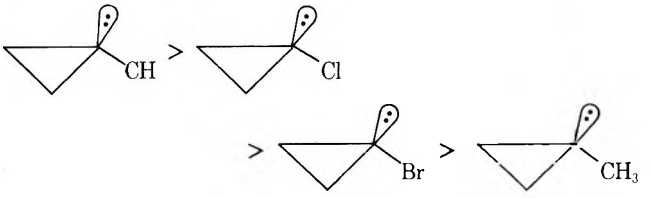
Scheme II



would occur at the halogen cis to the acetyl group since the latter, in a cisoid conformation,[16] is less bulky than R_1, particularly when R_1 = *i*-Pr or *t*-Bu.

(2) With the α,β-dialkyl dihalo ketones F–H, dichloro ketones led predominantly to cis isomers and dibromo ketones predominantly to trans isomers. These results are consistent with an enhanced zinc attack in position cis to the carbonyl and with a slower inversion of bromo carbanions.

(3) Conversely, with the β,β-dialkyl dihalo ketones I and J, the cis isomer was preferentially formed from dibromo ketone and the trans isomer from dichloro ketone. The major initial zinc attack would be reversed, due to steric effects, and followed by a more important inversion with the chloro carbanions. Slower inversion of the α-bromo carbanions vs. the α-chloro carbanions is compatible with previously reported results about carbanion stability.[3,17-18] According to these results we can write the following sequence of inversion barriers:



Moreover, the β-acetyl group will be a stabilizing group for α-chloro and α-bromo carbanions, allowing an intermediate inversion rate.

For synthetic purposes it is interesting to note that, with this reducing agent, in addition to the monoreduction, *gem*-dihalocyclopropyldioxolanes or ketones can lead to completely reduced compounds if no proper precautions are taken. Thus, the easily available starting compounds and the easy total reduction with zinc can allow the formation of cyclopropyl ketones or dioxolanes of any substitution (Scheme II). The dihalocarbonic addition to ketones gives higher fields, but fails with R_1 = H.[12] In the latter case it is necessary to utilize olefinic dioxolanes.

Experimental Section

Infrared spectra were recorded from thin liquid films on Perkin-Elmer 237 or 521 instruments. ^{1}H NMR spectra were obtained on a Perkin-Elmer R-10 nuclear magnetic resonance spectrometer.

General Procedure. Typically, the ketones or the corresponding dioxolanes (2 g) were added to ethanolic potassium hydroxide (10%, 20 mL) and stirred with zinc powder (6 g). Overall comparison showed that ketones were reduced more easily than dioxolanes and that total reduction was avoided only with moderate reaction temperature. Comparatively to dioxolanes, temperature and time reaction of monoreduction of ketones required greater control (Table I), but this reduction proved to be equally general.[19] As examples we can describe the preparation of **7t** and **7c** for ketones and general methods m_1, m_2, and m_3 for dioxolanes.

Table V. Values of Δ (hertz) for 1c,t–4c,t

isomers	R	X	H_4	H_3	H_2
1c	Me	Cl	492	1055	498
1t	Me	Cl	900	996	468
2c	Me	Br	510	1086	510
2t	Me	Br	905	1000	462
3c	*i*-Pr	Cl	460	1075	510
3t	*i*-Pr	Cl	1055	1085	450
4c	*i*-Pr	Br	475	1100	520
4t	*i*-Pr	Br	1055	1110	450

Table VI. Evaluation of Δ for Protons H_3 and H_4 in Ketones Corresponding to Dioxolanes 14c,t and 15c,t

	corresponding ketones		
dioxolanes	X	ΔH_3	ΔH_4
14c	Cl	894	432
14t	Cl	810	720
15c	Br	918	450
15t	Br	780	720

***cis*- and *trans*-1-Acetyl-2-bromo-1,3-dimethylcyclopropanes (7t and 7c).** 1-Acetyl-2,2-dibromo-1,3-dimethylcyclopropane (G; 2 g, 7.4 mmol) was mixed with zinc powder (6 g) and ethanolic potassium hydroxide (10%, 20 mL). The reaction was followed by VPC and after 18 h at 53 °C the yield of the monoreduction increased no more and reached 70%, while a large amount of total reduction (30%) was unavoidable. With a lower reaction temperature (50 °C) total reduction was avoided, but the monoreduction was greatly slowed down and reached only 30% after 24 h of reaction. With a higher reaction temperature (60 °C) only total reduction was observed. The reaction mixture was then filtered and 200 mL of water was added to the filtrate. After extraction of the aqueous layer with ether, added organic layer and ethereal extract were neutralized with an ammonium chloride solution and then dried and concentrated in vacuo.

Method m_1. The starting crude dioxolane[20] (2 g, 6.3–9.5 mmol) was added to an ethanolic potassium hydroxide and zinc powder mixture. This mixture was stirred for a variable time (6–90 h) and generally with refluxing ethanol temperature.[21] Extraction and separation were unchanged compared with ketones.

Method m_2. The starting dioxolane (2 g) was stirred with lithium aluminium hydride ($LiAlH_4$; 0.5 g, 13 mmol) and 25 mL of refluxing DME was carefully dried over potassium hydroxide. After about 15 h of reaction a few drops of water were added, permitting separation of organic layer and mineral aggregate. After neutralization by ammonium chloride solution the organic layer was dried and concentrated in vacuo with slight warming.

Method m_3. Similar to method m_2 except THF replaced DME.

Characterization. In a general way dibromodioxolanes appeared more susceptible to total reduction than dichlorodioxolanes. It was difficult to isolate monohalodioxolanes with a satisfactory purity. Indeed, often they were transformed into corresponding ketones during the chromatographic isolation. Consequently satisfactory elemental analyses were obtained only with ketones (Cl ±0.3%, Br ± 0.5%). However, by analytical chromatography with the use of moderate injector temperature, it was easy to observe the products of reduction without decomposition. Comparison with retention times of monohalocarbenoic adducts of olefinic dioxolanes and transformation into corresponding ketones[13] allowed unambiguous identification of these monoreduced dioxolanes.

In VPC it is noteworthy to note that trans stereoisomers always show retention times smaller than cis stereoisomers.

Configuration. Lanthanide Induced Shifts (LIS Effect). Determination of the configuration for **1c** to **4c** and **1t** to **4t** required study of the LIS effect. Relative shifts of protons, after addition of $Eu(dpm)_3$, in a molecule containing a complexation center such as a carbonyl, is a very useful tool for this determination.[22] Halogens were not involved in the complexation[23] and the LIS effect allowed unambiguously the attribution of configuration for monohalo-substituted compounds 1–4. The slope, Δ, of the equation

$$\delta_i = \delta_c - \delta_0 = f(C_{Eu}/C_0)$$

where δ_0 = shift without chelate, C_{Eu} = molar concentration of chelate, δ_c = shift with chelate, and C_0 = molar concentration of halo-

ketone, is characteristic for each proton.[24] Δ is higher for H_3 than for H_4 and H_2 with isomers **1c** to **4c** and lower for H_2 than for H_3 and H_4 with isomers **1t** to **4t**. Values of Δ (in hertz) are given in Table V.

Likewise, for the determination of the configurations of dioxolanes we used the LIS effect of corresponding ketones. The configuration of dioxolanes **12t**, **12c**, **13t**, and **13c** was determined by the study of ketones **1t**, **1c**, **2t**, and **2c**. We assigned the configuration of dioxolanes **14c**, **14t**, **15c**, and **15t** by the evaluation of Δ for protons H_3 and H_4 in corresponding ketones (Table VI).

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Registry No.—Zinc, 7440-66-6.

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(19) With the exception of the *trans*-1-acetyl-2,2-dibromo-3-methylcyclopropane obtained from dioxolane O, which gave probably a substitution product after the reduction with incorporation of an ethoxy group in the isolated product of reaction.
(20) Crude materials, from dihalocyclopropanation, are used as starting dioxolanes because they are easily decomposed into their corresponding ketones by distillation or chromatographic isolation. However, their assay by analytical chromatography showed a satisfactory purity.
(21) With exceptions for O and especially Q, which are fully reduced into the cyclopropane derivatives with boiling ethanol.
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Side-Chain Inversion of Steroidal Olefins Promoted by Hydrogen Chloride

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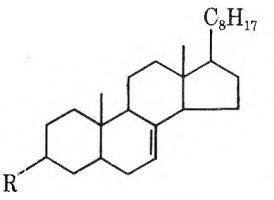
The reaction of hydrogen chloride on 7-, 8(14)-, and 14-ene steroids was investigated. A 14α-chloro compound is the product of kinetically controlled addition of the acid. A 14β-chloro compound with the side chain in the 17α configuration originates in diethyl ether at temperatures lower than −30 °C in the presence of hydrogen chloride, via a carbocation at C_{14}. There is evidence that the inversion occurs through two distinct rearrangements involving the intermediary formation of a 12,14α-cyclo-12,13-seco-5α-cholest-13(17)-ene.

In a previous communication[1] we reported that 3β-acetyloxy-5α-cholest-7-, -8(14)-, or -14-enes (**1a**, **2a**, and **3a**) undergo inversion of the side chain by the action of hydrogen chloride in diethyl ether at −60 °C to yield 3β-acetyloxy-14-chloro-5α,14β,17β*H*-cholestane (**4a**), possibly through the intermediary formation of 3β-acetyloxy-12,14α-cyclo-12,13-seco-5α-cholest-13(17)-ene (**5a**). Caspi et al.[2] simultaneously described the isolation of 3β-acetyloxy-5α,17β*H*-cholest-14-ene (**6a**) by the action, on **2a**, of hydrogen chloride in chloroform at −78 °C and prolonged treatment with $NaHCO_3$. More recently it has been shown that the same rearrangement is also caused by hydrogen bromide.[3]

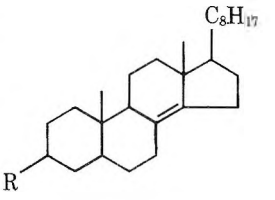
In order to clarify the mechanism of the side chain inversion, we decided to explore the processes involving the action of hydrogen chloride on 7-, 8(14)-, and 14-ene steroids.

Hydrogen chloride has long been considered to promote the direct isomerization of the 7 or 8(14) double bond of steroids to the 14 position.[4] In fact 14- and 8(14)-ene steroids in an approximately 1:1 ratio were isolated when the reaction was carried out at 0 °C in chloroform solution.[5] However Cornforth et al.,[6] operating at −30 °C on 3β-benzoyloxy-5α-cholest-8(14)-ene (**2b**), isolated a compound to which the structure of 3β-benzoyloxy-14α-chloro-5α-cholestane (**7a**) was attributed. When a chloroform solution containing this adduct was shaken with aqueous $NaHCO_3$, dehydrochlorination occurred and 3β-benzoyloxy-5α-cholest-14-ene (**3b**) was obtained.

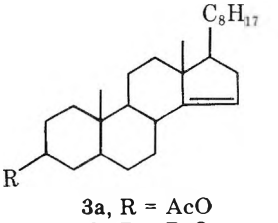
In order to definitively prove that the 14-ene (**3b**) is never formed by the direct action of hydrogen chloride on 8(14)-ene



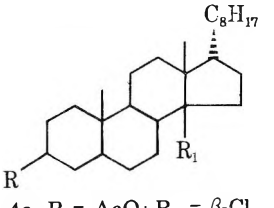
1a, R = AcO
b, R = BzO



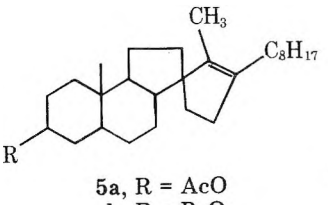
2a, R = AcO
b, R = BzO



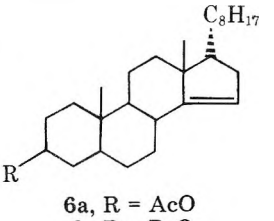
3a, R = AcO
b, R = BzO



4a, R = AcO; R_1 = β-Cl
b, R = BzO; R_1 = β-Cl
c, R = AcO; R_1 = β-H



5a, R = AcO
b, R = BzO



6a, R = AcO
b, R = BzO

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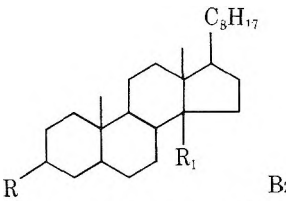
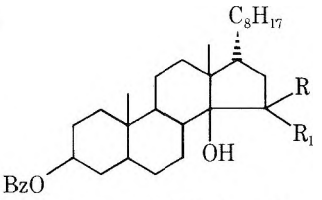
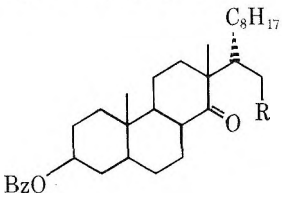


7a, R = BzO; R_1 = α-Cl
b, R = BzO; R_1 = β-Cl
c, R = AcO; R_1 = β-H

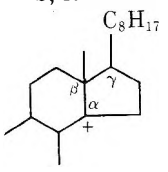


8a, R = 15β-OH; R_1 = H
b, R = R_1 = O

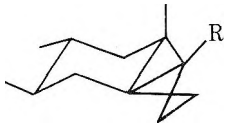


C_8H_{17} $C_8H_{17}{}^{17}CH{=}CH^{15}CHO$
10

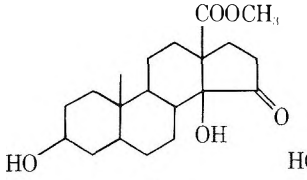
9a, R = CHO
b, R = COOH



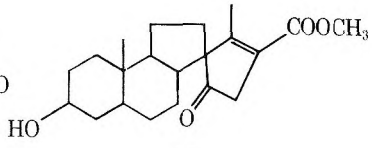
11



12



13



14

(**2b**), we submitted **3b** at −30 °C in chloroform to the action of hydrogen chloride. 7-Ene (**1b**) and 8(14)-ene (**2b**) were treated under the same conditions in separate experiments. In each case the ^1H NMR spectrum of the residue, obtained from the evaporation of the reaction mixture, did not show any signal attributable to olefinic protons. The only product isolated by crystallization was the chloro derivative, to which the structure **7a** is now assigned on the basis of ^1H NMR evidence. The mother liquors did not contain any 8(14) isomer. The ^1H NMR spectrum of **7a** shows a singlet for the C-18 protons at δ 0.92. The C-18 protons resonate at δ 1.18 in the 14β-chloro derivative **4b.** Since side-chain inversion from the 17α to the 17β configuration causes an upfield shift of 0.06 ppm as measured in 3β-acetyloxy-5α,14β-cholestane (**7c**)[7] and in 3β-acetyloxy-5α,14β,17β*H*-cholestane (**4c**),[2] a value of δ 1.12 is expected for the C-18 protons of the as yet unknown 3β-acetyloxy-14-chloro-5α,14β-cholestane (**7b**). Moreover the 0.27-ppm downfield shift for the C-18 protons of **7a,** with respect to the 14α-unsubstituted compound, compares well with the reported value of 0.25 ppm downfield shift for the C-19 protons of the 5α-chloro steroids.[8]

Solid **7a** was stable at room temperature for at least 1 year. It was rapidly transformed in chloroform solution at 25 °C (and more slowly at 0 °C) into **2b** and **3b** in a 1:4 ratio, both in the presence or absence of 0.5 M $NaHCO_3$, as determined by TLC on silica gel–$AgNO_3$.[9] **7a** was quantitatively transformed into **3b** by treatment with a 0.5 M methanolic solution of triethylamine. The high rate of solvolysis of **7a** is in good agreement with the postulated effect of strong steric strain in enhancing the rates of solvolysis of highly branched tertiary chlorides.[10-12] Formation of both **2b** and **3b** indicates that carbonium ion intermediates are involved in the reaction.

The electrophilic addition of hydrogen chloride to olefins has long been considered to involve intermediates with carbonium ion character.[13,14a] Moreover, there is evidence that the structure of the olefin plays a role in the reaction mechanism.[14b] The exclusive formation of a 14α-chloro derivative from 7-, 8(14)-, and 14-enes indicates that a common C-14 carbonium ion intermediate is involved in the reaction.

When the addition of hydrogen chloride was carried out in diethyl ether at −30, −60, or −78 °C for 3–7 h to 0.01-M solutions of **1b, 2b,** or **3b,** respectively, 3β-benzoyloxy-14-chloro-5α,14β-17β*H*-cholestane (**4b**) was quantitatively isolated.[15,16] **4b** was stable at 25 °C in chloroform or ether solution, as well as in the presence of 0.5 M $NaHCO_3$; it was quantitatively transformed into the epimerized 14-ene **6b** by triethylamine in methanol at 50 °C, and was solvolyzed in methanol at the same temperature to yield the compounds **6b** and **5b**[17] in 20:1 ratio as determined by GLC and TLC on silica gel–$AgNO_3$.

The epimerized 14-enes **6a** and **6b** were quantitatively reconverted into the 14β-chloro compounds **4a** and **4b** by addition, at −78 °C, of hydrogen chloride for few minutes, and transformed into the spiranic compounds **5a** and **5b** by treatment with 4-toluenesulfonic acid in boiling benzene.

The addition of hydrogen chloride to either **2b** or **3b** in diethyl ether at −78 °C for 20 min resulted in the quantitative formation of the 14α-chloride **7a,** which was quantitatively transformed into the epimerized 14β-chloro compound **4b** by further exposure to the hydrogen chloride.

These results prove that the epimerized 14-chloro compounds originate from the "natural" 14α-chloro compounds, the products of kinetically controlled addition of hydrogen chloride to an 8(14)- or a 14-ene steroid, and suggest that **7a** is transformed into **4b** via a discrete cationic intermediate.[14b] This was proven by submitting **7a** at −78 °C to hydrogen chloride enriched in ^3HCl. The labeled **4b** was dehydrochlorinated with triethylamine in methanol to give **6b,** showing a 25% loss of radioactivity associated to a hydrogen of the 15 position. The location of the residual radioactivity was ascertained as follows. The labeled **6b** was oxidized to the diol **8a** with OsO_4. The configuration of the 14β-OH (and by consequence of the 15β-OH) was assigned by measurement of the shift of the C-18 proton signal in the solvent pair deuteriochloroform–pyridine.[18] The observed value (0.16 ppm) was identical with that calculated for a dihedral angle of 60° between the C-18 methyl group and the 14β-hydroxy group. The labeled **8a** was oxidized with chromium trioxide to the hydroxy ketone **8b,** which contained 50% of the radioactivity of the labeled **4b,** thus proving that both the 15-hydrogens were labeled. The hydroxy ketone **8b** was oxidized with chromium trioxide to the keto acid **9b,** which contained 25% of the original radioactivity of **4b** after alkaline exchange at room temperature and rebenzoylation, thus indicating that 25% of the radioactivity of **4b** was associated with the 8-hydrogen. To locate the residual 25% of the radioactivity of **4b,** the compound **6b** was ozonized and the resulting keto aldehyde **9a** was pyrolyzed[6] to give the unsaturated aldehyde **10** (isolated as the semicarbazone) which contained 51% of the total radioactivity. The semicarbazone of the aldehyde **10** was degraded to the (*R*)(−)-2,6-dimethylheptanoic acid,[19] isolated as the amide,[20] which showed a complete loss of radioactivity. This fact indicated that the label in fragment **10** is located at the aldehydic hydrogen (25%) and at the 17-hydrogen (25%). Position 16 could be excluded, since at least part of the radioactivity in this position should be lost in the retro-Michael reaction on the keto aldehyde **9a.**

It can be concluded that, in the rearrangement of **7a** to **4b,** the discrete cation **11** should be formed. Moreover a hydrogen is lost from the 17α position and a hydrogen added at the 17β position.

Transformation of the cation **11** into the 14β-chloro compound **4b** requires inversion at the γ carbon to the charge. Intermediary formation of the very strained pentacyclic

compound 12 appears very unlikely, as both junctions of the cyclopropane ring are trans. A more reasonable hypothesis appears to be consistent with intermediary formation of the spiranic olefin **5b**. Some facts are in agreement with this assumption: (a) methyl 3β,14β-dihydroxy-15-oxo-5β,14β-androstane-17β-carboxylate (**13**) was transposed by thionyl chloride in pyridine into the spiranic compound **14**;[21] (b) the acetate **3a** was transformed in part into the spiro compound **5a** by boron trifluoride in benzene;[22] (c) spiro compounds such as **5** are formed by treatment of 7-, 8(14)-, and 14-ene steroids with 4-toluenesulfonic acid in refluxing benzene.[17] However, it seems unlikely that transposition is promoted by a classical, planar carbocation **11**, since there is no conformation of the molecule in which the C_{12}–C_{13} bond is aligned with the vacant p orbital at C_{14}, as it appears from molecular models. This assumption is supported by the evidence that the transposition of the 10β-methyl group of 5α-cholestane-4α,5α-diol 4α-acetate occurs owing to the alignment of the C_{10}–C_{19} bond with the vacant p orbital at C_5.[23] Moreover the presence of the label at the 8 and 15 position of **4b** proves that 8(14)- and 14-enes are reversibly formed during the transposition, which could occur by addition of hydrogen chloride to the Δ^{14} double bond by way of an Ad_E3 mechanism[14c] involving a transition state in which the chlorine atom of acid interacts with the β side of the carbocation. The interaction allows alignment of the C_{12}–C_{13} bond and promotes ring C contraction and formation of the spiro compound, with the loss of the 17α-hydrogen.

Final evidence of intermediary formation of the spiro compounds requires that the action of hydrogen chloride on these products should afford epimerized 14β-chloro compounds. In fact **5b** was instantaneously transformed into **4b** when dissolved at −78 °C in hydrogen chloride saturated ether. It can be inferred that a proton attacks **5b** at the 17β position, promoting ring C enlargement with final introduction of a chloride ion at the 14β position.

Experimental Section

All melting points are uncorrected. Infrared spectra were taken as Nujol mulls and absorptions are reported as reciprocal centimeters, NMR spectra were taken on a Varian HA-100 as chloroform-d_1 solutions and are reported as δ units relative to Me_4Si, and optical rotations were taken as chloroform solutions. Gas–liquid chromatography (GC) was done on 1 or 3% SE 30 columns (2 m × 2.5 mm). The mass spectra were determined on an LKB 9000 spectrometer either by GC (on 3% SE 30 column, 2 m × 2.5 mm) or by direct inlet (di). Radioactivity determinations were carried out as reported previously.[24] Molar radioactivity (MR) was expressed in nCi/nmol.

3β-Benzoyloxy-14-chloro-5α,14α-cholestane (7a). The benzoates **1b, 2b,** and **3b** in $CHCl_3$ were treated with HCl under the same conditions described by Cornforth[6] for **2b**. In each case the obtained solid white residue did not show any signal attributable to olefinic protons in the NMR spectrum at 0 °C. Crystallization of the residue from petroleum ether at −30 °C gave pure 3β-benzoyloxy-14-chloro-5α,14α-cholestane (**7a**): mp 157 °C (lit.[6] mp 153–156 °C); NMR (0 °C) δ 0.92 (s, C-13 Me), 0.83 (s, C-10 Me); mass spectrum (di) *m/e* 490 (M^+ − HCl), 475, 377, 255. Anal. Calcd for $C_{34}H_{51}O_2Cl$: C, 77.5; H, 9.7; Cl, 6.7. Found: C, 77.6; H, 9.9; Cl, 6.8.

7a was also obtained in 20 min by treating a 20–25 mM solution of **1a, 2a,** or **3a** in diethyl ether at −78 °C.

A solution of **7a** (100 mg) in $CHCl_3$ (10 mL) was left at 25 °C for 2 h, cooled at 0 °C, and washed with ice–water. The aqueous solution was titrated for Cl^- ions (calcd 6.7 mg, found 6.6 mg). After usual workup of organic solution, chromatography of the residue on silica gel G–Celite–$AgNO_3$ (1:1:0.3) yielded **2b** (18 mg) and **3b** (76 mg), whose physical constants (mp, GC, and mass spectrum) were identical with those of authentic specimens. Treatment of **7a** with 0.5 M methanolic triethylamine, after usual workup, afforded pure **3b** in quantitative yields.

3β-Benzoyloxy-14-chloro-5α,14β,17βH-cholestane (4b). In typical experiments the benzoates **1b, 2b,** and **3b** (500 mg) in diethyl ether (100 mL) were treated with HCl at −60 °C for 5 h. The pressure in the reaction vessel was then lowered to about 20 mm without interrupting the cooling. The residue was poured into ice water and extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and evaporated in vacuo to give solid 3β-benzoyloxy-14-chloro-5α,14β,17β*H*-cholestane (**4b**): mp 130–132 °C; NMR δ 1.18 (s, C-13 Me), 0.81 (s, C-10 Me); mass spectrum (di) *m/e* 490 (M^+ − HCl). Anal. Calcd for $C_{34}H_{51}O_2Cl$: C, 77.5; H, 9.7; Cl, 6.7. Found: C, 78.0; H, 9.5; Cl, 6.7.

3β-Benzoyloxy-5α,17βH-cholest-14-ene (6b). 3β-Benzoyloxy-14-chloro-5α,14β,17β*H*-cholestane (**4b**; 500 mg) in methanol (50 mL) and triethylamine (5 mL) was refluxed for 30 min. After usual workup, 3β-benzoyloxy-5α,17β*H*-cholest-14-ene (**6b**; 470 mg) was obtained as an oil. Crystallization from methanol gave pure **6b**: mp 67–70 °C; $[\alpha]^{21}_D$ +61.1°; NMR δ 5.08 (m, C-15 H), 1.09 (s, C-13 Me), 0.87 (s, C-10 Me); mass spectrum *m/e* 490 (M^+). Anal. Calcd for $C_{34}H_{50}O_2$: C, 83.2; H, 10.3. Found: C, 83.5; H, 10.2.

Radioactive 3β-Benzoyloxy-14-chloro-5α,14β,17βH-cholestane (4b). 3β-Benzoyloxy-14-chloro-5α,14α-cholestane (**7a**; 300 mg) in diethyl ether (60 mL) was treated at −78 °C with ^3HCl for 5 h. After usual workup **4b** was obtained by crystallization from petroleum ether (MR 156, unchanged after repeated crystallizations). Localization of radioactivity was determined after dilution of the product (1:9) with unlabeled **4b**.

Radioactive 3β-Benzoyloxy-5α,17βH-cholest-14-ene (6b). Radioactive **4b** (MR 15.6) was dehydrochlorinated as described above and tritiated **6b** was crystallized to constant radioactivity (MR 11.7; 75% of **4b**).

Radioactive 3β-Benzoyloxy-5α,17βH-cholestane-14α,15β-diol (8a). Osmium tetroxide (360 mg) was added to a solution of radioactive **6b** (500 mg) in diethyl ether (7 mL) containing pyridine (0.5 mL) and the mixture was allowed to stand at room temperature in the dark for 24 h. After usual workup, the diethyl ether–dichloromethane solution was shaken with potassium hydroxide (1.5 g) and D-mannitol (1.5 g) in water (15 mL). The product was isolated with the usual washing and drying procedures. Crystallization from MeOH gave 430 mg of radioactive 3β-benzoyloxy-5α,17β*H*-cholestane-14β,15β-diol (**8a**): mp 173–174 °C; $[\alpha]^{21}_D$ −11°; NMR ($CDCl_3$) δ 4.28 (m, 15α-H), 1.07 (s, C-13 Me), 0.77 (s, C-10 Me); NMR (pyridine-d_5) δ 4.4 (m, 15α-H), 1.23 (s, C-13 Me), 0.81 (s, C-10 Me); mass spectrum (di) *m/e* 506 (M^+ − 18), 354, 216; MR 11.7. Anal. Calcd for $C_{34}H_{52}O_4$: C, 77.8; H, 10.0. Found: C, 77.5; H, 9.8.

Radioactive 3β-Benzoyloxy-14-hydroxy-5α,14β,17βH-cholestan-15-one (8b). Compound **8a** (300 mg) in pyridine (0.5 mL) was added at 0 °C to a solution of chromium trioxide (300 mg) in pyridine (3 mL) and dichloromethane (12 mL) and the mixture was stirred for 5 min. After usual workup and crystallization of the crude residue from methanol, radioactive **8b** was obtained: mp 135–137 °C; mass spectrum *m/e* (di) 522 (M^+); IR 3310, 1740, 1720 cm^{-1}; MR 7.8 (50% of **4b**). Anal. Calcd for $C_{34}H_{50}O_4$: C, 78.1; H, 9.6. Found: C, 78.3; H, 9.4.

Radioactive 3β-Benzoyloxy-14-oxo-14,15-seco-5α,17βH-cholestan-15-oic acid (9b). Chromium oxide (56 mg) in acetic acid (2.8 mL) was added at 0 °C to a solution of radioactive **8b** (200 mg) in acetic acid (8 mL) and benzene (1 mL). The mixture was allowed to stand at room temperature for 2 h. After usual workup and crystallization of the residue from isooctane–diethyl ether, radioactive **9b** was obtained: mp 159–161 °C; $[\alpha]^{25}_D$ −33°; mass spectrum (di) *m/e* 520 (M^+ − 18), 354 (M^+ −184); IR 1740, 1710 cm^{-1}; MR 7.8 (50% of **4b**). Anal. Calcd for $C_{34}H_{50}O_5$: C, 75.8; H, 9.3. Found: C, 75.5; H, 9.4. Me ester, mass spectrum (di) *m/e* 521 (M^+ − 31), 479 (M^+ − 73), 354 (M^+ − 196). Acid **9b** after saponification at 25 °C and rebenzoylation showed MR 3.9 (25% of **4b**).

Radioactive 3β-Benzoyloxy-14-oxo-14,15-seco-17βH-cholestan-15-al (9a) and its Pyrolysis. A solution of labeled **6b** (300 mg) in dichloromethane (5 mL) was ozonized at −70 °C until excess ozone was present. The solvent was removed and the residue was stirred for 2 h with acetic acid (7 mL) and Zn powder (0.5 g). After usual workup oily compound **9a** was obtained: IR 2700, 1720, 1714 cm^{-1}; NMR δ 9.67 (H_{15}, t, J = 1.5 Hz); mass spectrum *m/e* 522 (M^+), 354 (M^+ − 168). The keto aldehyde (**9a**) was heated at 15-mm pressure (capillary leak fed with N_2) to 200 °C; the temperature was raised during 2 h to 250 °C and maintained there for 3 h. The volatile product, trapped in a receiver at −30 °C, was taken up in a little diethyl ether and washed with $NaHCO_3$ solution. The solvent was removed to give the crude aldehyde **10**. This was transformed in its semicarbazone: mp 134 °C; $[\alpha]^{21}_D$ −23°; mass spectrum *m/e* 225 (M^+); MR 7.7 (49% of **4b**). Anal. Calcd for $C_{12}H_{23}N_3O$: C, 64.0; H, 10.2; N, 18.7. Found: C, 64.3; H, 9.8; N, 18.4.

(*R*)(−)-2,6-Dimethylheptanoic Acid Amide. Potassium permanganate was added to a boiling acetone solution of the semicarbazone of the unsaturated aldehyde **10**. After usual workup the acid fraction was treated with thionyl chloride. The resulting acid chloride

gave the amide, which was crystallized from *n*-hexane to yield the pure product: mp 75–77 °C;[20] MR 0.0.

3β-Benzoyloxy-12,14α-cyclo-12,13-seco-5α-cholest-13(17)-ene (5b). Compound **6b** (500 mg) was added to a mixture of anhydrous 4-toluenesulfonic acid (250 mg) and benzene (125 mL) and refluxed for 5 min. After usual workup the crude residue was chromatographed on silica gel G–Celite–$AgNO_3$ (1:1:0.3). Fractions eluted with petroleum ether gave **5b** (400 mg): oil; NMR δ 1.46 (t, J = 0.7 Hz, C-13 Me), 0.93 (d, J = 7 Hz, C-20 Me), 0.84 (d, J = 6 Hz, C-25 Me_2), 0.8 (s, C-10 Me); mass spectrum (di) *m/e* 490 (M^+), 206, 121. Anal. Calcd for $C_{34}H_{50}O_2$: C, 83.2; H, 10.3. Found: C, 83.4; H, 10.0.

Treatment of 3β-Benzoyloxy-12,14α-cyclo-12,13-seco-5α-cholest-13(17)-ene (5b) with Hydrogen Chloride. The spiro olefin (**5b**;[17] 200 mg) was dissolved in hydrogen chloride saturated ether (20 mL) at −78 °C. The solution was poured instantaneously into a $NaHCO_3$ saturated solution and extracted with diethyl ether; the organic layer was dried (Na_2SO_4) and evaporated in vacuo to give 3β-benzoyloxy-14-chloro-5α,14β,17β*H*-cholestane (**4b**).

Acknowledgments. This research was supported by the Italian Research Council. We thank Professor G. Galli, Institute of Pharmacology and Pharmacognosy, University of Milan, for mass spectra.

Registry No.—**1a**, 2465-00-1; **1b**, 4356-22-3; **2a**, 6562-21-6; **2b**, 6673-65-0; **3a**, 40446-06-8; **3b**, 6673-66-1; **4b**, 66792-81-2; **5b**, 66792-87-8; **6b**, 66808-37-5; **7a**, 66808-38-6; **8a**, 66792-86-7; **8b**, 66792-85-6; **9a**, 66792-84-5; **9b**, 66792-83-4; **9b** methyl ester, 66792-82-3; **10**, 66792-88-9; **10** semicarbazone, 66792-89-0; (*R*)(−)-2,6-dimethylheptanamide, 66792-90-3.

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(15) The same reaction was carried out on the corresponding acetates with the same results already described. See ref 1.
(16) When the addition was carried out in chloroform on the same compounds, a high yield of **4a** or **4b**, respectively, was obtained only below −50 °C.
(17) M. Anastasia, A. Manzocchi Soave, and A. Scala, *J. Chem. Soc., Perkin Trans. 1*, in press.
(18) B. P. Hatton, C. C. Howard, and R. A. W. Johnstone, *J. Chem. Soc., Chem. Commun.*, 744 (1973).
(19) D. Arigoni and C. Jeger, *Helv. Chim. Acta*, **37**, 881 (1954).
(20) F. Koegl and A. G. Boer, *Recl. Trav. Chim. Pays-Bas*, **54**, 772 (1935).
(21) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **45**, 943 (1962).
(22) H. Izawa, Y. Kataoda, Y. Sakamoto, and Y. Sato. *Tetrahedron Lett.*, 2947 (1969).
(23) E. T. J. Bathurst, J. M. Coxon, and M. P. Hartshorn. *Aust. J. Chem.*, **27**, 1505 (1974).
(24) A. Fiecchi, M. Galli Kienle, A. Scala, G. Galli, R. Paoletti, and E. G. Paoletti, *J. Biol. Chem.*, **247**, 5898 (1972).

Importance of the Structure of the Phosphorus Functionality in Allowing Dihedral Angle Control of Vicinal ^{13}C–^{31}P Coupling. Carbon-13 NMR Spectra of 7-Substituted Bicyclo[2.2.1]heptane Derivatives[1]

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Carbon-13 NMR spectra were obtained on norbornenes with the 7 position bearing the following substituents: Cl_2P (syn and anti), Me_2P (syn and anti), $Me_2(S)P$ (anti), Me_3P^+ (anti). Norbornanes with 7-Cl_2P and 7-Me_2P were also studied. For the groups $Me_2(S)P$ and Me_3P^+, vicinal C–P coupling was clearly controlled by dihedral angle relations; carbons anti to P were strongly coupled (about 16 Hz), while carbons syn to P showed no coupling. This result is consistent with observations made previously for rigid cyclohexanes bearing these substituents in equatorial or axial positions, respectively. However, the trivalent groups Cl_2P and Me_2P showed no indication of their vicinal coupling (absolute), being minimized at the same dihedral angle; with these groups in either the syn or anti 7 position of norbornene or in the 7 position of norbornane, coupling to the two sets of vicinal carbons differed very little. Again this result is consistent with observations from cyclohexanes and leads to the conclusion that dihedral angle control of vicinal (C–P) coupling is not general in phosphorus chemistry. One-bond ^{13}C–^{31}P coupling was also considered; there was no consistent relation with steric crowding in the compounds studied. Chemical shifts of the phosphorus compounds followed the expected trends, with γ-gauche carbons shifted relatively upfield and anti carbons relatively downfield from the corresponding bicyclo[2.2.1]heptane. Curiously, in *syn*-7-bromonorbornene both types of γ carbon were shifted upfield.

From a study[2] of the effect of phosphorus functions on the ^{13}C NMR spectra of the cyclohexane ring came an indication that three-bond ^{13}C–^{31}P coupling was under steric control in a Karplus-like relation for tetravalent phosphorus functions (e.g., $Me_2(S)P$ and Me_3P^+) but not for some trivalent functions (e.g., Cl_2P and Me_2P). To illustrate, ^{31}P coupling to ring carbons 3 and 5 was 13 Hz when $Me_2(S)P$ was placed in the equatorial position of 4-*tert*-butylcyclohexane (dihedral angle about 180°), but only 4 Hz when in the axial position (dihedral angle about 60°), strongly suggestive of a Karplus effect. On the other hand, Cl_2P similarly placed gave $^3J_{PC}$ values of 11 and 9 Hz, respectively, and Me_2P gave values of 11 and 8 Hz. However, uncertainty about dihedral angles in the axially substituted cyclohexanes, which might be capable of distortion to skew-boat conformations, left the situation unclear. We also[3] encountered cases among some phosphorinane derivatives (**1**–**4**) where a dihedral angle control of vicinal coupling was suggested. Thus, two $^3J_{PC}$ path-

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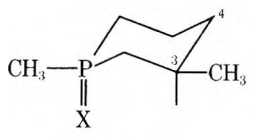
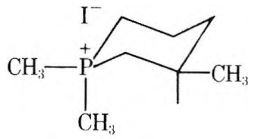
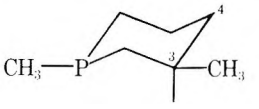
ways exist in 3-methyl derivatives, but that to the ring carbon (C-4) is mediated by a small dihedral angle (60° for an ideal chair) while that to CH_3 by a large angle (180°). In compounds **1**, **2**, and **3**, $^3J_{PC}$ was small (6–7 Hz) for C-4 and large for CH_3



1, X = O
2, X = S



3

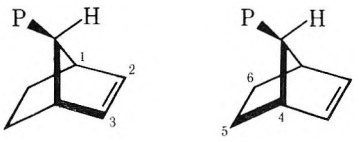


4

(16–18 Hz). In this series, the phosphine (**4**) also showed an apparent steric dependence for coupling (~0 Hz to C-4 and 5 Hz to CH_3).

We have now prepared a group of 7-substituted bicyclo[2.2.1]heptane derivatives partly to clarify this apparent inconsistency of steric control of ^{13}C–^{31}P coupling. This ring system is characterized by considerable rigidity and thus dihedral angles can be reasonably evaluated. In this paper, we will show unequivocally that the covalent character of the phosphorus atom does indeed have a commanding influence in allowing a normal Karplus relation to exist. These bicyclic compounds have other ^{13}C NMR spectral features of interest, and their ^{31}P NMR spectra, which are reported elsewhere,[4] are also of significance.

A sizable literature is developing on the existence of Karplus-like relations between $^3J_{PC}$ and dihedral angle. Such relations seem well established for phosphine oxides[5] and phosphonates.[6] However, our own previous studies[2,3] appear to be the only ones concerned with phosphine sulfides and phosphonium salts, as well as with trivalent functions. 7-Substituted bicyclo[2.2.1]heptane derivatives are of value in such studies because two different coupling paths with widely divergent dihedral angles are present, as shown below for the unsaturated system:

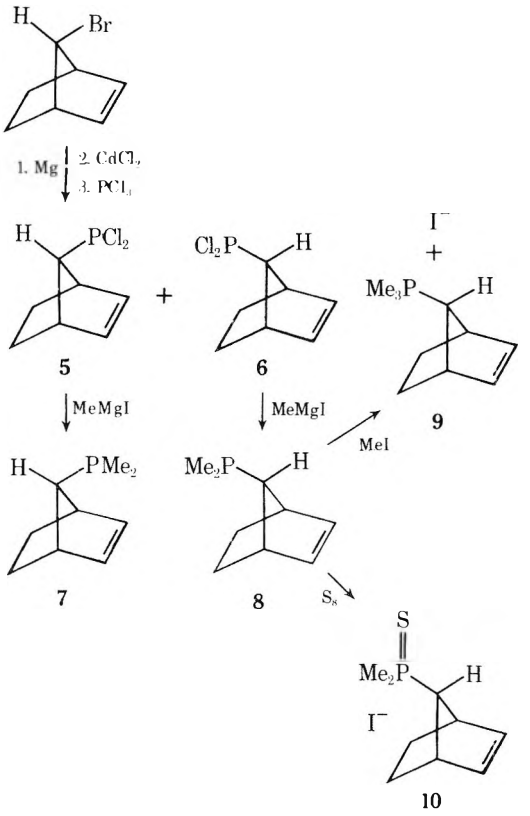


Dihedral angles are known[7] from X-ray analysis of *anti*-7-norbornenyl *p*-bromobenzoate to be 164° for PCCC-3 and 57° for PCCC-5. Angles in solution cannot deviate much from these values. Therefore, $^3J_{PC}$ should differ drastically to C-2,3 or C-5,6 if a normal Karplus relation prevails. The same effects would, of course, be present in *syn*-7-norbornene derivatives, and for norbornanes as well. Examples of each ring type are included in the present study.

Synthesis. The starting compound for all of our synthetic work was *syn*-7-bromonorbornene, which was prepared by the method of Kwart and Kaplan.[8] The Grignard reagent from this bromide was converted to the cadmium derivative[9] for alkylation of PCl_3. This reaction gave a low yield (16%) of a mixture of *syn*-7- (**5**, 20%) and *anti*-7-norbornenylphosphonous dichloride (**6**, 80%). The mixture was not separated but was used directly in the next reaction, that with methylmagnesium iodide (Scheme I). The mixture of phosphines **7** and **8** was then reacted with methyl iodide or sulfur. The products after purification were further enriched in the anti structures (**9** and **10**, respectively) and it was not possible to observe definite spectra for the minor isomers.

That the major isomer from the alkylation of PCl_3 had the anti structure was readily apparent from the ^{13}C NMR spectrum. This spectrum will be discussed in detail subsequently, where it will be seen that the steric crowding of Cl_2P with the syn methylenes (C-5,6) caused their ^{13}C shifts to be substantially upfield of the minor isomer. Other reactions (e.g., carbonation[10]) of Grignard reagents derived from 7-halonorbornenes likewise give mostly anti products.

Scheme I



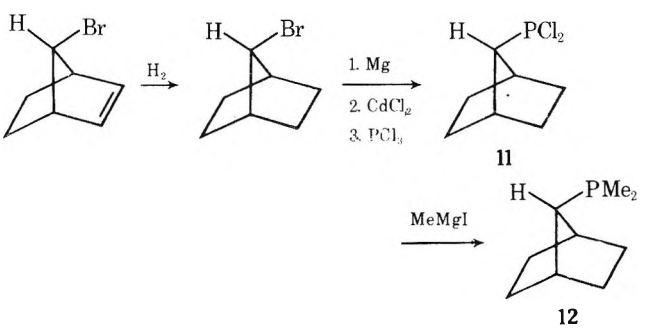
10

Hydrogenation of *syn*-7-bromonorbornene gave 7-bromonorbornane,[8] and this was converted to the phosphonous dichloride **11** and the phosphine **12** (Scheme II). The last reaction gave a product containing small but spectrally significant amounts of other products which were not easily removed by distillation. Usable spectral data for **12** nevertheless were collected on this crude product.

^{13}C NMR Spectra of 7-Substituted Norbornenes. Since the synthetic method led, as already noted, to considerably more of the anti isomers (**6**, **8**, **9**, **10**) than of the syn, spectral data were more readily collected for the anti series of compounds, and they form the basis of most of the ^{13}C NMR study. Assignment of peaks in the spectra of both anti and syn isomers was straightforward and requires no comment. Data appear in Table I.

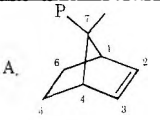
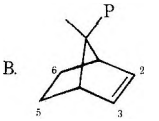
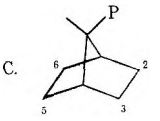
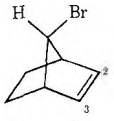
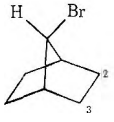
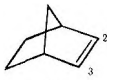
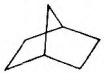
The data reveal in a striking way that a Karplus relation is most definitely in effect in the case of the phosphine sulfide (**10**) and the phosphonium salt (**9**). The $^3J_{PC}$ values to C-2,3, where the dihedral angles are large (164°[7]), are 15.9 and 16.5

Scheme II



12

Table I. ^{13}C NMR Spectral Data

	registry no.	C-1,4	C-2,3	C-5,6	C-7	P-CH_3
			P =			
			A. 			
Cl_2P	66793-02-0	44.0 (14.6)	136.6 (6.2)	22.1 (9.7)	71.2 (47.6)	
Me_2P	66793-03-1	44.1 (11.0)	137.3 (6.1)	22.8 (8.6)	64.5 (12.2)	13.1 (12.8)
$Me_2(S)P$	66793-04-2	43.7 (0)	138.5 (15.9)	22.8 (0)	58.6 (44.6)	21.8 (54.3)
$Me_3P^+(I)$	66793-05-3	43.5 (0)	137.7 (16.5)	23.8 (0)	52.5 (40.9)	10.2 (53.1)
			B. 			
Cl_2P	66793-06-4	*a*	134.8 (6.7)	25.5 (<1)	76.7 (40.3)	
Me_2P	66793-07-5	*a*	133.9 (3.7)	24.3 (2.6)	66.8 (6.1)	14.2 (12.6)
			C. 			
Cl_2P	66793-08-6	42.2 (13.4)	27.5 (10.4)	31.5 (6.1)	65.4 (45.8)	
Me_2P	66793-09-7	39.4 (12)	27.6 (10)	31.7 (7)	54.9 (11)	17.1 (14)
			D. Miscellaneous			
	20047-65-8	44.3	132.8	22.7	66.0	
	13237-88-2	42.8	27.5	27.5	58.5	
		41.8[b]	135.2[b]	24.6[b]	48.5[b]	
		36.1[b]	29.6[b]	29.6[b]	38.3[b]	

[a] Not clearly observed on spectrum. [b] Data of J. B. Stothers, C. T. Tan, and K. C. Teo, *Can. J. Chem.*, **51**, 2893 (1973).

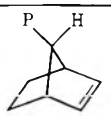
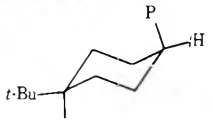
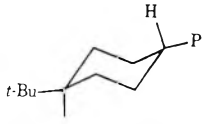
Hz, respectively, which are quite close to those reported[2] for equatorial substitution on the cyclohexane ring. On the other hand, no ^{31}P coupling was observed for C-5,6, where the dihedral angle should be about 57°.[7] This is near the angle (65°) of minimum coupling reported[11] for three-bond ^{13}C–^{13}C coupling in carboxylic acids in rigid systems. These results therefore provide confirmation of a small dihedral angle in the 1-axially substituted 4-*tert*-butylcyclohexanes where $^3J_{PC}$ is only about 4 Hz. This is a conformationally significant point, for it shows that the chair shape is largely retained in these cyclohexanes and that a skew-boat conformation, which would have quite large dihedral angles to C-3,5 (153–169°[2]), is not adopted.

The trivalent phosphorus functions Cl_2P and Me_2P, on the other hand, show no semblance of a normal Karplus relation. Coupling to C-5,6, which should be minimal in such a relation, is even larger than that to C-2,3. This, of course, confirms the observation made previously for these groups as substituents on cyclohexanes[2] and results in the conclusion that the nature of the phosphorus functionality does play a controlling role in determining if stereodependence of three-bond coupling will prevail. Stereodependence of two-bond coupling is also determined by the phosphorus function,[12] but here no strong relation exists for the tetracovalent functions of phosphorus, and it is the trivalent state that exhibits the steric control. Also, a recent observation of two substantially different $^3J_{PC}$ values for 1,6-diphosphatriptycene, where the dihedral angles involved are the same, suggests that an influence on ^3J may arise from orientation of the lone pair orbital.[13]

The two trivalent derivatives in the syn series (**5** and **7**) show the same absence of a minimum for $^3J_{PC}$ to the carbon(5,6) related by small dihedral angle, thus establishing that the situation holds for both sp^3 and sp^2 carbon. (It will be seen in the next section that the norbornyl derivatives also fail to have the Karplus minimum.)

Chemical shift differences in an isomer pair at the carbons γ oriented to phosphorus were of immediate value in assigning their structures. Thus, it is known[14] from studies of other 7-substituted norbornenes that relative to norbornene itself the 1,3-interactions between a 7-substituent syn to a CH_2 group (C-5,6) cause these ring carbons to be upfield shifted. The same effect is observed for the other isomer but at the sp^2 carbons. Such upfield shifts, routinely observed for carbons with a γ-gauche oriented substituent, have commonly been explained by the operation of steric compression, although the effect is not yet fully understood and may have a more complex origin.[15] Indeed, upfield shifts of a smaller magnitude are sometimes experienced for carbon in the γ-antiperiplanar

Table II. Comparison of α Effects and $^1J_{PC}$ for Phosphorus Compounds[a]

	Cl_2P		Me_2P		$Me_2(S)P$		Me_3P^+	
	α	^1J	α	^1J	α	^1J	α	^1J
	22.7	47.6	16.0	12.2	10.1	44.6	4.0	40.9
	21.6	44	12.3	10	9.0	51	1.5	48
	20.7	45	11.6	9	13.5	53	4.4	51
$CH_3CH_2CH_2CH_2P$	29.7	44	19.4	12	21.4	54		

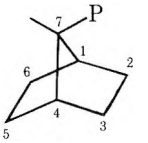
[a] Cyclohexyl data of ref 2 are used; the α effect was determined by subtracting the value for cyclohexane (δ 27.7) from the C-1 chemical shifts. Butyl data are given in ref 17.

relation.[16] The operation of the γ-gauche interaction in the isomeric phosphonous dichlorides **5** and **6**, and in their corresponding dimethyl derivatives **7** and **8**, is clearly evident, and allows the assignment of their structure. For one dichloride and its dimethyl derivative, C-5,6 are upfield by about 2 ppm of the value for norbornene, and these compounds are assigned the anti structures **6** and **8**, respectively. For the other pair, it is C-2,3 which are upfield shifted, and these compounds are assigned the syn structures **5** and **7**. Support for these assignments comes from the chemical shifts of C-7; the 1,3 interaction between the C-7 substituent and the CH_2 groups of the anti isomers is greater than that involving the sp^2 carbon of the syn isomers, and the C-7 chemical shifts for the anti isomers are considerably upfield of the syn isomers (Cl_2P, 5.5 ppm; Me_2P 2.3 ppm). Coupling information also is applicable to the structure assignments. As already noted, the three-bond P–C coupling in the sulfide (**10**) and the salt (**9**) is dependent on the dihedral angle, and only the anti assignment to these compounds allows the Karplus-like relation expected from the earlier cyclohexane studies[2] to prevail.

The phosphorus substituents give the expected downfield shifts at C-7 relative to norbornene. These α effects were of very similar magnitude to those seen for substitution on cyclohexane.[2] The one-bond ^{13}C–^{31}P coupling was also similar, in spite of the fact that the hybridization at C-7 of the bicyclic compounds differs from that of a cyclohexane carbon. More s character is diverted into the exocyclic bonds of the bicyclics to allow for the contraction of the internal bond (C_1–C_7–C_4 is 96° in *anti*-7-norbornenyl *p*-bromobenzoate[7]), but there is no clear trend in the data to show relevance to P–C coupling. Thus, in the anti series, the two trivalent groups have slightly enhanced J_{PC} values, as would be expected from increased s character, but the tetravalent functions had slightly smaller values. Inconsistencies also were present when an open-chain model[17] was used for comparison. Data that illustrate these divergencies are collected in Table II. The absence of a clear relation between ring strain and ^{13}C–^{13}C coupling has also been noted for COOH bonded to various strained cyclic carbons.[11]

For the two phosphorus compounds in the syn series, values for $^1J_{PC}$ are smaller by several hertz than they are in the anti series. Recent reports[6b,6c,18] have noted that $^1J_{PC}$ for phosphonates is slightly smaller in sterically congested structures, but in the trivalent phosphorus derivatives of the norbornenes (and in the cyclohexanes as well; see Table II), the opposite is seen to be true, since steric crowding is obviously smaller in the syn than in the anti series. It is therefore premature to draw any broad conclusions about the influence of steric congestion on the magnitude of $^1J_{PC}$. Thus, a proposal[19] that bond angles increase to relieve steric congestion, and that this angle effect is to be associated with increased $^1J_{PC}$, must be viewed with caution, for it is not a general phenomenon.

^{13}C NMR Spectra of the 7-Norbornyl System. The two



11, P = Cl_2P
12, P = Me_2P

norbornyl derivatives **11** and **12** gave ^{13}C NMR spectra that were easily assigned (Table I). The steric crowding of C-2,3 caused these carbons to resonate several ppm to higher field than comparable carbons in norbornane (for **11**, 2.1; for **12**, 2.0 ppm). This has been observed for 7-COOH[11] and 7-CH_3[14] norbornanes. Also seen in these latter two compounds is a downfield shift for C-5,6 (1.4 and 2.1 ppm, respectively) relative to norbornane, and this effect is reproduced in the phosphorus compounds ([[= [/9: [2= 2/[PPM(/ The net effect is to create for these compounds a considerable difference between CH_2 groups syn and anti to the 7-substituent. There are exceptions to this situation, however; it has been reported that 7-OH causes upfield shifts of equal magnitude at both C-2,3 and C-5,6,[20] and we have found that this is true also for 7-bromonorbornane.[21] This curious effect was also noted in our work with *syn*-7-bromonorbornene; both the crowded sp^2 carbons as well as the uncrowded CH_2 groups were shielded (2.4 and 1.9 ppm, respectively) relative to norbornene, whereas for *syn*-7-methylnorbornene[14] and the two phosphorus compounds **5** and **7**, deshielding occurs at the CH_2 groups. There is obviously a danger in assuming for the 7-substituted bicyclo[2.2.1]heptane system that the usual consistency in the direction of substituent effects prevails without exception.

The expectation that $^3J_{PC}$ for **11** and **12** would fail to show minima in the usual Karplus region was realized. In fact, for both compounds the value for $^3J_{PC\text{-}5,6}$, where the dihedral angle is large, was considerably smaller than that for $^3J_{PC\text{-}2,3}$. These two compounds are important to our argument that the trivalent groups Cl_2P and Me_2P (and possibly others) are not generally to be associated with the usual Karplus control of $^3J_{PC}$; here both coupling pathways are to carbons of sp^3 hybridization, whereas our previous examples depended on structures with mixed sp^2 and sp^3 carbons. It is possible that a minimum in the absolute three-bond coupling occurs at

some quite different dihedral angle than is encountered for the tetravalent functions. At present, however, no experimental data are available that bear on this point.

Finally, we emphasize that only absolute values for $^3J_{PC}$, as obtained in the routine practice of NMR spectroscopy, are considered in this paper; sign determinations have not been made. However, it seems quite unlikely for a sign difference to exist for a pair of syn and anti (or cis and trans[2]) isomers that have nearly the same absolute values for ^3J, and for the present we are ignoring a sign change as a possible explanation for the apparent absence of a Karplus minimum in the absolute values for the trivalent derivatives. Nevertheless, while very little work has been done on the signs of three-bond C–P coupling, it is known that in phosphines the sign may be either positive (in aromatic derivatives[13,22]) or negative (in acetylenic derivatives[23]). In the study of acetylenic compounds,[23] it was noted that the sign for the tetravalent derivatives was the opposite of that for the trivalent derivatives and that for the two types of phosphorus functions different degrees of importance had to be attributed to the several factors usually considered in the coupling mechanism (Fermi contact, spin dipolar, and orbital terms). A difference in coupling mechanism would seem to offer a possible explanation for the variability in dihedral angle control of $^3J_{PC}$ as noted in the present study.

Experimental Section

General. Proton-decoupled Fourier transform ^{13}C NMR spectra were obtained with a JEOL FX-60 Spectrometer at 15 MHz. All samples were run in $CDCl_3$ solution. Analyses were performed by MHW Laboratories, Garden City, Mich. All reactions involving phosphorus compounds were conducted under nitrogen. Melting points are corrected; boiling points are uncorrected.

***syn*-7-Bromonorbornene.** This compound was prepared by the procedure of Kwart and Kaplan,[8] which involves first the addition of bromine to norbornene to form 2,7-dibromonorbornene, and then dehydrohalogenation with potassium *tert*-butoxide. The product had bp 42 °C (3.2 mm) (lit.[8] bp 68–70 °C (13 mm). Its ^{13}C NMR spectrum is given in Table I.

7-Norbornenylphosphonous Dichloride (*syn*- 5 and *anti*-6). The Grignard reagent was prepared from 4.86 g (0.20 mol) of magnesium and 17.3 g (0.10 mol) of *syn*-7-bromonorbornene in 100 mL of anhydrous ether. The reaction was initiated with methyl iodide. To the refluxing dark solution was added 18.3 g (0.10 mol) of cadmium chloride (dried at 110 °C) in small portions from a reservoir attached by Gooch tubing. The mixture was cooled to room temperature and the precipitate of metallic halides removed by filtration in a nitrogen atmosphere. The filtrate containing the organocadmium reagent was added dropwise to a solution of 27.0 g (0.20 mol) of phosphorus trichloride in 500 mL of anhydrous ether at −78 °C. A voluminous precipitate formed and was removed by filtration under nitrogen after the mixture was warmed to room temperature. The mixture was distilled through a short Vigreaux column and the fraction boiling at 75–78 °C (3 mm) was collected as product (2.3 g, 16.4%). The ^{31}P NMR spectrum, to be discussed in detail elsewhere,[4] had signals for the anti isomer (**6**) at δ +190.9 (80%) and the syn (**5**) at δ +199.7 (20%). The ^{13}C NMR spectrum is given in Table I. The ^1H NMR ($CDCl_3$) spectrum only showed separate signals for the isomers in the vinyl region (anti, δ 6.2 (m, 79%); syn, δ 6.1 (m, 21%)); others were δ 1.2 (m, 2 H, *endo*-H-5,6), 1.8 (m, 2 H, *exo*-H-5,6), 2.6 (m, 1 H, H-7), 3.5 (m, 2 H, H-1,4).

Dimethyl(7-norbornenyl)phosphine (*syn*-7, and *anti*-8) and Methiodide (9). A mixture of phosphonous dichlorides 5 and 6 (14.4 g, 0.078 mol) was added dropwise to the Grignard reagent prepared from 6.08 g (0.25 mol) of magnesium turnings and 35.3 g (0.25 mol) of methyl iodide in 300 mL of ether. Gentle reflux was permitted. At the end of the reaction, a saturated solution of ammonium chloride was added. Layers were then separated and the ether layer was dried ($MgSO_4$). Distillation left an oil that was fractionated with a Vigreaux column. After three distillations, the fraction (2.4 g, 20%) of bp 48–52 °C (2.5 mm) was taken as product. The ^{13}C NMR spectrum (Table I) showed that the anti isomer accounted for about 80% of the product. Analysis was performed on the methiodide (**9**), prepared in benzene solution and recrystallized from benzene–chloroform, mp 270–273 °C dec. The ^{13}C NMR spectrum of **9** is given in Table I. The only signal attributable to the syn isomer was that of the methyl carbon (δ 12.5 ($^1J_{PC}$ = 53.7 Hz)). The analysis of **9** follows.

Anal. Calcd for $C_{10}H_{18}IP$: C, 40.54; H, 6.08. Found: C, 40.30; H, 6.06.

Dimethyl(*anti*-7-norbornenyl)phosphine Sulfide (10). A mixture of 2.8 g (0.018 mol) of phosphine 8 prepared as above and 3.0 g of sulfur in 200 mL of benzene was refluxed for 4 h. The mixture was cooled to room temperature and excess sulfur was removed by filtration. After four recrystallizations from ethanol–water, the product (**10**) had mp 133–135 °C. The ^{13}C NMR spectrum obtained on this sample was only that of the anti isomer; ^{31}P NMR analysis[4] did reveal that a few percent of the syn isomer was still present.

Anal. Calcd for $C_9H_{15}PS$: C, 58.06; H, 8.06. Found: C, 57.89; H, 8.26.

7-Bromonorbornane. *Syn*-7-bromonorbornene was hydrogenated as first described by Kwart and Kaplan,[8] using a PtO_2 catalyst at 50 psi. Occasionally hydrogen uptake was incomplete; the sample was distilled and again subjected to the hydrogenation. The product had bp 40 °C (3 mm) (lit.[8] bp 70–72.5 °C (15 mm)); its ^{13}C NMR spectrum is recorded in Table I.

7-Norbornylphosphonous Dichloride (11). The Grignard reagent was prepared from 35.0 g (0.20 mol) of 7-bromonorbornane and 4.86 g (0.20 mol) of magnesium turnings in 200 mL of ether. Initiation of the reaction by methyl iodide was required. The cadmium reagent was then prepared by the slow addition, at reflux, of 18.3 g (0.10 mol) of anhydrous cadmium chloride. The solution from removal of precipitated metallic halides was added to a solution of 54 g (0.39 mol) of phosphorus trichloride in 300 mL of ether at −78 °C. After solids had been removed by filtration, the solution was fractionally distilled (Vigreaux column) twice and the product (**11**) collected at 80–85 °C (4.0 mm), yield 12.7 g (32%). The ^{13}C NMR spectrum is given in Table I.

Dimethyl(7-norbornyl)phosphine (12). To the Grignard reagent prepared from methyl iodide (21.3 g, 0.15 mol) and 3.63 g (0.15 mol) of magnesium in ether was added 10.0 g (0.05 mol) of 7-norbornylphosphonous dichloride (**11**). After addition of saturated ammonium chloride solution, layers were separated; the ether layer was dried ($MgSO_4$) and distilled. Product (**12**) was collected at 48–52 °C (2.5 mm), yield 6.3 g. The sample was difficult to purify; its ^{13}C NMR spectrum was obtained on the crude product (Table I).

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Solid-State Studies on Crowded Molecules. Crystal and Molecular Structures of 2,2,3-Trimethyl-1-phenylphosphetane 1-Oxide[1a] and 2,2,3,3,4-Pentamethyl-1-phenylphosphetane 1-Oxide[1b]

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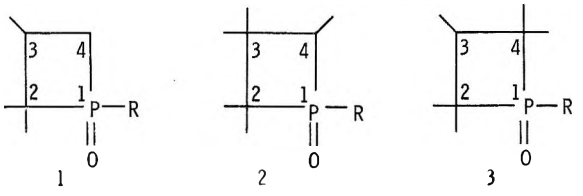
The crystal and molecular structures of the two unsymmetrically substituted phosphetane oxides, 2,2,3-trimethyl-1-phenylphosphetane 1-oxide (TPO) and 2,2,3,3,4-pentamethyl-1-phenylphosphetane 1-oxide (PPO), have been determined by X-ray analysis and the single methyl group was found to be trans to the phenyl substituent in both instances. Both structures exhibit P–C bond distances to the least substituted ring carbon atom that are substantially shorter [1.788 (5) Å, TPO; 1.799 (5) Å, PPO] than previously reported values for this class of compounds. The four-membered ring in TPO is puckered with an angle of 16.7°, while the ring in PPO is puckered at an angle of 29.8°. These two structures are compared to five structures from the literature which contain the phosphetane ring system. The degree of puckering has been related (qualitatively) to the number of interactions between methyl substituents on the four-membered ring. The ring systems all pucker such that a lone methyl substituent on the ring occupies a pseudoequatorial position. Both compounds crystallize in the monoclinic space group $P2_1/c$ with TPO having unit cell dimensions of a = 10.582 (7), b = 12.688 (7), c = 10.229 (4) Å, and β = 119.03 (4)° and PPO having unit cell dimensions of a = 17.165 (16), b = 7.226 (2), c = 11.365 (10) Å, and β = 102.24 (7)°. The final R values are 0.047 for TPO and 0.065 for PPO.

The chemistry of the four-membered heterocyclic phosphetanes has received considerable attention over the past nine years.[3] This is due in part to the fact that ring constraint in this system provides a structural asset for the analysis of phosphorus stereochemistry (particularly in polytopal rearrangements).[4] Also, a ring methyl substituent bearing a cis or trans relationship to a functional group on phosphorus (structures **1**–**3**) provides a convenient probe for following stereochemical changes about phosphorus in chemical reactions.[5a,b]



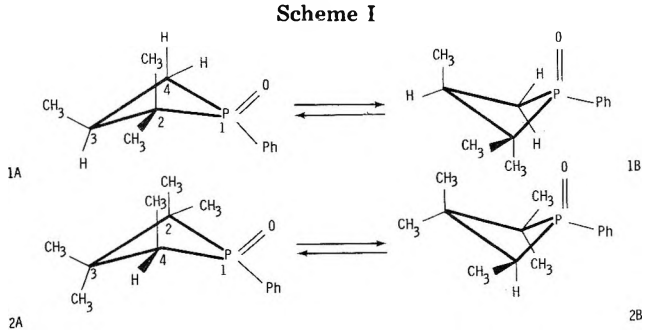
1 2 3

R = ALKYL, ARYL, Cl, OH, OCH_3

Previous X-ray studies have focused on derivatives of **3**[6a,c,d] and the resultant isomer assignments have been valuable for spectral and stereochemical correlations.[7] The X-ray results of **2** have already been applied in a ^{13}C NMR study and the X-ray data for **1** is in agreement with the assignments in that same study.[7b]

Moreover, the inherent properties of ring strain, ring puckering, and conformational preference provided special interest in carrying out the X-ray work. With regard to conformational aspects, the following equilibria can be considered (Scheme I).

Scheme I



Although the preference in the solid state may not parallel that in solution, several features are noted. The conformational energy difference between **1A** and **1B** is not clear cut. The C(3)–CH_3 group might be expected to favor a pseudoequatorial position (**1A**); however, because of the long P–C bonds (relative to C–C) the usual preference rules for carbocyclics may not be applicable. Conformational analysis involving second row elements may require different considerations.[8] Conformer **2B** with pseudoequatorial groups at positions 1 and 4 does not contain the apparent energetically unfavorable nonbonded repulsions (CH_3···CH_3 and CH_3···Ph) found in **2A**, thus indicating **2B** as the more stable conformer.

Moret and Trefonas[6b] have suggested that a study of an unsymmetrically substituted phosphetane ring should be carried out to determine whether the 1,2 P–C bond distance would be longer than the 1,4 P–C bond as suggested by its ring-opening reactions or whether they would be equivalent. In fact, subsequent chemical reactions have shown that the ring can be cleaved at either position depending on the cleavage reagent. For example, treatment of 1,2,2,3,3-pentamethyl-1-phenylphosphetanium bromide with phenyllithium opens the ring at the more substituted P–C bond,[5e] whereas sodium hydroxide treatment of either 1,2,2,3-tetramethyl-1-phenylphosphetanium iodide or 1,2,2,3,3-pentamethyl-1-phenylphosphetanium iodide gave ring opening at the least-substituted P–C bond.[5f] Alkaline hydrolysis of PPO also opens the ring at the least-substituted position.[5f] The basis for the direction of ring opening is dependent on the relative ground state–transition state free-energy differences. It is really not valid to relate the direction of cleavage to the relative length of the P–C bonds in the starting material.

The heterocycles 2,2,3-trimethyl-1-phenylphosphetane 1-oxide (**1**, TPO, with R = phenyl) and 2,2,3,3,4-pentamethyl-1-phenylphosphetane 1-oxide (**2**, PPO, with R = phenyl) represent the first examples of unsymmetrically substituted phosphetane oxides whose three-dimensional structures have been determined.

Experimental Section

Crystal Data. Both TPO and PPO were recrystallized from cyclohexane. The compounds were prepared by published methods[5c,d]

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Table I. Crystal Data and Experimental Conditions

	TPO ($C_{12}H_{17}PO$)	PPO ($C_{14}H_{21}PO$)
a, Å	10.582 (7)	17.165 (16)
b, Å	12.688 (7)	7.226 (2)
c, Å	10.229 (4)	11.365 (10)
β, deg	119.03 (4)	102.24 (7)
Z	4	4
D_{calcd}, g/cm^3	1.150	1.14
D_{expt}, g/cm^3	1.140	1.12
μ, cm^{-1}	2.01	1.78
vol of unit cell, Å^3	1200	1379
crystal dimensions, mm	0.63 × 0.38 × 0.32	0.18 × 0.64 × 0.65
θ–2θ scan time		
background count and time, s	10	10
take off angle, deg	4	4
scan rate, deg/min	2	2
scan width, deg	2	2
total reflections scanned	1215	1712
obsd reflections	997($I > 2\sigma$I)	1244($I > 3\sigma I$)
radiation MoKα	0.71069	0.71069
final R factor	0.047	0.065
R_w	0.042	0.080

Table II. Selected Bond Distances and Angles for TPO and PPO with Their Standard Deviations in Parentheses

TPO		PPO	
	Bond Distances, Å		
P–O	1.472 (3)	P–O	1.477 (4)
P–C(2)	1.835 (4)	P–C(2)	1.840 (5)
P–C(4)	1.788 (5)	P–C(4)	1.799 (5)
P–C(8)	1.800 (3)	P–C(10)	1.819 (5)
C(2)–C(3)	1.548 (7)	C(2)–C(3)	1.584 (7)
C(2)–C(5)	1.535 (6)	C(2)–C(8)	1.515 (8)
C(2)–C(6)	1.504 (6)	C(2)–C(9)	1.527 (8)
C(3)–C(4)	1.536 (6)	C(3)–C(4)	1.584 (7)
C(3)–C(7)	1.515 (9)	C(3)–C(6)	1.525 (8)
C(8)–C(9)	1.366 (8)	C(3)–C(7)	1.519 (8)
C(8)–C(13)	1.345 (6)	C(4)–C(5)	1.513 (8)
C(9)–C(10)	1.388 (9)	C(10)–C(11)	1.350 (7)
C(10)–C(11)	1.362 (9)	C(11)–C(12)	1.387 (8)
C(11)–C(12)	1.359 (10)	C(12)–C(13)	1.393 (10)
C(12)–C(13)	1.374 (8)	C(13)–C(14)	1.331 (11)
	Bond Angles, deg		
C(2)–P–C(4)	79.4 (2)	C(2)–P–C(4)	80.8 (2)
O–P–C(8)	111.4 (2)	O–P–C(10)	109 4 (2)
O–P–C(2)	121.3 (2)	O–P–C(2)	116.2 (2)
O–P–C(4)	122.3 (2)	O–P–C(4)	117.4 (2)
C(2)–P–C(8)	108.9 (2)	C(2)–P–C(10)	116.8 (2)
C(4)–P–C(8)	109.4 (2)	C(4)–P–C(10)	114.1 (2)
P–C(2)–C(3)	89.3 (2)	P–C(2)–C(3)	86.9 (3)
C(2)–C(3)–C(4)	97.3 (3)	C(2)–C(3)–C(4)	96.3 (4)
C(3)–C(4)–P	87.8 (2)	C(3)–C(4)–P	88.3 (3)

and the melting points were in agreement with values from the literature (TPO = 84–86 °C, PPO = 135–136 °C). Table I gives lattice parameters and experimental conditions.

Both data sets were reduced in the usual manner after application of Lorentz and polarization corrections.[9] Form factors for P, O, and C were taken from the International Tables.[10a] The hydrogen scattering factors were from Stewart, Davidson, and Simpson.[11] Anomalous scattering corrections for phosphorus were also included.[10b] The PPO data were corrected for absorption[12] (μ = 1.78 cm^{-1}), but no correction was applied to the TPO data.

Structure Determination and Refinement. The structures of both TPO and PPO were solved by Patterson syntheses. Both structures were refined by full-matrix least-squares techniques. Difference Fourier syntheses were used to locate the position of the hydrogen atoms at an intermediate state (R = 0.091 for TPO, R = 0.084 for PPO). In the final stages of the refinements, atomic coordinates and anisotropic thermal parameters were adjusted for the P, O, and C atoms and positional and isotropic parameters were allowed to vary for the H atoms. The weighting scheme used in the final stages of refinement was a statistical one based on that suggested by Stout and Jensen.[13] The residuals for TPO were R = 0.047 and R_w = 0.042 and R = 0.065 and R_w = 0.080[14] for PPO.

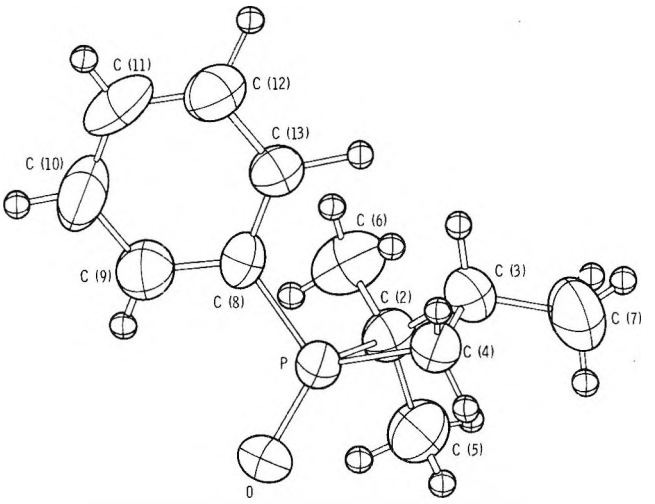

Figure 1. ORTEP plot of TPO at the 50% probability level. The hydrogen atoms are arbitrarily assigned isotropic temperature factors of 1.0 in this illustration.

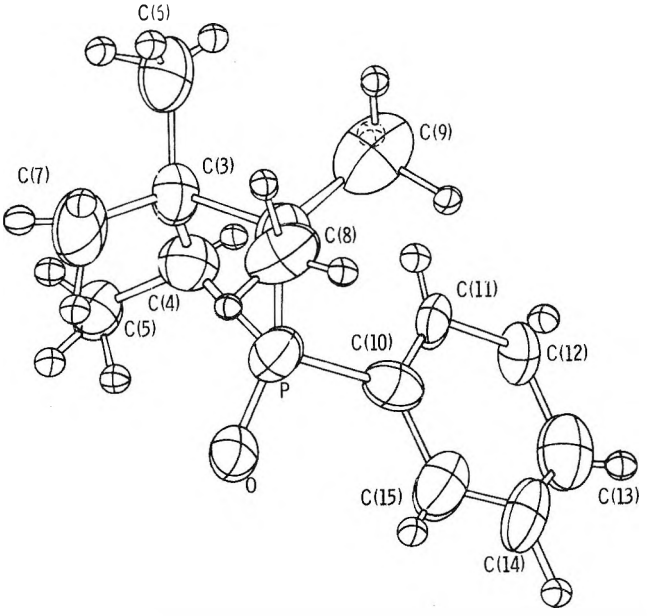

Figure 2. ORTEP plot of PPO at the 50% probability level. The hydrogen atoms are arbitrarily assigned isotropic temperature factors of 1.0 in this illustration.

Results

Figures 1 and 2 are ORTEP[9] drawings of TPO and PPO. Selected bond distances and angles are listed in Table II.

Structural Details of the Phosphetane Ring System. The lone ring methyl group [C(7) in TPO and C(5) in PPO] is trans to the phenyl group in both structures.

The structural details that will be emphasized are those for which differences are observed between these compounds and previous structures. Structural data on several phosphetane derivatives are shown in Figure 5 for purposes of comparison. The P–C bond lengths involving an unsubstituted α carbon (1.788 (5) Å, TPO) and a monosubstituted α carbon (1.799 (5) Å, PPO) are the shortest distances of this type reported to date. Previously reported values range from 1.83 to 1.94 Å. The

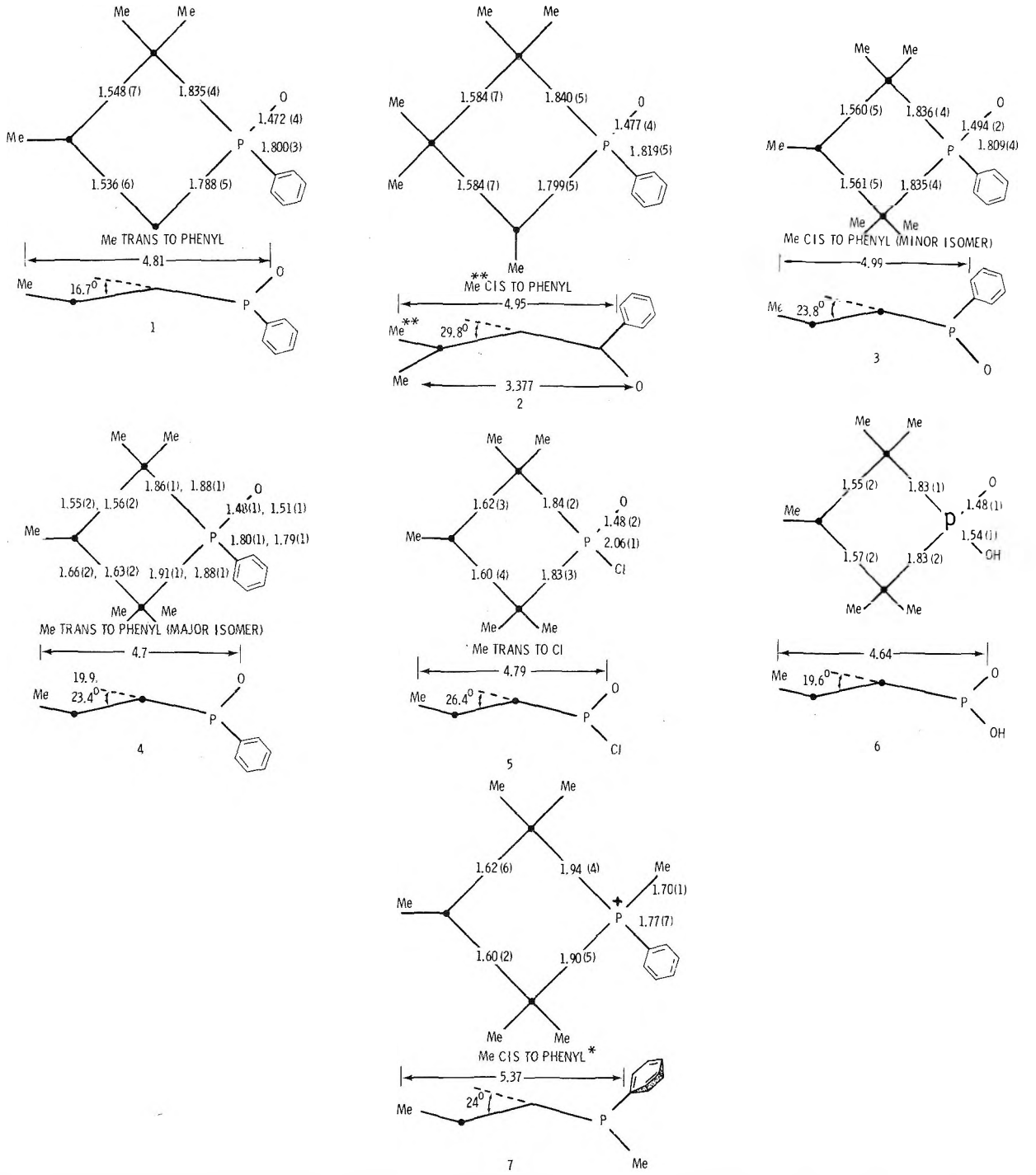

Figure 5. Summary of pertinent data for several phosphetane structures. Structures 1 and 2 are from this work. Structures 3–5 were reported by Haque,[6c,d] structure 6 was reported by Swank and Caughlan,[6a] and structure 7 was reported by Moret and Trefonas.[6b] Estimated standard deviations are in parentheses.

(*) The phenyl group is rotated by 90° with respect to the phenyl substituents on P in structures 1–4.

phosphoryl bond lengths (1.472 (3) Å, TPO; 1.477 (4) Å, PPO) are both shorter than previously observed values[6] (1.48–1.51 Å) though still longer than the normal phosphoryl distance of 1.45 Å.[15]

The C–C distances in the four-membered ring of TPO are shorter than have been observed in phosphetane ring systems in the past. For TPO, these distances are 1.548 (7) Å and 1.536 (4) Å. Previously reported values range from 1.55 (2) to 1.66 (2) Å.

Table IV summarizes the intramolecular distances that are less than or approximately equal to the sum of the van der Waals radii.[16] Since TPO contains fewer substituents than previous phosphetane derivatives, the number of substituent–substituent interactions is reduced to where the ring C–C distances approach normal values. The P=O bond is shortened and the P–C(4) bond length approaches the average found in other compounds containing tetravalent phosphorus.[17a,b] The greater length of the 1,2 versus the 1,4 P–C bond (about 0.04 Å) may have a steric origin and may be related to the C(8)–O (PPO) and C(5)–O (TPO) distance (Table IV); the apparent discrepancy for compound 4 is not completely understood at this time.

Although TPO apparently shows a methyl–phenyl interaction, based on sums of van der Waals radii (see Table IV), this interaction is of less importance than the methyl–methyl and methyl–phosphoryl oxygen interactions. The P–C (phenyl) distance of 1.800 (3) Å is in good agreement with values reported in the literature[17b] and does not differ from values

Table IV. Intramolecular Distances in TPO and PPO That Are Less Than or Approximately Equal to the Sum of the van der Waals Radii

	PPO	TPO
methyl–methyl[a]	C(5)–C(7) = 3.011 Å C(6)–C(9) = 2.885 Å C(7)–C(8) = 2.882 Å	C(5)–C(7) = 2.966 Å
methyl–methyl (diaxial)	C(5)–C(8) = 4.858 Å	
methyl–phenyl[b]	C(9)–C(10) = 3.287 Å	C(6)–C(8) = 3.250 Å
methyl–oxygen[c]	C(5)–O = 3.314 Å C(8)–O = 3.169 Å C(7)–O = 3.37 Å[d]	C(5)–O = 3.178 Å

[a] Bondi[16] estimates r_w ($C_{aliphatic}$) = 1.70 Å; therefore, an intramolecular distance <3.4 Å may be significant. [b] Bondi[16] estimates r_w ($C_{aromatic}$) = 1.77 Å, and since the effective size of the phenyl group is related to its rotational position an intramolecular distance <3.4–3.5 Å may be significant. [c] Bondi[16] estimates r_w (=O, normal to bond axis) = 1.6–1.7 Å; therefore, an intramolecular distance <3.3–3.4 Å may be significant. [d] The C(7)–O distance of 3.377 Å in PPO is a diaxial cross-ring interaction and probably serves to prevent further puckering of the phosphetane ring.

previously observed for this class of compounds.[6c,d] No apparent shortening of the P–C (phenyl) bond due to a decreased amount of crowding is observed in TPO.

Of the three apparent methyl–phosphoryl oxygen interactions in PPO only one is significantly less than the sum of the van der Waals radii. This reduction in the number of significant Me–O interactions in PPO (relative to the symmetrical pentamethyl isomers) apparently allows the P–C(4) bond length to approach the expected value for this type of bond and the P–O bond to be shortened (although perhaps not significantly). The P–C phenyl bond length of 1.819 (5) Å is within the limits for a normal bond of this type, again indicating that no undue crowding of the phenyl substituent takes place in the symmetrically substituted compounds.

All phosphetane ring structures to date exhibit puckering of the four-membered ring. The amount of pucker in the four-membered ring is defined as the angle between the planes C(2)–P–C(4) and C(2)–C(3)–C(4). For TPO the amount of pucker is 16.7°, while PPO is puckered with an angle of 29.8°. Qualitatively, these variations may be explained in terms of the number of substituent interactions; packing interactions have been assumed to be negligible as there are very few intermolecular distances significantly less than the sums of the van der Waals radii. The number and type of substituent interactions for several phosphetane derivatives are summarized in Table V. An interaction is considered to exist only between substituents which are attached to adjacent ring atoms and cis to one another with respect to the phosphetane ring system (the diaxial cross-ring Me–O interaction observed in PPO is also included).

Energetically, the most important interactions are the methyl–methyl interactions as they result in distances substantially less than 3.4 Å distance based on van der Waals radii (see Table IV). Variations in puckering due to the type of substituent on the P atom are expected to be small relative to the variation in puckering due to different numbers of substituent interactions. PPO with three methyl–methyl interactions is puckered to a greater extent than any other phosphetane ring system, while TPO with only one methyl–methyl interaction displays less puckering than any of the symmetrically substituted compounds which have two methyl–methyl interactions.

The average puckering angle for the symmetrically substituted compounds is 22.9° with a standard deviation of 2.6° and a standard deviation of the mean of 1.1°.[18] The two unsymmetrical structures have puckering angles that are substantially different from this mean value. One might expect that an unsubstituted phosphetane ring system would exhibit less puckering than any of the structures studied to date.

In the solid state, TPO exists in the form **1A** with an O–C(7) distance of 4.81 Å. For PPO, which is in form **2B** in the crystalline state, the C(7)–O distance of 3.37 Å and the methyl–phenyl distance [C(6)–C(10)] of 4.95 Å agree well with distances measured from the molecular model of **2B.** Both structures contain methyl–oxygen distances [C(5)–O = 3.178 Å in TPO; C(8)–O = 3.169 Å] that are somewhat less than the sum of the van der Waals radii (3.3–3.4 Å).[16]

Some observations can be made concerning the direction of puckering and the substitution pattern of the ring system. On examination of Figure 5 (compounds 1 and 3–7) and Figure 2 (compound 2), it is apparent that the direction of puckering is such that a single methyl group attached to a ring carbon is pseudoequatorial in all examples studied to date. A more detailed analysis (still of a qualitative nature) can be based on the substituents on C(3) and P; some of the possible puckering forms are illustrated in Figure 6. In six cases (compounds 1 and 3–7 in Figure 5), there is a single methyl substituent on C(3). The phosphetane ring system puckers such that cross-ring interactions between the substituents on P and C(3) are minimized. Since interactions involving a pseudoaxial C(3)–H substituent are relatively small, the larger possible diaxial cross-ring interaction between the other substituent on C(3) and the substituent on P determines the direction of puckering in these phosphetane ring systems. Form **1A** is the minimum energy form for compounds 1 and

Table V. Summary of Number and Type of Substituent Interactions in Phosphetane Ring Systems

compd	registry no.	no. of methyl–methyl interactions	no. of methyl–X interactions	no. of methyl–Y interactions	puckering angle, deg
1	34136-10-2	1	1 (X = Ph)	1 (Y = O)	16.7
2	35623-55-3	3	1 (X = Ph)	1 (Y = O)[a]	29.8
3	20047-46-5	2	2 (X = Ph)	2 (Y = O)	23.8
4	16083-91-3	2 (1)[b]	2 (X = Ph)	2 (Y = O	19.9, 23.4
5	26674-18-0	2	2 (X = Cl)	2 (Y = O)	26.4
6	17405-94-6	2	2 (X = O)	2 (Y = O)	19.6
7	35623-39-3	2	2 (X = Ph)[c]	2 (Y = CH_3)	24

[a] Compound 2 contains two Me–O interaction distances that appear to be too long to be significant in this analysis. The distances are both >3.3 Å and are shown in Table IV. Therefore, only one of these three interactions has real significance (see Table IV and text). [b] Value in parentheses involves possible cross-ring diaxial methyl–methyl interactions. Compound 4 exhibits cross-ring Me–Me distances of 3.52 (molecule 1) and 3.48 Å (molecule 2) which are probably not significant relative to the interactions between methyl groups that are cis to each other and attached to neighboring ring carbon atoms. [c] The plane of the phenyl group is oriented ~90° away from the phenyl group plane in the other structures containing a phenyl substituent on the P atom.

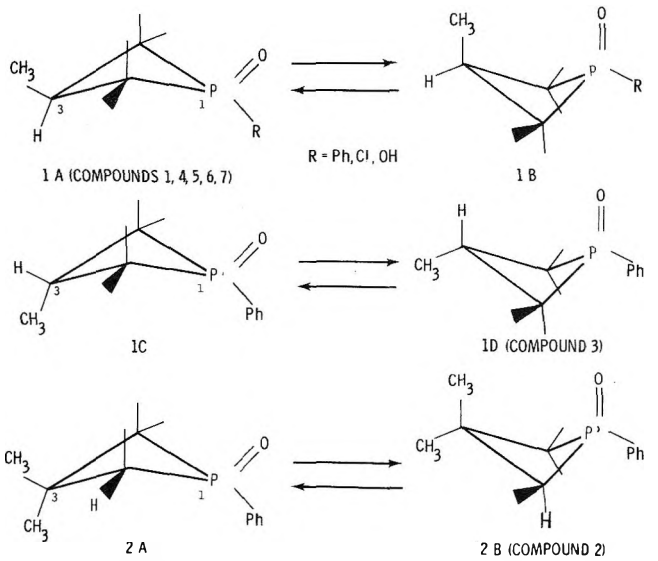

Figure 6. Puckering direction of the four-membered rings in several phosphetane derivatives.

4–7. Compound **3** exists in form **1D** (Figure 6) and is different from compounds **1, 4, 5,** and **7** when the substituents on P are taken into consideration; the phenyl group, which is larger than the oxygen substituent, is cis to the C(3)-methyl group and occupies a pseudoequatorial position.

Compound **2,** with two methyl groups on C(3), is a case where the relative size of the two substituents on P become important when the possible diaxial cross-ring interactions are considered in terms of the direction of ring puckering. In this work, compound **2** was found to exist in form **2B,** which is very similar to form **1D** in terms of diaxial cross-ring interactions. There are two possible diaxial cross-ring interactions to consider in compound **2;** a methyl–oxygen interaction (form **2B**) or a methyl–phenyl interaction (form **2A**). The methyl–phenyl diaxial interaction would be an energetically unfavorable situation, whereas the methyl–oxygen interaction that occurs in form **2B** is the minimum energy form for this system.

Based on these observations, it is reasonable to suggest that the direction of ring puckering is determined by the possible diaxial cross-ring interactions between substituents on C(3) and P in the phosphetane ring systems. The two possible sets of cross-ring interactions between cis-pseudoaxial substituents in any phosphetane derivative must be considered, and the lowest energy cross-ring interaction form will correspond to the observed puckering form. Forms **3A** and **3B** (Scheme II) illustrate the situation in general terms. When $R_3 \approx R_4$ in size (based on van der Waals radii) and $R_1 \gg R_2$, then the phosphetane ring system will exist in form **3A.** If $R_2 \gg R_1$ and $R_3 \approx R_4$, the ring system will exist in form **3B.** For the case where $R_1 \approx R_2$ and $R_3 > R_4$, the most stable form for the ring system will be form **3A.** If $R_1 \approx R_2$ and $R_3 < R_4$, then the ring will be puckered in form **3B.** For the two cases where (a) $R_1 > R_2$ and $R_3 < R_4$ or (b) $R_1 \approx R_2$ and $R_3 \approx R_4$, the probability of a correct prediction for the form of ring puckering is decreased.

Both ^{13}C and ^{1}H NMR analyses of TPO and PPO in solution with lanthanide shift reagents, which includes angular as well as distance considerations, indicate that the structures in solution parallel that of the crystalline state. The details of this study will be published elsewhere.[19]

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Supplementary Material Available: Positional and thermal parameters and structure factors for both TPO and PPO (Tables IIIa and IIIb) and all of the bond angles and distances (Figures 3 and 4) (12 pages). Ordering information is given on any current masthead page.

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Mass Spectral Behavior of 5(6)-Substituted Benzimidazoles

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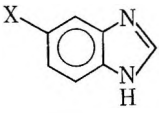
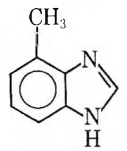
Three general classes of 5(6)-substituted benzimidazoles were compared according to common or similar fragmentation pathways in the mass spectrometer. The 5(6)-alkyl derivatives fragment through a common intermediate of *m/e* 131 as demonstrated by metastable ion ratios for the 2-^{13}C-labeled compounds. It is suggested that this intermediate possesses a ring-expanded structure resembling that of 1,3-diazaazulene whose fragmentation behavior is very similar. For both species, competitive pathways exist for loss of the 2 carbon and carbocyclic ring carbons with HCN or CN· fragments. Moreover, the expected loss of the 2 carbon of the imidazole ring with these fragments is *not* the predominant process. The second general group of derivatives fragments by complete loss of the 5(6) substituent (NO_2, Cl, CO_2H, $COCH_3$) to give a common ion of *m/e* 117. Again, the metastable losses of HCN and H^{13}CN from the 2-^{13}C-labeled derivatives confirms the common structure of this ion and indicates predominant loss of carbocyclic ring carbons. Finally, the similar behavior of several 5(6)-alkenylbenzimidazoles implies fragmentation through a common 143 ion which may result from a ring-expansion process similar to that of styrene. The three main fragmentation pathways observed here should be general for a variety of benzimidazole derivatives. More importantly, the metastable ratio technique for common ion identification is found to be much more reliable for ^{13}C-labeled compounds than for those with ^{2}H labeling. Increased availability of ^{13}C-enriched reagents makes this technique one of broad applicability in mass spectral investigations.

The application of mass spectrometry to the identification and structure determination of heterocyclic compounds has recently been experiencing explosive growth. For such application, the observation of straightforward fragmentation behavior general to a given class of heterocycles would be most desirable. Such is not often the case, however. A recent survey indicates that rearrangements and competitive fragmentation pathways are very common for heterocyclic compounds.[1] These processes make difficult the understanding of the details of the mass spectral behavior. In this paper, we discuss the general and detailed behavior of several 5(6)-substituted benzimidazoles (structures I–XVI). Isotopic labeling is employed to indicate possible fragmentation mechanisms and probable intermediate structures. The techniques presented here are general and should be useful for indicating and establishing ionic structures and fragmentation pathways for other heterocycles.



I, X = CH_3
II, X = CH_2CH_2OH
III, X = CH_2CH_2Cl
VII, X = CO_2H
VIII, X = $COCH_3$
IX, X = NO_2
X, X = Cl
XI, X = $CH(OH)CH_3$
XII, X = $CH{=}CH_2$
XIII, X = $CH{=}CHCO_2H$
XIV, X = $CH{=}CHCO_2CH_3$
XV, X = $CH{=}CHCO_2CH_2CH{=}CH_2$
XVI, X = $CH{=}CHCONHCH_2CH{=}CH_2$



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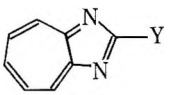
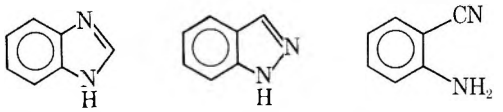


V, Y = SH
VI, Y = SH

An extensive literature investigation of benzimidazoles revealed a paucity of mass spectral information despite widespread industrial and academic interest in this family of heteroaromatics.[2] Only recently, during the course of our work, did reports appear concerning more detailed investigations of the parent benzimidazole[3,4] and 1-ethylbenzimidazole.[5] This work supports our contention that common fragmentation pathways may exist for compounds which are structurally similar or even quite different. For example, for benzimidazole, indazole, and *o*-aminobenzonitrile (below), rearrangement of the molecular ions of all three compounds to a common structure is observed prior to fragmentation of the metastable ions.[3,4] Our work with substituted benzimidazoles and related heterocycles indicates that extensive rearrangement to common structures probably occurs for many daughter ions as well as molecular ions.



In this paper, extensive use is made of ^{13}C labeling in the 2 position of benzimidazoles for two purposes. In our initial observations on unlabeled and ^{2}H-labeled benzimidazoles, it was apparent that rearrangement processes and/or competitive fragmentations were occurring for many derivatives. It was necessary to determine whether either or both of these possibilities involved only hydrogen scrambling or if carbon atoms were involved as well in skeletal rearrangements. The second goal was to develop a technique involving the labeled carbon to confirm common ionic structures. This technique involves metastable ions and requires two or more competitive fragmentations of the ion suspected of a common structure. For two major groups of 5(6)-substituted benzimidazoles, common structures were found for the major daughter ions using this technique. In addition, skeletal rearrangements and competitive fragmentations were found to be quite extensive for all derivatives studied.

The details of the fragmentation behavior are discussed in terms of general pathways and behavior. Three major groups were observed with classification made according to the most intense pathway. Of course, with heterocycles such as benzimidazoles, several competitive pathways may be observed for any given derivative and some of the more interesting and useful of the minor paths will be described on an individual basis.

Procedures

The syntheses of several deuterium-labeled derivatives as well as the 2-^{13}C-labeled compounds are given in the Exper-

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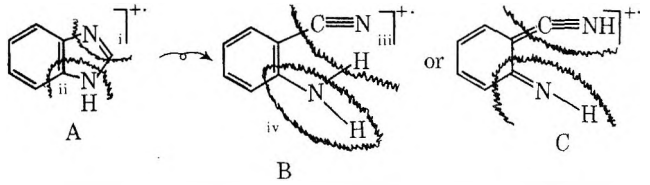
imental Section. The procedure developed for the latter was based on generality as well as conservation of the expensive carbon-13-containing reagent used. Phillip's original synthesis of benzimidazoles[6] employs ring closure of an aromatic ortho diamine with a large excess of formic acid in refluxing 4 N hydrochloric acid. We found that only a slight excess of formic acid is necessary to give almost quantitative yields under similar conditions. Furthermore, rather than using commercially available [^{13}C]formic acid, the much less expensive sodium [^{13}C]formate was employed with in situ liberation of the acid. These two measures brought the cost of 2-^{13}C-labeled benzimidazoles enriched to 90% down to ca. $30 per 200 mg sample.

For replacement of exchangeable hydrogens with deuterium, prior exchange by recrystallization or reprecipitation from $^{2}H_2O$ gave disappointing results. Reexchange of the deuterium in the sample with exchangeable hydrogens absorbed on the walls of the source is the probable explanation, since more than adequate time exists for ca. 50 collisions with the source walls before ionization takes place.[7] This problem was overcome by introducing a $^{2}H_2O$ slurry of the sample into the source on the solid probe. Repeated spectral scans were then made for several minutes after operating pressures were reached. The amount of exchangeable deuterium incorporated into the parent ions varied in a nonregular manner with time, and the spectrum or spectra with the highest isotope incorporation were employed. Deuterium exchange was routinely increased to 90% or better with this method.

The procedure presented here for the comparison of ionic structures in the mass spectrometer is based on two requirements. The ion under consideration must undergo two or more competitive fragmentations and each must exhibit a measurable metastable peak. The comparison is made of the ratio of intensities of the metastable peaks of the competitive fragmentations. For ions of the same structure but from different parent or precursor species, the ratio of metastable intensities will be the same.[8-11]

The requirement of competitive fragmentations is generally satisfied by losses of fragments of different molecular weight and composition.[9,10] However, with nitrogen-containing heteroaromatics such as benzimidazoles, almost all fragmentations involving the skeletal framework result in loss of HCN. The hydrogen, carbon, and nitrogen atoms lost with this fragment may come from different parts of the molecule, however. For example, in the scheme below, two possible intermediates for partial or complete "scrambling" of carbon atoms involved in HCN loss are presented. For structure A,



it is possible that two mutually exclusive, competitive fragmentations occur which do not require prior rearrangement of the benzimidazole nucleus. Thus, fragments i and ii would involve completely different HCN molecules. The second possibility involves rearrangement of the nucleus prior to fragmentation, for example, to structure B or C. Structure B might then lose HCN by competitive loss of fragments iii and iv.

A further consideration is the energy of the species under consideration. Thus, for example, one can envision a situation where the ionic lifetime is comparable to the time required for rearrangement. Competitive losses of HCN could occur from structure A via fragment i and from structure B via fragment iii. A priori, the presence of a ^{2}H or ^{13}C label would not distinguish among these three (and other) possibilities. However, because of energetic requirements, it is possible to eliminate some of these possibilities from consideration.

It is well known that ionization of molecules with 70 eV electrons results in molecular ions with a broad range of energies and lifetimes.[8] For our purposes, it is possible to break this distribution down into three general groups.[8] First, those parent ions with insufficient energy to fragment before arriving at the detector are seen as molecular ions. Second, those parent ions with sufficient energy to fragment in the source are detected as daughter ions. (Qualitatively, the higher the initial ionic energy, the greater the probability of continued fragmentation to daughter ions of lower molecular weight.) Finally, parent ions with intermediate energies and lifetimes fragment between the source and the detector and are observed as metastable peaks. For each daughter ion, of course, similar energetic requirements again lead to observation of the daughter ion, a metastable ion, or a second daughter ion.

Examining the processes discussed above for structures A and B, for example, it is possible to qualitatively relate the type of process with the relative energy and lifetime of the ion under consideration.[12] That is, it has been observed that direct cleavage fragmentations, e.g., loss of i or ii from A, are favored at high energies. Rearrangement processes, e.g., to structure B or C, are favored at lower energies and longer lifetimes. Thus, if competitive fragmentations are occurring from two different structures, e.g., i from A and iii from B, the former should be most evident with the stable (parent and daughter) ion peaks while the latter should predominate almost completely with metastable peaks. To rephrase, if rearrangement is taking place it will generally be complete on the time scale of the metastable peaks.

This conclusion has been widely supported by experimental observations involving both alkanes and heteroatom-containing compounds.[3,4,9-11,13,14] In almost all cases, rearrangement processes which were incomplete for stable ions were found to be complete for the longer lived metastables. An example of special interest involves the monodeuterated derivatives of benzimidazole, indazole, and *o*-aminobenzonitrile previously mentioned.[3,4] For all three isomeric compounds, losses of HCN and ^{2}HCN were competitive for both the stable and metastable ions. With the stable ions, the ratios of HCN to ^{2}HCN lost from the parent ions were widely different for the three compounds. However, the ratios of metastable peaks for these two losses were within experimental error for all three. The two conclusions which may be drawn from the identical isotopic metastable ratios are, first, that the competitive losses of HCN and ^{2}HCN involve rearrangement that may be incomplete for stable ions but complete for metastable ions; and second, the rearranged structures are identical for all three compounds. The obvious corollary to the former is that for the stable ions, fragmentation may be occurring from both the rearranged and unrearranged structures, the amount from each being somewhat dependent on how similar the common rearranged structure is to each of the three parent structures.

In this paper, the confirmation of a common structure relies on the ratio of metastable peak intensities for the competitive losses of H^{13}CN and H^{12}CN. While this would be a trivial comparison if no rearrangement processes were taking place and a single fragmentation mechanism were observed, such is definitely not the case for benzimidazoles. The a priori prediction for 2-unsubstituted benzimidazoles in general is that loss of HCN should involve the 2 carbon almost exclusively.[15] In fact, loss of carbocyclic carbons compares favorably or predominates for all the 2-labeled derivatives studied here.[16] Thus, the 2-^{13}C label provides a means of confirming common structure as well as assisting in the elucidation of the nature of the rearranged structures and the types of compet-

Table I. Summary of the Mass Spectral Behavior of 5(6)-Substituted Benzimidazoles

5(6)-substituent	registry no.	base ion (M = parent)	M − HCN	no. of paths[a]	major path	ring exp.[b]	^2H[c]	^{13}C[d]	synth. ref
(VII) CO_2H	15788-16-6	155 M	no	1	M − OH − CO − HCN	no			6
(VIII) $COCH_3$	58442-16-3	145	no	1	M − CH_3 − CO − HCN	no	117	117	*e*
(IX) NO_2	94-52-0	163 M	no	2	M − NO_2 − HCN	no	?	117	6
(X) Cl	4887-82-5	152 M	yes	2	M − Cl − HCN M − HCN − HCN	no	?	117	6
(XI) $CH(OH)CH_3$	66792-92-5	119	no	2	M − CH_3 − CO − HCN				
(XII) $CH{=}CH_2$	4070-35-3	144 M	yes	3	M − C_2H_2 − HCN	144? 143	144 143		23
(XIII) $CH{=}CHCO_2H$	51819-00-2	188 M	no	2	M − OH − CO − HCN	143			27
(XIV) $CH{=}CHCO_2CH_3$	66792-93-6	202 M	no	2	M − CH_3O − CO − HCN	143			*e*
(XV) $CH{=}CHCO_2CH_2$-$CH{=}CH_2$	66792-94-7	171	no	2	M − $CH_2{=}CH$-CH_2O − CO − HCN	143			*e*
(XVI) $CH{=}CHCONHCH_2$-$CH{=}CH_2$	66792-95-8	171	no	2	M − $CH_2{=}CHCH_2NH$ − CO − HCN	143			*e*
(I) CH_3	614-97-1	132 M	yes	2	M − H − HCN	131	131	131	6
(II) CH_2CH_2OH	15788-11-1	131	no	2	M − CH_2OH − HCN	131	131		28
(III) CH_2CH_2Cl	14984-14-6	131	no	2	M − CH_2Cl − HCN	131			28
(IV) 4(7)-CH_3	4887-83-6	132 M	yes	2	M − H − HCN	131	131	131	6
(V) DAA	275-94-5	130 M	yes	2	M − HCN	no	no	no	19
(VI) DAA-2-SH	15852-41-2	162 M	yes	2	M − HCN	no	no	no	19

[a] Number of major, competitive fragmentation pathways at 70 eV. [b] Ring expansion probable in the listed ions. [c] ^2H labeling indicates hydrogen scrambling in the ions listed. [d] ^{13}C labeling indicates skeletal rearrangement in the ions listed. [e] New compounds.

itive fragmentation mechanisms involved in HCN loss from benzimidazoles.

Results and Discussion

Benzimidazole. The details of the fragmentation behavior of the parent benzimidazole will be discussed in a subsequent paper in relation to similar heterocycles. A few general observations are important, however, for comparison with the behavior of the 5(6)-substituted derivatives described here. Both ^2H and ^{13}C labeling[3] indicate that fragmentation of the parent ion occurs by competitive processes apparently involving both unrearranged and rearranged structures. Rearrangement is complete for metastable ions, although competitive loss of labeled and unlabeled HCN is still observed. For metastable ions of benzimidazole, therefore, either the rearrangement process results in specific partial scrambling of both carbon and hydrogen or competitive mechanisms exist for fragmentation of the rearranged species. The latter has been assumed to be the case by Maquestiau and co-workers in their conclusion that the most reasonable common structure for fragmentation of benzimidazole, indazole, and *o*-aminobenzonitrile ions is through the latter structure with loss of the amine nitrogen and a ring carbon predominating. Our work with multiple labeling, i.e., ^2H in the 1 and 2 positions and ^{13}C in the 2 position, clearly confirms competitive mechanisms for the metastable fragmentations. That is, losses of HCN, $^2H^{13}CN$, and either or both ^2HCN and $H^{13}CN$ exhibit significant metastable peaks. Since rearrangement to a common structure is required by the ^2H-labeling experiments,[3] competitive mechanisms for HCN loss from this structure must exist and partial, incomplete hydrogen scrambling is occurring as required by loss of HCN from the trilabeled benzimidazole.

For benzimidazole, then, the following conclusions can be drawn. Metastable ions, and perhaps most of the stable ions, have rearranged completely before fragmentation. This process involves both the rearrangement of the carbon–nitrogen skeleton and scrambling of hydrogens on the imidazole ring with a *limited* number of hydrogens on the carbocyclic ring. Separate mechanisms probably exist for skeletal and hydrogen rearrangements. Competitive loss of labeled and unlabeled HCN may, therefore, result from partial scrambling of the label (^2H) and/or competitive mechanisms for fragmentation involving different atoms of the rearranged structure (^{13}C and ^2H). Evidence for the 5(6)-substituted benzimidazoles studied here indicates that both of these possibilities take place. That is, scrambling and rearrangement processes combine with competitive fragmentation mechanisms for many of these benzimidazoles.

Substituted Benzimidazoles. The 5(6)-substituted benzimidazoles and the two 1,3-diazaazulenes examined here are listed in Table I along with some important features of their mass spectral behavior. The inherent stability to fragmentation of this family of heteroaromatics is attested to by the intensity of the parent ion peak which, for more than half of the derivatives, is the base or most intense peak in the spectrum. In contrast to the fragmentation of benzimidazole, the parent ions of most derivatives do not lose HCN (column four). In fact, the major fragmentation path in all cases (last column) involves initial loss of all or part of the substituent rather than part of the benzimidazole nucleus. These initial steps, then, should be observed generally with similarly-substituted aromatic compounds, while later steps are unique to the benzimidazoles. Three families of derivatives are evident from the major pathways followed: (1) the alkyl derivatives fragmenting through a 131 ion; (2) those derivatives

Table II. Deuterium and Carbon Isotope Ratios for the Competitive Loss of HCN/^{2}HCN and HCN/H^{13}CN, respectively, from Selected Ions [a]

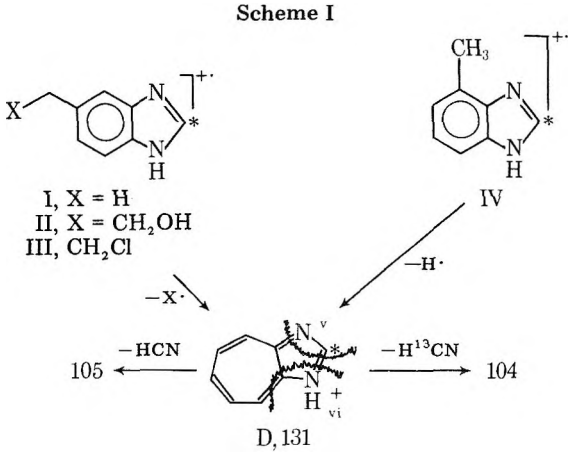
benzimidazole substituent and ions	deuterium [ion − ^{2}HCN][b]/[ion − ^{2}HCN]	deuterium [m*(HCN)][c]/[m*(^{2}HCN)]	carbon [ion − HCN][b]/[ion − H^{13}CN]	carbon [m*(HCN)][c]/[m*(H^{13}CN)]
H 119 ($M^{+\cdot}$)	1.0[d]	1.4[d]	1.2	2.6
118 ($M^{+\cdot}$ − H·)				(1.8)
92 ($M^{+\cdot}$ − HCN)				5
5(6)-Cl				
153 (^{35}Cl − $M^{+\cdot}$)	1.2	1.5	1.3	3.5
126 (153 − HCN)	(0.3)	0.4		0.6
118 ($M^{+\cdot}$ − Cl)	(1.1)	(0.7)	(0.7)	1.7
91 (118 − HCN)	(0.3)	(0.4)		(2)
5(6)-NO_2				
118 ($M^{+\cdot}$ − NO_2)	0.8	0.7	0.5	1.7
106 ($M^{+\cdot}$ − NO − CO)			(1–2)	(2–3)
91 (118 − HCN)	0.3	0.4	(<1)	(1.3)
5(6)-$COCH_3$				
118 ($M^{+\cdot}$ − CH_3 − CO)			0.6	1.7
91 (118 − HCN)				(1.5)
5(6)-CH_3				
132 ($M^{+\cdot}$ − H·)			<0.6	1.3
105 (132 − HCN)				0.8
4(7)CH_3				
132 ($M^{+\cdot}$ − H)	1.2	2.4	<0.7	1.4
105 (132 − HCN)				0.8
4(7)-CH_3-2-^{13}C-1,2-$^2H_2$[e]				
134 ($M^{+\cdot}$ − H)	$\frac{m^*HCN + m^*H^{13}CN}{m^*HCN + m^*H^{13}CN} = 2.4$		$\frac{m^*H^{13}CN + m^{*2}H^{13}CN}{m^*HCN + m^{*2}HCN} = 1.5$	

[a] Values in parentheses are inexact because of additional daughter ions from competing reactions or from very small m^* intensities. [b] Daughter ion intensity ratios. [c] Metastable ion intensity ratios. [d] Values from ref 3. [e] Combined metastable ratios for both carbon-13 and deuterium.

which lose the substituent completely to give an intermediate 117 ion; and (3) the alkenyl compounds which exhibit a strong 143 ion. While two of the derivatives display a single fragmentation pathway (column five), most exhibit two apparently independent sequences starting from the parent or immediate daughter ions. Nonetheless, the major pathway in almost all cases accounts for most of the total ion current and offers an easily recognized and characteristic feature of the type of substituent present.

Alkyl Substituents. 131 Ions. It is immediately evident from the similarity of the stable ion spectra of the 5(6)-alkyl derivatives (I–III) that the most important fragmentation pathway probably involves a common intermediate.[17] In all cases (Scheme I), the initial loss gives an ion of *m/e* 131 which is by far the most intense daughter ion. The intensity of this ion may reasonably be ascribed to charge stabilization through extensive delocalization. The ring-expanded structure D was

Scheme I



initially postulated in accord with similar ring expansions reported for other heteroaromatics such as the isomeric methyl quinolines.[18] If D is the structure of this intermediate, one would expect the 4(7)-methyl derivative (IV) to also fragment via this structure. Indeed, the mass spectra of I and IV are almost superimposable, strongly supporting common structures and fragmentation pathways for the stable ions of these isomers.

Proof of common structure, however, rests on the 2-^{13}C-labeled derivatives of the methyl isomers I and IV. In Table II are given the metastable ratios for loss of H^{12}CN to H^{13}CN from the 132$^+$ ions (131$^+$ plus the label), i.e., via the two paths in Scheme I. The experimentally equal values for I and IV show that metastable fragmentation must occur through ions of common structure which most probably result from ring expansion. The ratios for the stable ions are also approximately equal, although these values are much less accurate due to the presence of daughter ions of the same *m/e* values resulting from different fragmentation pathways involving both the parent ion and the (M − H) ion. The necessity of using metastable ions for confirmation of common structure is again indicated here. Stable ion daughter peaks may consist of ions resulting from fragmentation of more than one precursor ion, making comparisons between less similar species, e.g., the other alkyl benzimidazoles, very difficult. Metastable ions, however, identify both the parent and daughter ions unambiguously. Additionally, the similar energy and generally complete rearrangement of metastables ensures comparisons of the same structure and usually eliminates competing direct cleavage processes involving unrearranged ions.

The postulated structure D is assumed to be the common structure for the 131 ions of the other 5(6)-alkyl derivatives II and III as well as for I and IV. Although isotopic labeling was not employed for these derivatives, the preponderance of the

Table III. Comparison of Parent (m_1^+), Daughter (m_2^+), and Metastable (m^*) Ion Intensities for Successive Fragmentations of 131^+ Ions[a]

	131/104			104/77			77/51				
	m_1^+/m_2^+	m_1^+/m^*	m_2^+/m^*	m_1^+/m_2^+	m_1^+/m^*	m_2^+/m^*	m_1^+/m_2^+	m_1^+/m^*	m_2^+/m^*	m^*131/m^*104	m^*104/m^*77
4(7)-CH_3	7.2	6.7	0.9	0.8	1.3	1.6	1.3	6.3	5.1	1.5	3.8
5(6)-CH_3	8.2	7.3	0.9	0.7	1.3	1.8	1.4	7.1	5.3	1.4	3.9
5(6)-CH_2CH_2OH	26	11	0.4	0.5	0.6	1.2	1.5	(12)	(7)	1.4	(10)
5(6)-CH_2CH_2Cl	57	15	0.3	0.4	0.5	1.1	1.4	(12)	(9)	1.7	(11)
diazaazulene				1.4	5.8	4.2	1.9	37	21		9

[a] Values of m_1^+/m^* and m_2^+/m^* times 10^2 units; values are averages of 6–10 consecutive spectra with standard deviations of 6–17%; values in parentheses are estimates with ±50% error.

Table IV. Exact Mass Determination of the 104–102 Peaks of V[a]

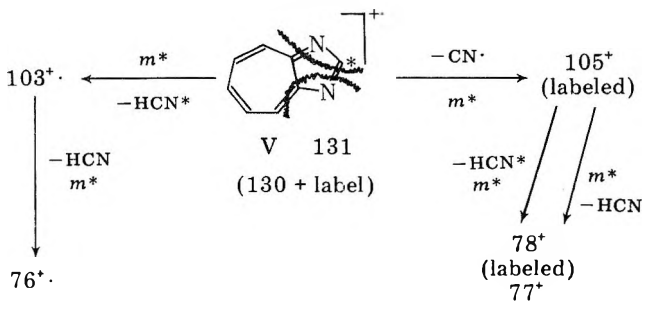
peak	formula	calcd	obsd mass
104	$C_6H_4N_2$	104.0374	
	C_7H_6N	104.0500	104.0494
103	$C_6H_3N_2$	103.0296	
	C_7H_5N	103.0422	103.0424
102	$C_6H_2N_2$	102.0203	
	C_7H_4N	102.0344	102.0355

[a] Obtained by peak matching with a resolution of 5000 at m/e 100 using perfluorotributylamine standard, reference peak at 99.99361.

131 ions in the spectra and the similarity of daughter and metastable ion intensities for subsequent fragmentations of this ion (Table III) strongly support this assumption.[17] With D as the common structure, the loss of $H^{12}CN$ probably involves the two carbons in the seven-membered ring attached to nitrogen. Two competing mechanisms are suggested, one of which involves loss of the 2-^{13}C label, the other results in loss of unlabeled HCN. Alternatively, the rearrangement process involving ring expansion of the carbocyclic ring could also involve rearrangement of the imidazole nucleus to some other structure such as a seven-membered ring analogue of o-aminobenzonitrile. The question, then, is whether the common ring-expanded species possesses structure D or further rearrangement takes place involving the imidazole nucleus as found for benzimidazole itself. To help answer this question, an analogue of structure D was examined. The somewhat unstable compound 1,3-diazaazulene (cycloheptimidazole (V)) was synthesized according to the literature procedure[19] and the 2-^2H- and 2-^{13}C-labeled derivatives were obtained by slight modification of this synthesis.

The initial fragmentation steps of V (Scheme II) involve the loss of 26 and 28 mass units for both the ^2H- and ^{13}C-labeled compounds (26 and 27 for nonlabeled). While the former could a priori involve either H_2C_2 or CN·, exact mass determination of the M − 26 and related daughter ions (Table IV) is consistent with a single nitrogen atom in these ions. Further, the loss of CN· is reasonable in that a cation is formed from the parent radical cation by this process. Surprisingly, the losses of both

Scheme II



CN· and HCN fragments involve no detectable scrambling of either the deuterium or carbon-13 label for either stable or metastable ions.[20] This lack of rearrangement before fragmentation attests to the relative stability of the charged 1,3-diazaazulene nucleus and strongly supports a similar structure for the common 131^+ ions of benzimidazoles I–IV. In addition, the observation of two clearly separate fragmentation pathways for V (Scheme II) is excellent support for two analogous paths for the 131 ions of I–IV, i.e., the competitive losses of fragments v and vi from structure D in Scheme I.

It could be argued that a direct comparison of the behavior of the V radical cation (130 m/e) with the 131 cation of I–IV is not justified on the basis of different electronic states for these two ions. It is our feeling that the major differences between the radical cation and cation of similar structure here is that the former should be relatively less stable and undergo losses of small radical molecules as well as neutral molecules. For the 1,3-diazaazulene radical cation, these two differences are evident in relatively greater daughter ion intensities and loss of CN·, respectively. Nonetheless, both loss of CN· and HCN in the spectrum of V display strong metastable peaks. These ions possess energies and lifetimes similar to the 131^+ ions, although the (former) radical cations show no evidence of rearrangement prior to fragmentation. Unless such long-lived radical cations are inherently less prone to rearrangement, an unreasonable assumption in view of the extensive rearrangement observed for the benzimidazole radical cation, the 131^+ ion, should also be relatively unsusceptible to rearrangement because of the charge delocalization in structure D.

To clarify the nature of the scrambling or rearrangement processes leading to competitive losses of $^1H/^2H$ and $^{13}C/^{12}C$ with HCN, the trilabeled compound [1,2-$^2H_2$-2-^{13}C]-4(7)-methylbenzimidazole was synthesized and examined. Although the major metastable losses from the M − 1 ion of this derivative involve $^2H^{13}CN$ and either ^2HCN or $H^{13}CN$, a significant loss of HCN occurs. Since this loss must involve hydrogens of the carbocyclic ring, limited scrambling of these hydrogens with the imidazole hydrogens is taking place. This suggests a hydrogen scrambling mechanism in addition to that proposed for competitive loss of carbons. Separate mechanisms for hydrogen scrambling and skeletal rearrangement have been reported for benzene[7] and were observed for benzimidazole in this work. It is possible that the exchangeable hydrogen of structure D is responsible for promoting such limited scrambling, especially in view of the lack of scrambling of the 2 hydrogen of V with the carbocyclic ring hydrogens.

Our view of the overall fragmentation behavior of the common 131 ions of I–IV involves the basic nuclear framework of V. The loss of a small radical molecule from the parent ion via β cleavage of the 5(6) substituent occurs with rearrangement to the ring-expanded structure D. Like the parent ion of V, subsequent fragmentation occurs via two competitive mechanisms involving loss of the 2 carbon and either of the

two carbocyclic ring carbons, respectively. Rearrangement of the nuclear framework of structure D or V prior to fragmentation is not evident. A mechanism exists for limited scrambling of the hydrogens of D which is separate from that involving competitive loss of carbon. The existence of common ion D and its subsequent behavior offers a ready means of identifying benzimidazole derivatives with alkyl substituents on the carbocyclic ring. Similar structures are possible for alkylbenzimidazoles with additional substituents on the carbocyclic ring. Derivatives with additional substitution on the imidazole ring, however, exhibit more complicated behavior with the possibility of other ring-expanded intermediates, and these structures will be discussed in a subsequent paper.

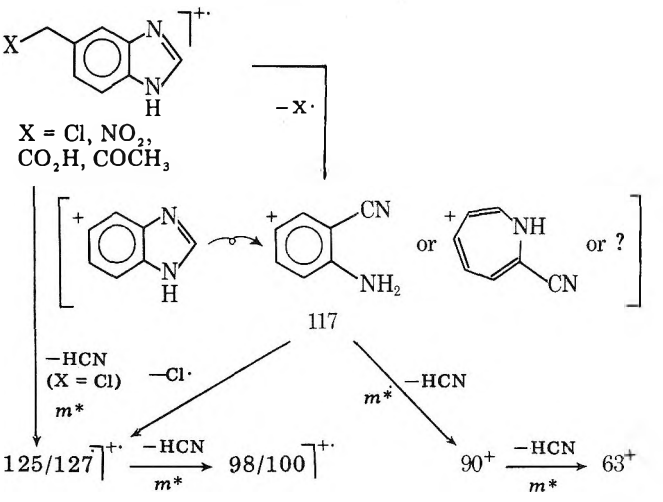
Fragmentation via the 117 Ion. In addition to ring expansion on loss of part of the 5(6) substituent, complete loss of a substituent may occur with formation of a 117 ion, i.e., an ion possibly similar to the M − 1 ion of benzimidazole. The four derivatives which follow this pathway are VII–X. Although the relative intensity of the 117 ions compared to subsequent daughter ions is less than that of the common 131 ions above, this ion is still one of the most intense and is the intermediate in the preferred fragmentation pathway of VII–X. The presence and behavior of the 117 ion, then, represents an identifying characteristic for the benzimidazole nucleus of these derivatives.

Scheme III depicts the general mass spectral behavior of VII–X. For the carboxyl and acetyl derivatives, the two-step loss of the substituent to give the 117 ion is the exclusive fragmentation pathway. For the chloro compound (IX), a competitive pathway exists involving loss of HCN from the parent ion followed by loss of either the chloro group or a second HCN molecule. The nitro derivative (X) also displays a characteristic alternative in the sequential loss of NO and CO.[21] These alternative paths for IX and X will be discussed in more detail later.

It was initially suspected that the 117 ions of VII–X possessed a common structure. The relative intensities of the 117 ions with respect to daughter and metastable ions associated with the sequential loss of two HCN molecules were very similar for VII–X as well as for the M − 1 ion of benzimidazole. Initial ^{2}H-labeling studies involving replacement of the 1 hydrogens of IX and X were disappointing, however. The competitive metastable ratios for losses of HCN and ^{2}HCN were not similar (Table II). Carbon-13 labels were therefore incorporated in the 2 positions of VIII–X and the fragmentations of the labeled 118 ions observed. For all three compounds, the ratios of metastable loss of HCN to H^{13}CN were essentially identical (Table II). Even the benzimidazole M − 1 ion, although much less intense and, therefore, exhibiting weak metastables, displayed an approximately similar ratio. One can conclude, then, that these 117 ions all possess the same structure.

The establishment of a common structure for these 117 ions raises the question of the nature of this structure. A priori, the benzimidazole nucleus might be expected to maintain its integrity prior to fragmentation. The common behavior of benzimidazole, imidazole, and o-aminobenzonitrile indicates that skeletal rearrangement occurs even for the parent radical cation.[3,4] Nuclear rearrangement of the 117 ion is therefore quite probable, especially in view of the predominate metastable loss of unlabeled HCN from the 2-^{13}C-labeled 117 ions of VIII–X. Although the *o*-aminobenzonitrile structure is presumed for benzimidazole,[3] a variety of other structures are possible (Scheme III). The present labeling studies allow no differentiation among possibilities and additional suitably labeled models are not readily available. Thus, until further labeling is carried out on the carbocyclic ring of these compounds and appropriate models are constructed, choosing a specific structure for the common 117 ions is not possible.

Scheme III



The success of the carbon-labeling experiment in demonstrating common structure for the 117 ions despite inability of the deuterium label to do so points to an important advantage of this technique. The common ions examined here, both the 131 and 117 species, arise from prior fragmentation of different molecular ions. In the successful application of deuterium labeling to common structure proof,[3,4] only the parent ions of different molecules were examined. It is entirely possible (as shown for the trilabeled derivative of benzimidazole and IV) that facile hydrogen scrambling may occur independent of or in addition to skeletal rearrangements. This may be especially true for compounds such as benzimidazoles which have a labile and exchangeable hydrogen in the 1 position. It is not unreasonable to assume that partial hydrogen scrambling occurs to different extents prior to formation of a common daughter ion for widely different derivatives, i.e., IX and X. Thus, carbon-13 labeling is much more likely to substantiate common structures than deuterium labeling for ions resulting from fragmentation of different parent ions. For parent ions of common structure but different origin, both methods may be effective.

As mentioned previously, both the chloro and nitro derivatives exhibit fragmentation pathways other than via the 117 ion. For the chloro compound, the initial step in two additional paths involves HCN loss and the 2-^{13}C label shows that competitive mechanisms are involved. The M − HCN fragment thus formed may then lose either HCN or Cl· with subsequent fragmentation of the daughter ions thus obtained. While the molecular ion preferentially loses H^{12}CN over H^{13}CN in metastable transitions (with a ratio of 3.5), the M − HCN ion undergoes predominant loss of H^{13}CN. This sequential loss of two HCN molecules seemingly parallels the behavior of benzimidazole, $118^{+\cdot} \rightarrow 91^{+\cdot} \rightarrow 64^{+\cdot}$. However, the M − HCN ion at *m/e* 91 shows complete scrambling of retained carbon-13 before fragmentation. Thus, similar molecular fragments are lost for both carbons, but differences in the amounts of carbon scrambling or in the competitive fragmentation pathways are observed.

The alternate pathway for 5(6)-nitrobenzimidazole (IX) involves the well-documented[21] loss of NO with transfer of an oxygen atom to the ring. Subsequent loss of CO leads here to an ion of *m/e* 106. While it would be interesting to postulate a structure similar to a protonated 1,3-diazapentalene for this ion, the nuclear rearrangements observed for benzimidazole and in I–IV preclude such speculation. It is highly probable that imidazole moiety ring opening is combined with other skeletal rearrangements to give a 106 ion whose structure is quite different from the parent molecule.

Table V.[a] Comparison of 143^+ Ions of Vinylbenzimidazoles using the Relative Intensities of m^+ (143^+), d^+ (116^+), and m^* (94.1)

substituent X	m^+/d^+	$(m^+/m^*) \times 10^{-2}$	$(d^+/m^*) \times 10^{-2}$
H	2.4	1.4	0.6
CO_2H	1.7	1.3	0.7
CO_2CH_3	1.6	0.6	0.4
$CO_2CH_2CH{=}CH_2$	1.8	0.7	0.4
$CONHCH_2CH{=}CH_2$	1.8	0.7	0.4

[a] Values obtained are averages of two or more spectra run consecutively.

The final derivative (XI) classed with these 117 ions is included because of the similarity of its behavior to the acetyl derivative although its base peak and main fragmentation path are through a 119 rather than 117 ion. For this α-hydroxyethyl compound, sequential loss of CH_3· and CO parallels VIII. In this case, however, concomitant transfer of two hydrogen atoms occurs to the benzimidazole nucleus. The 119 ions thus obtained are relatively intense (as the base peak) and its relative stability may well be due to charge delocalization within the benzimidazole framework. However, in view of extensive skeletal rearrangement in the other derivatives, it is quite possible that the subsequent sequential loss of two HCN molecules from the 119 ion involves rearrangement and quite probable that competitive fragmentation mechanisms exist.

Our main interest in this derivative was in the nature of the hydrogen transfer from the side chain. To study this in more detail, the α-deuterio derivative was synthesized by sodium borodeuteride reduction of the acetyl compound. Very little scrambling of the ^2H with the methyl hydrogens is observed prior to CH_3· loss. Almost all of the ^2H is transferred to the nucleus on CO loss, analogous to the general behavior of benzyl alcohols.[21] In contrast to simple benzyl alcohols, however, this 119 ion does not evidence loss of an H_2 molecule but shows sequential loss of two HCN. In addition, the metastable loss of ^2HCN is observed in the statistical amount from both the 119 and 92 ions. Complete hydrogen scrambling is therefore occurring in the metastable ions in contrast to the limited hydrogen scrambling of the benzimidazole 118 ion and the common 131 and 117 ions. This 119 ion, although exhibiting the sequential losses of two HCN, does not behave like other derivative cations and radical cations. This unique behavior must be related to the presence of the additional hydrogen atoms in promoting hydrogen scrambling and perhaps skeletal rearrangements. This possibility may be further investigated using combined ^{13}C and ^2H labeling.

5(6)-Vinyl Derivatives. The vinyl derivatives studied include the parent 5(6)-vinylbenzimidazole (XII) and four derivatives of β-[5(6)-benzimidazole]acrylic acid (XIII–XVI). While the mass spectral behavior of the latter compounds is fairly straightforward, i.e., via initial loss of carboxylic acid fragments, the behavior of the parent is complex. Three major fragmentation pathways are evident involving (in decreasing importance): (a) initial loss of H· followed by HCN, (b) loss of C_2H_2, and (C(c) direct loss of HCN. Although HCN loss is the least important of the three, the fact that this fragmentation of the molecular ion is observed for only two of all the derivatives examined (XII and X) attests to the relative stability of these two substituents to fragmentation. For most derivatives, the initial loss involves all or part of the substituent, while for the chloro and vinyl groups a significant number of molecules lose HCN initially from the benzimidazole framework.

The loss of C_2H_2 is the second most important fragmentation of XII. With ^2H labeling in the α position of the vinyl group, almost complete loss of the label is observed in this process. This is consistent with one of two possibilities with regard to hydrogen scrambling in the side chain. Assuming a four-membered transition state involving transfer of the terminal hydrogen prior to loss of acetylene molecule, either no hydrogen scrambling occurs prior to fragmentation or scrambling does occur and a large deuterium isotope effect greatly favors transfer of hydrogen over deuterium. The latter is consistent with scrambling observed in the major fragmentation path.

The predominant fragmentation of XII involves initial loss of H· from the parent ion followed by two HCN molecules. Incorporation of deuterium in the α position results in loss of both hydrogen and deuterium in the initial step in the ratio of 3.4 and 3.6 for stable and metastable ions, respectively. These values are consistent with complete scrambling of side-chain hydrogens coupled with a deuterium isotope effect of 1.7–1.8 for hydrogen atom loss. Observation of the same hydrogen/deuterium ratios for stable and metastable ions indicates fast hydrogen scrambling before fragmentation, since a slow rearrangement process would be expected to give a significantly different value for the two energetically different types of ions.

In line with the behavior of the alkyl-substituted derivatives and with the behavior of styrenes,[22] it seems reasonable to postulate a ring-expanded structure for the M − 1 (143) ion of XII. The relative stability of this ion is attested to by its intensity compared to other daughter ions and subsequent fragmentation. The observed fragmentations of this ion do not involve the side-chain, but rather sequential loss of two HCN molecules. Further, essentially complete hydrogen–deuterium scrambling occurs in the labeled 143 ions prior to loss of HCN or ^2HCN. While a reasonable structure for this ion would be an eight-membered carbocyclic ring similar to that postulated for styrene,[22] the tendency of many of the benzimidazole derivatives to undergo extensive skeletal rearrangement makes other structures possible.

For the remaining vinyl carboxylic acid derivatives, the initial fragmentation involves loss of all or part of the carboxylic acid group. By far the most important process in all cases is formation of the 143 ion via loss of CO from the low intensity vinyl acrylonium ion. Similar to the behavior of the 143 ion of the parent vinyl compound, fragmentation of these ions involves loss of two HCN molecules. A comparison of relative stable and metastable ion intensities[17] (Table V), as was presented in Table III for the 131 ions, strongly supports a common structure for the 143 ions derived from all five alkenyl compounds. This 143 ion, then, represents a general fragmentation pathway for these derivatives and should serve as an identifying characteristic for related compounds.

Conclusions

The representative 5(6)-substituted benzimidazoles studied here may be classed into three groups according to common fragmentation pathways. Within two of these groups, proof of common intermediate structure is presented for selected 131 and 117 ions employing ^{13}C labeling with the metastable ratio technique. Strong supporting evidence of common structure for the remaining 131 species and for the 143 ions is provided by comparison of relative stable and metastable ion intensities.

The use of ^2H and ^{13}C labeling further indicated that skeletal rearrangements and/or competitive fragmentation mechanisms exist for most, if not all, derivatives for the parent or common intermediate ions of the major fragmentation pathways. The exact nature of these rearrangements and mechanisms is not apparent from this work for most derivatives. For the common 131 ions, however, very good evidence exists for a ring-expanded structure similar to 1,3-diazaazu-

lene with the competitive fragmentations involving the 2 carbon and carbocyclic ring carbons. In addition to skeletal rearrangements, independent hydrogen scrambling takes place for several derivatives and may, indeed, be a general phenomena.

The detailed examination of these benzimidazoles indicates that, in general, their mass spectral behavior is much more complex than previously postulated.[15,16] Nonetheless, the fact that common intermediates and fragmentation pathways exist allows classification into general families of derivatives. These general paths should be valuable for identification and characterization of additional benzimidazoles according to the type of substitution present. Furthermore, the use of the metastable ratio technique developed here for common structure proof of carbon-13-labeled compounds should be generally applicable to many isotopically labeled compounds. Such isotopic labeling (^{13}C, ^{15}N, and ^{17}O) will become increasingly important in elucidating the complex mass spectral behavior of heterocyclic compounds.

Experimental Section

All aromatic diamines (except 2,3-diaminotoluene) used in the synthesis of the various benzimidazoles were commercially available or previously described in the literature. DCME (α,α-dichloromethyl methyl ether) was purchased from Aldrich; this material may be carcinogenic and must be handled with due precautions. The carbon-13-labeled compounds used in the synthesis of ^{13}C-labeled derivatives (sodium [^{13}C]formate and [^{13}C]thiourea) were 90% enriched and purchased from Merck Isotopes. All other reagents and solvents were commercially available and purified as needed.

General Synthesis of Benzimidazoles. A. Phillip's Procedure (Formic Acid). The appropriate aromatic diamine (Aldrich) (0.01 mol) was slurried with excess formic acid in 20 mL of 4 N HCl. The mixture was heated at reflux for 6–8 h and charcoal added carefully to the dark reaction mixture. After filtering and cooling, the strongly acidic mixture was neutralized with dilute NaOH or $NaHCO_3$ to pH 7. The precipitated benzimidazole was collected by filtration and air dried. Generally, recrystallization from water or aqueous ethanol gave the desired pure product. Several of the derivatives, such as the 5(6)-chloro, 5(6)-methyl, and 5(6)-acetyl compounds, are extremely hydroscopic. These materials could be readily purified by column chromatography on silica with ethyl acetate solvent. All mp's and IR data agreed with those previously reported.

B. Alternative Procedure (DCME). One equivalent of the reagent α,α-dichloromethyl methyl ether (DCME) was added dropwise to a cooled (0 °C) mixture of 1 equiv of aromatic ortho diamine plus 1 equiv of tri-*n*-butylamine in dry THF. After complete addition, the reaction mixture was allowed to warm to room temperature and stirring continued for 4–24 h. The pure product precipitated as the hydrochloride salt, and may be neutralized with dilute $NaHCO_3$. This procedure gave the following isolated yields of benzimidazoles (substituent and percent yield): H, 100%; 5(6)-CH_3, 61%; 4(7)-CH_3, 80%; 5(6)-NO_2, 70%; 5(6)-$COCH_3$, 62%; 5(6)-Cl, 74%.

Complete characterization of the previously unreported 5(6)-acetylbenzimidazole is given in ref 23.

2,3-Diaminotoluene. A suspension of 2-nitro-6-methylaniline (1.0 g, 0.007 mol) in 45 mL of 3 N sodium hydroxide containing 9 g of sodium dithionite was heated at 80 °C with stirring for 3 h. The orange starting material gradually dissolved to give a clear, colorless solution which was filtered hot and allowed to cool. Extraction with ether, which was then dried with 4A molecular sieves and evaporated, gave the desired product as tan crystals in 90% yield, mp 77–78 °C.

[2-^{13}C]-4(7)-Methylbenzimidazole (IV). A mixture of 2,3-diaminotoluene (0.244 g, 0.002 mol) and sodium [^{13}C]formate ^{13}C (0.167 g, 0.0024 mol) was added to 2–3 mL of 5 N hydrochloric acid. The mixture was heated at 90 °C for 4 h, diluted to 6 mL, and made slightly basic with concentrated ammonium hydroxide. The oil which initially separated rapidly solidified to give a light yellow product in 85% yield, mp 142–144 (lit.[24] mp 145 °C).

The following compounds were obtained with the above procedure and quantities from commercially available diamines which were first purified by sublimation in vacuo at 80 °C.

[2-^{13}C]Benzimidazole. An 80% yield of needles was obtained on cooling the hot neutralized reaction mixture, mp 170 °C (lit.[24] mp 170 °C).

[2-^{13}C]-5(6)-Chlorobenzimidazole (X). An 85% yield of off-white precipitate was obtained from the neutralized reaction mixture, mp 125 °C (lit.[25] mp 125–126 °C).

[2-^{13}C] 5(6)-Nitrobenzimidazole (IX). The reddish-brown crude material was obtained in 90% approximate yield. A small sample was recrystallized from water, mp 199–200 °C (lit.[26] mp 209–210 °C).

[2-^{13}C]-5(6)-Acetylbenzimidazole (VIII). This material was isolated in the same manner as the 5(6)-methyl derivative above. Synthesis of the starting diamine has been described.[23]

[α-^2H]-5(6)-(α-Hydroxyethyl)benzimidazole (XI). 5(6)-Acetylbenzimidazole was reduced with a 10% excess of $NaBD_4$ in ethanol. This material was isolated as described.[23] The NMR of this material exhibited no α-hydrogen resonance, while the methyl group was observed as a singlet.

[α-^2H]-5(6)-Vinylbenzimidazole. Dehydration of the α-deuterio derivative described above was carried out in the manner described.[23] The NMR of this material showed no splitting of the terminal methylene hydrogens by an α hydrogen.

β-[5(6)-Benzimidazole]acrylic Acid Chloride. β-[5(6)-Benzimidazole]acrylic acid[27] (1.0 g, 0.005 mol) was refluxed with 10 mL of thionyl chloride for 4 h. The slurry thus obtained was dried in vacuo to remove excess thionyl chloride to give an off-white dry solid which was used as obtained.

Methyl β-[5(6)-Benzimidazole]acrylate (XIV). To a cooled (0 °C) 5-mL sample of methanol was added the acid chloride prepared above (0.5 g, 0.002 mol). After stirring 4 h, the grey precipitate was filtered, dissolved in water, and neutralized with $NaHCO_3$. Extraction with chloroform twice followed by solvent evaporation gave an off-white product in 89% yield which was used as obtained.

Allyl β-[5(6)-Benzimidazole]acrylate (XV). This material was obtained in 68% yield in the same manner as XIV using allyl alcohol. A small analytical sample was prepared by sublimation at 80 °C and 0.5 mm Hg: mp 100 °C; NMR (Me_2SO-d_6) δ 7.4 (H_2, s), 7.12–6.73 (3 aromatic H + 1 vinyl H, m's), 5.68 (1 vinyl H, J_{trans} = 16 Hz), 5.08 (1 allyl H, m), 4.52 (2 allyl H, m), 3.85 (2 allyl H, ~d, $J \simeq 5$ Hz).

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 67.82; H, 5.39; N, 11.87.

***N*-Allyl-β-[5(6)-benzimidazole]acrylamide (XVI).** This material was obtained in 75% yield from the acid chloride and excess allyl amine. The crude reaction mixture was cooled to −5 °C overnight to give golden needles of product. Recrystallization from 50% aqueous methanol gave pale yellow needles: mp 232–238 °C (thermal polymerization); NMR (Me_2SO-d_6) δ 8.10 (H_2, s), 7.85–6.85 (4 H, m's), 6.68 (1 vinyl H, d, J = 16 Hz), 5.9 (1 H, m), 5.15 (2 H, m), 3.9 (2 H, m); IR (KBr pellet) 3320, 3100–2600, 1660, 1615, 1540, 1465, 1420, 1350, 1315, 1300, 1285, 1260, 1225, 1210, 1035, 1005, 970, 950, 890, 860, 820 cm^{-1}.

[2-^{13}C]-1,3-Diazaazulene-2-thiol (VI). This material was prepared according to the procedure of Nozoe, Makai, and Murato,[19] except that [^{13}C]thiourea was used instead of thiourea in the condensation with methyl tropolone.

[2-^{13}C]-1,3-Diazaazulene (V). Using the above carbon-13-labeled material, the literature procedure[19] was used for the oxidative desulfurization in dilute nitric acid. After neutralization of the product solution, the desired material could be isolated in very pure form by chloroform extraction, drying over 4A sieves, and solvent evaporation to give bright yellow crystals. Rapid air oxidation of this material requires cold storage under argon or nitrogen.

[2-^2H]-1,3-Diazaazulene. The unlabeled thiol derivative VI was slurried with D_2O containing 10% HNO_3 and normal desulfurization carried out to give the desired material with greater than 90% deuterium incorporated in the 2 position.

Mass Spectra. All spectra were obtained on the AIE-MS902 operating at low resolution unless otherwise noted for specific exact mass determinations. Spectra of compounds with deuterium-replaced exchangeable hydrogens were obtained by repeated scanning of a D_2O slurry of the compound introduced on the probe directly into the source. For labeled compounds, the amount of isotope incorporation was determined by using a minimal ionizing potential (~8–14 eV) to directly observe the parent ions. Spectral comparisons involving ratios of parent, daughter, and metastable peaks (e.g., Table V) were carried out on a series of spectra run consecutively for each compound. The compounds being compared were run in rapid succession under conditions as nearly identical as possible. It should be noted that these ratios, i.e., p^+/m^* and d^+/m^*, have no absolute significance and may vary greatly with small changes in operating conditions or machine configurations.

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Registry No.—2,3-Diaminotoluene, 2687-25-4; 2-nitro-6-methylaniline, 570-24-1; β-[5(6)-benzimidazole]acrylic acid chloride, 66792-91-4; 5(6)-chlorobenzotriazole, 94-97-3.

Supplementary Material Available: Table of mass spectra data for benzimidazole substituents (6 pages). Ordering information can be found on any current masthead page.

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Carbon-13 Nuclear Magnetic Resonance Chemical Shifts of Substituted Benzimidazoles and 1,3-Diazaazulene

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The ^{13}C NMR chemical shifts of a variety of substituted benzimidazoles and two 1,3-diazaazulenes are presented. Peak assignment is made with substituent-induced chemical shifts (SCS) and long-range ^{13}C–^{1}H and ^{13}C–^{13}C coupling constants. The SCS of benzimidazole derivatives are compared to those of benzenes. Excellent correlations of $\delta(C_2)$ are observed with σ_p and σ_6 for 5(6) substituents. Similar correlations involving the para carbon (C_8) exhibit greater scatter than those of the 2 carbon. The $\delta(C_2)$ values also correlate well with pK_a, and this correlation is used to predict a pK_a of 3.4 for 5(6)-acetylbenzimidazole. The ^{13}C spectrum of 1,3-diazaazulene is unambiguously assigned. The chemical shifts do not agree with previously calculated charge densities. The average chemical shifts of the carbocyclic carbons indicate decreasing electron density in the seven-membered ring in the series azulene, 1,3-diazaazulene, protonated 1,3-diazaazulene, and tropylium ion.

The determination and assignment of ^{13}C NMR chemical shifts is rapidly becoming routine in many laboratories. This routine use is dependent on the confirmation of shift assignments by techniques such as partial or complete coupling of carbons to hydrogens. Increases in instrument sensitivity as well as the development of gated decoupling has made the acquisition of completely coupled spectra readily feasible. The interpretation of these coupled spectra is simplified by the fact that first-order analysis is generally sufificient for determination of not only one-bond but two- and three-bond coupling constants at the resolutions normally available. These long-range coupling constants should be characteristic of specific molecular subunits as are long-range hydrogen–hydrogen coupling constants in ^{1}H NMR spectroscopy.

One of the most obvious and useful examples of long-range ^{13}C–^{1}H coupling involves the methyl group. Unlike the small to negligible ^{1}H–^{1}H coupling of ring and methyl hydrogens, ring carbons exhibit large exocyclic coupling constants to methyl hydrogens. For both pyridine[2] and quinoline[3] derivatives, the $^{2}J_{^{13}C-^{1}H}$ of the ipso carbon is found to be approximately 6 Hz, while the $^{2}J_{^{13}C-^{1}H}$ of the ortho carbons generally falls between 4 and 5 Hz. These coupling constants should be characteristic for methyl-substituted compounds and should allow ready identification of both the ipso and ortho carbon resonances in coupled spectra. Furthermore, the relatively small effect of a methyl substituent on the chemical shift of carbons other than the ipso carbon should allow identification of the ^{13}C resonances of the unsubstituted compounds once the spectrum of the methyl derivative is assigned. Thus, the examination of the spectrum of a methyl analogue is useful for the assignment of the spectrum of the parent compounds.

The ^{13}C NMR spectrum of benzimidazole has been reported previously in comparison with the spectra of purine derivatives.[4] The spectra of the benzimidazole HCl salts and the sodium salt of the anion were also given. Protonation of either the anion or the neutral benzimidazole resulted in downfield shifts of $C_{5,6}$ along with upfield shifts of C_2, $C_{4,7}$, and $C_{8,9}$. These characteristic protonation shifts were then applied to purine spectra to determine the site of protonation of this material.[4]

In this paper, we report the ^{13}C chemical shifts of a number of substituted benzimidazoles. The long-range coupling of methyl hydrogens is used to more completely assign the

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Table I. The ^{13}C Chemical Shifts of Benzimidazoles and 1,3-Diazaazulenes[a]

compound	registry no.	carbon 2	4	5	6	7	8	9	10 or CH_3
I[b]		141.46	115.41	122.87	122.87	115.41	137.92	137.92	
I·HCl[b]		139.58	114.44	127.29	127.29	114.44	129.79	129.79	
I′		141.95	115.64	123.23	123.23	115.64	(138.5)	(138.5)	
I[c]	51-17-2	141.41	115.87	127.52	127.52	115.87	132.19	132.19	
I[g]		139.6	115.5	127.6	127.6	115.5	130.4	130.4	
II′		141.69	115.28	134.23	125.79	115.24	135.96	137.32	21.70
II[c]	614-97-1	(141.1)	115.57	138.38	129.40	115.69	130.61	132.80	22.44
III′		141.80	126.23	124.07	123.70	113.59	138.07	138.39	17.04
III[c]	4887-83-6	140.67	126.75	127.85	127.56	112.95	131.54	131.69	16.99
IV	615-15-6	152.89	115.14	123.11	123.11	115.14	139.60	139.60	14.31
IV[c]		152.92	115.49	127.38	127.38	115.49	132.82	132.82	13.51
V[d]	312-73-2	(141.4)	116.88	124.78	124.78	116.88	138.44	138.44	(119.8)
V[c]		141.50	117.29	125.80	125.80	117.29	138.00	138.00	119.87
VI′	4887-82-5	143.72	116.98	129.23	124.09	116.01	(132.3)	(137.5)	
VII′	58442-16-3	145.18	118.05	133.14	124.09	115.64	141.48	138.87	26.79[f]
VIII	94-52-0	147.15	113.63	(147.2)	119.38	115.79	(145.1)	(139.3)	
VIII′[c]		147.48	114.14	146.39	121.08	117.07	140.83	137.14	
IX[e]	15852-41-2	187.09	139.16	123.45	134.79	123.45	139.16	157.78	157.78
X[e]	275-94-5	167.83	136.14	134.55	140.20	134.55	136.14	161.67	161.67
X[g]		155.90	143.16	140.98	149.53	140.98	143.16	154.81	154.81
azulene[h]		137.7	136.7	123.0	137.2	123.0	136.7	140.6	140.6

[a] In CD_3OD or 1:4 CD_3OD + CH_3OH unless otherwise noted. [b] Values reported in ref 4. [c] In CD_3CO_2D or 1:4 CD_3CO_2D + CH_3CO_2H. [d] 1:2:2 CH_3OH + $CDCl_3$ + Me_2SO-d_6. [e] In Me_2SO-d_6. [f] $\delta(COCH_3)$. [g] In Me_2SO-d_6 + 10% concentrated HCl. [h] Reference 18.

spectra of methyl derivatives: $^2J_{C-CH_3}$ equals 6.5–8.0 and $^3J_{C-CH_3}$ falls between 4.0 and 6.0 Hz. Substituent-induced chemical shifts are correlated with various substituent parameters and with pK_a. Finally, a procedure is established for carbon identification in ^{13}C spectra employing long-range ^{13}C–^{13}C coupling in enriched samples. This procedure allows unambiguous assignment of the spectrum of 1,3-diazaazulene.

Experimental Section

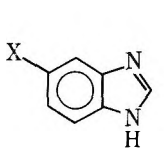
The syntheses of the various compounds are described in the preceding paper in this series.[1] Carbon-13 enriched sodium formate and thiourea were used to obtain enriched benzimidazoles and 1,3-diazaazulene derivatives, respectively.

Most of the NMR spectra were obtained with a JOEL-PFT-100 although a Varian CFT-20 was used for several samples with identical results for overlapping data. The resolution obtained was 0.3 to 0.7 Hz for the former instrument and 1.0 Hz for the latter. Solvent mixtures of deuterated and nondeuterated materials were generally employed to reduce overall cost. Hydrogen-decoupled spectra were obtained in 5 min to 3 h while coupled spectra required 4 to 18 h for adequate signal acquisition of even concentrated solutions. All chemical shifts are relative to internal Me_4Si or calculated with respect to Me_4Si from solvent resonance frequencies reported by Levy and Nelson.[5] Any values reported in parentheses are approximate due to low intensity or unresolved coupling.

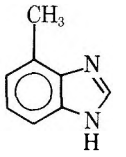
Results and Discussion

The compounds studied consist of the parent benzimidazole (I); three isomeric methyl benzimidazoles (II–IV); 2-trifluoromethylbenzimidazole (V); 5(6)-chloro- (VI), 5(6)-acetyl- (VII), 5(6)-nitrobenzimidazole (VIII); and two 1,3-diazaazulene derivatives (IX and X). Compounds I–III and VI–X were also prepared with 90% ^{13}C enrichment in the 2 position and these enriched compounds are designated by a prime, e.g., I′. The ^{13}C chemical shifts of I and its two ions have been previously reported.[4]

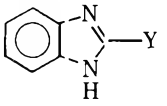
The ^{13}C chemical shifts of I–X are presented in Table I for all of the solvent systems employed. The literature values for benzimidazole, protonated benzimidazole, and azulene are given for comparison. The greater solubility of the compounds studied here in methanol, acetic acid, and dimethyl sulfoxide (Me_2SO) led to the use of these solvents since concentrated solutions greatly facilitate acquisition of spectra. Comparison



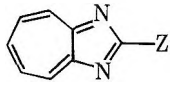
I, X = H
II, X = CH_3
VI, X = Cl
VII, X = $COCH_3$
VIII, X = NO_2



III



IV, Y = CH_3
V, Y = CF_3



IX, Z = SH
X, Z = H

of chemical shifts, however, must be made with the awareness that solvent and concentration changes can cause several ppm differences in chemical shift.[5] Carbon assignments were initially made by application of substituent-induced chemical shifts (SCS) for monosubstituted benzenes to the shifts of the parent benzimidazole. The characteristic quartet for two- and three-bond coupling to methyl hydrogens was then used to identify the ipso and ortho carbon peaks of II–IV in the ^{13}C–^1H coupled spectra. This technique was especially important for the 4(7)-methyl derivative (III′) for which the chemical shifts of the C_5 and C_6 peaks were within 0.5 ppm of each other, as were those of C_8 and C_9. The three-bond coupling to the methyl hydrogens, however, allowed ready identification of C_5 and C_9, respectively.

For the 2-^{13}C-enriched derivatives, large three-bond ^{13}C–^{13}C couplings through the imidazole nitrogens were observed in all cases. The much smaller two-bond couplings to the quaternary 8 and 9 carbons were not always resolved and in some cases merely resulted in peak broadening. The 4,8 and 5,7 peaks in the spectrum of X were surprisingly close together. With X′, however, a doublet was observed for the 4,8 peak with $^3J_{^{13}C-^{13}C}$ = 12.2 Hz.

The effect of solvent on ^{13}C chemical shift has not been extensively evaluated in the literature, although Levy and

Table II. Substituent-Induced Chemical Shifts (SCS) of Substituted Benzimidazoles in CD_3OD[a]

substitutent	2	4	5	6	7	8	9
5-CH_3 (II)	−0.3	−0.4	*11.0*	2.6	−0.4	−2.5	−1.2
4-CH_3 (III)	−0.2	*10.6*	0.8	0.5	−2.1	−0.4	–
2-CH_3 (IV)	*10.9*	−0.5	−0.1	−0.1	−0.5	1.1	1.1
2-CF_3 (V)	*−0.6*	1.2	1.6	1.6	1.2	−0.1	−0.1
5-Cl (VI)	1.8	1.3	*6.0*	0.9	0.4	−1.0	−6.2
5-$COCH_3$ (VII)	3.2	2.4	*9.9*	0.9	0.0	3.0	0.4
5-NO_2 (VIII)	5.2	−2.0	*24.0*	−3.9	0.2	6.6	0.8

[a] Ppm from the corresponding carbon substituent[6] of benzimidazole; positive values indicate downfield shifts. [b] The ipso carbon is italic.

co-workers have investigated a few benzene derivatives.[5] Generally, a change of solvent does not greatly change chemical shifts (<1–2 ppm) unless strong solvent–solute interactions occur such as protonation or hydrogen bonding. Interacting substituents such as carboxyl, acetyl, and amino groups are then most affected. A careful investigation of the ^{13}C shifts of imidazole, however, revealed that even for such diverse solvents as $CDCl_3$, Me_2SO-d_6, acetone-d_6, and water, the chemical shifts varied by less than 1.1 ppm.[6]

In this study, the use of methanol, acetic acid, and dimethyl sulfoxide (Me_2SO) was dictated by solubility requirements. With methanol and Me_2SO only small differences were observed with the reported shifts of benzimidazole in ethanol.[4] Even on protonation in Me_2SO, the benzimidazolium carbon peaks were within 1.5 ppm of the values given for an ethanol solution.[4]

The effect of acetic acid on chemical shifts is complicated, of course, by partial protonation. The pK_a of acetic acid is 4.75 while that of protonated benzimidazole is 5.53,[7] indicating that complete protonation of I will not occur in this solvent. Correspondingly smaller changes should be observed in the shifts of I in acetic acid than in HCl·Me_2SO-d_6, although qualitatively similar changes should occur. On protonation of both the anionic and neutral benzimidazole, upfield shifts are observed for C_2, $C_{4,7}$, and $C_{8,9}$ and a downfield shift for $C_{5,6}$.[4] In acetic acid, however, only the $C_{8,9}$ peak is moved upfield and the $C_{5,6}$ peak downfield by more than 1 ppm. For the more basic methyl isomers (II–IV), C_5 and C_6 change 3.6–4.3 ppm while C_8 and C_9 move −4.5 to −6.8 ppm. The much less basic 2-trifluoromethylbenzimidazole (V) exhibits no peak shifts greater than 1 ppm in acetic acid, suggesting little or no protonation. Partial protonation in acetic acid, then, adequately accounts for the changes in chemical shift of I–IV, since even for completely protonated benzimidazole, the C_2 and $C_{4,7}$ peaks change by only 1–2 ppm.[4] Interestingly enough, the use of acetic acid greatly reduces the difference in relative intensity of hydrogen-substituted and quaternary carbons. Indeed, with short pulse delays, integration becomes possible for I–IV.

The substituent-induced chemical shifts (SCS) of several benzimidazoles are presented in Table II and may be compared to corresponding values for monosubstituted benzene derivatives.[5] While both the ipso and para SCS for the 4(7)-methyl and the four 5(6)-substituents parallel the benzene values, the ortho values do not. Only the para chlorine SCS is more than 20–30% different than the benzene values for the ipso and para SCS, and even this value lies in the correct direction. Such good agreement is encouraging for the use of literature SCS for initial spectrum interpretation of multiply substituted benzene derivatives such as benzimidazoles. Using the appropriate parent compound for comparison, both the ipso and para carbons of most derivatives should be readily assignable on the basis of direction and, in most cases, amount of SCS. Since meta carbons generally exhibit SCS of ≤1 ppm for the benzimidazoles as for the benzene derivatives, identifying meta carbons is straightforward. Only the ortho carbons are not easily assigned for benzimidazoles on the basis of benzene SCS. Anomalously large ortho values are observed for C_6 of II′ and for C_4 of VII′. Furthermore, an anomalously large para SCS is observed for C_9 of VI, although the assignment of this peak is certain. While it would be tempting to attribute the anomalous SCS for C_4 of VII′ to a preferred conformation of the acetyl group, the observations on substituted benzaldehydes[8] suggest this is not the case. The difference in the SCS of C_4 and C_6 of VII′ may, however, reflect disparate electronic interactions of the 5(6) substituent with these two positions. For all three electron-withdrawing groups (Cl, CH_3CO, and NO_2), the C_4 resonance is shifted farther downfield or less far upfield than that of C_6. This effect may well be related to structural proximity to the electron-rich imidazole nucleus. Further studies of N-alkylated (nontautomeric) derivatives should clarify this effect.

Assuming that the overall electronic effects of 5(6) substituents of benzimidazole are transmitted normally, i.e., through a combination of field and resonance contributions, then correlations should exist between chemical shifts of specific carbons and various substituent parameters. By analogy with benzene derivatives,[9] the carbon para to the substituent should exhibit the best correlations. In addition, there is some discussion in the literature about the amount and kind of electronic interaction between the benzene and imidazole nuclei of benzimidazoles.[10] If strong interaction is occurring in the ground state, substituent correlations should also exist for the 2 carbon.

Figures 1 and 2 give plots of SCS for C_8 and C_2 with respect to σ_p and σ_p^+.[9,11] The straight lines drawn are included merely for comparison; a least-squares analysis does not seem justified for four experimental points. The values for C_8 give about equal scatter with σ_p and σ_p^+. For C_2, however, excellent correlations are apparent with σ_p and σ_6, while σ_p^+ gives much greater scatter. The parameters σ_6 refer to pK_a's of 6-substituted 1-naphthoic acids.[11] The correlations for C_2 are, in general, much better than for the para carbon C_8. The fact that C_2 correlates so well with σ_p indicates that the electronic effect of the 5(6) substituent is transmitted to the 2 carbon by a combination of resonance and field contributions in about equal amounts.[11]

The relatively poor correlation for C_8 with σ_p or σ_p^+ may be related to the disparate electronic interactions previously postulated to account for the anomalous shifts of C_4 in VI′–VIII′. That is, interaction of the 5(6) substituent with the imidazole nitrogens and 2 carbon interrupt or compete with interaction with the 8 carbon. The Hammett-type parameters employed here probably do not reflect the correct *relative* amounts of resonance and field effects.[11] Thus the observed correlation is not good.

On the basis of the good correlations of C_2 SCS with σ_p, it might be expected that $\delta(C_2)$ would also be related to other physical properties of these derivatives. Figure 3 is a plot of $\delta(C_2)$ against literature values of pK_a of 5(6)-substituted

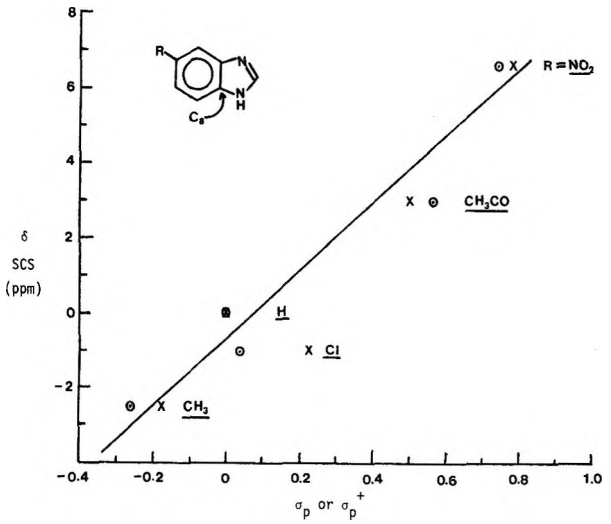


Figure 1. The C_8 SCS of 5(6)-substituted benzimidazoles are plotted against σ_p (×) and σ_p^+ (⊙) values taken from ref 11.

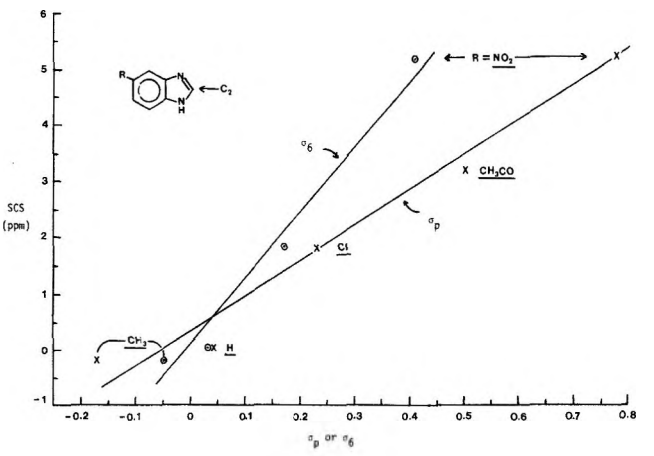


Figure 2. The C_2 SCS of 5(6)-substituted benzimidazoles are plotted against σ_p (×) and σ_6 (⊙) values taken from ref 11.

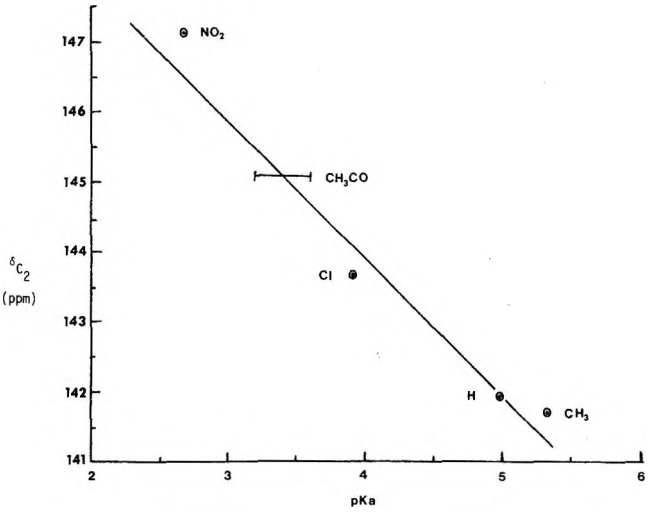


Figure 3. ^{13}C NMR chemical shifts of C_2 are plotted against pK_a of 5(6)-substituted benzimidazoles taken from ref 12.

benzimidazolium ions.[12] The correlation is relatively good, considering that the ^{13}C NMR spectra were obtained in methanol while the pK_a values were determined for 1:1 ethanol–water mixtures.[12] From Figure 3 it seems apparent that the pK_a of a new 5(6)-substituted benzimidazole can be approximated from the ^{13}C chemical shift of the 2 carbon. Thus, the pK_a of VII′ is predicted to be approximately 3.4 on the basis of its $\delta(C_2)$ of 145.18 ppm. It seems reasonable to suggest that analogous heterocyclic acids and bases would obey similar relationships and that the use of ^{13}C NMR spectroscopy for estimation of physical properties might be extremely beneficial.

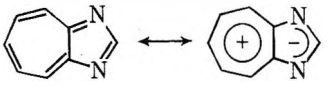
In addition to the above generalizations, specific comments should be made on the SCS values for the methyl and trifluoromethyl derivatives. For all three methyl isomers, the ipso SCS lies between 10.6 and 11.0 ppm, values which are almost 2 ppm greater than that of toluene. In addition, the chemical shift of the methyl carbon at the 2 position is at much higher field than those at the 5 and the 4 positions. This is the reverse of the relative ordering of chemical shifts of the ring carbons in the parent compound, for which the order $C_2 > C_5 > C_4$ is observed with C_2 farthest downfield. This latter order is consistent with both the calculated σ and π charge densities.[4] The large upfield shift of the 2-methyl carbon may reflect greater substituent shielding by the electron-rich π cloud of the imidazole ring or electron transfer from the imidazole ring to the 2 substituent through the σ bond. The carbon of the 2-CF_3 group also resonates at higher field than expected, occurring at 119.8 ppm compared to 124.5 for α,α,α-trifluorotoluene.[13] The relatively high electron density of the α carbons of these 2 substituents may well be related to the unusual reactivity of functional groups at this position.[14] A further unusual feature of the 2 position is the ipso SCS of the 2-CF_3 group. A value of −0.6 ppm for V may be compared to one of −9.0 ppm for α,α,α-trifluorotoluene.[13] It is evident, then, that the 2 position of benzimidazole displays unusual behavior in the ^{13}C NMR in terms of its own chemical shifts and that of substituents attached at this position.[20]

The ^{13}C NMR spectra of the ^{13}C-enriched benzimidazoles were determined to establish a procedure for peak assignment via long-range ^{13}C–^{13}C coupling. From reported observations on ^{13}C-labeled naphthalene and pyridine derivatives,[15] it was expected that $^3J_{^{13}C-^{13}C_3}$ would be larger than either $^2J_{^{13}C-^{13}C}$ or $^4J_{^{13}C-^{13}C}$. Indeed, $^3J_{^{13}C-^{13}C}$ was found to be greatly enhanced through the nitrogen of pyridine compared to similar coupling constants in benzene derivatives.[16] With the benzimidazole derivatives, $^3J_{^{13}C-^{13}C}$ of the 2 carbon to the 4 and 7 carbons was the largest in all the spectra at 5–6 Hz, while $^4J_{^{13}C-^{13}C}$ and $^2J_{^{13}C-^{13}C}$ were on the order of 0 and 1–2 Hz, respectively. Thus, with imidazole-containing heterocycles labeled with ^{13}C in the 2 position, long-range ^{13}C–^{13}C readily identifies carbons three bonds away.

This procedure was then applied to 1,3-diazaazulene similarly labeled in the 2 position. The unlabeled compound exhibits three distinct groups of peaks in the ^1H-decoupled spectrum: a low intensity $C_{9,10}$ peak; a pair of peaks of medium intensity for the C_2 and C_6 carbons; and a close pair of peaks of high relative intensity attributed to the 4,8- and 5,7-carbon pairs. While calculations of π electron density have been carried out on this molecule, the large discrepancies in values make them useless in peak assignment.[17] The 2-^{13}C label, however, clearly distinguishes the C_2 from the C_6 peak and the large doublet ($^3J_{^{13}C-^{13}C}$ = 12.2 Hz) observed for the $C_{4,8}$ peak confirms its identity. Thus, the use of a readily available ^{13}C-labeled derivative of X allows unambiguous assignment of its ^{13}C NMR spectrum.

The chemical shifts observed for X can be compared to those of azulene. In decreasing chemical shift (low to high field), the order for X is 2 > 9,10 > 6 > 4,8 > 5,7, differing from that of azulene[18] only in a reversal of 2 and 9,10. Comparison of the relative order with calculated π electron density[17] is disappointing. None of the three calculations gives even general agreement with the observed chemical shifts, indicating that additional theoretical consideration of X is warranted.

Comparison of the individual carbon chemical shifts of X with those of azulene indicates a definite transfer of electron density from the seven- to the five-membered ring. While the $C_{4,8}$ shifts are similar, those of C_6 and $C_{5,7}$ are 3.0 and 11.6 ppm further downfield for X than for azulene. This is consistent with the 4.05 D dipole moment of X[17] and a charge-distribution structure such as that drawn below. The tropylium-like character of the seven-membered ring of X is further enhanced by protonation of the imidazole ring. For benzimid-



azole in HCl/Me_2SO, the peaks of the 2 and 8,9 carbons are moved upfield by 1.9 and 8.1 ppm, respectively, while the 4,7 peak remains unchanged and the 5,6 peak moves downfield 4.4 ppm. Under the same conditions, the 2 and 9,10 peaks of X are also moved upfield (11.9 and 6.9 ppm, respectively). All of the remaining carbon peaks of the seven-membered ring, however, are shifted downfield by 6.4–9.3 ppm, a much greater average shift than for I. The average chemical shift of carbons 4–8 of X is 136.3 and of protonated X, 143.6 ppm. Both of these values are closer to the chemical shift of tropylium ion (155.3 ppm[19]) than the average for azulene of 131.2 ppm. The series of seven-membered ring derivatives azulene, X, protonated X, and tropylium ion is one of gradually decreasing average electron density in the carbocyclic ring. As expected from the dipole measurement, X exhibits a greater electron transfer from the seven- to the five-membered ring than azulene.

Conclusions

The determination of long-range ^{13}C–^{1}H and ^{13}C–^{13}C coupling constants is extremely useful for peak assignment in ^{13}C NMR spectroscopy. Observation of exocyclic coupling to methyl hydrogens allows assignment of the ipso and ortho carbons of methyl compounds, while the $^{3}J_{^{13}C-^{13}C}$ of 2-^{13}C-enriched imidazole derivatives identifies carbons three bonds distant. For 5(6)-substituted benzimidazoles, correlations of ^{13}C chemical shifts with various Hammett σ parameters are observed, the most useful of which should be the relationship of $\delta(C_2)$ to pK_a. The chemical shifts of carbons in the carbocyclic ring of 1,3-diazaazulene indicate qualitatively a lower average electron density for this ring than in azulene. Protonation of the imidazole ring further decreases the average electron density and makes the seven-membered ring even more tropylium-like for this azulene analogue.

Acknowledgments. The determination of many of ^{13}C NMR spectra by and the helpful discussions with Frank Parker are gratefully acknowledged. Support from the National Institutes of Health under Grant No. 2R01-GM15256 and the Macromolecular Research Center is also gratefully acknowledged.

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Preparation and Absolute Stereochemistry of Isomeric Pyridylethanols and *threo*-Di(2-pyridyl)ethanediol

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Optically active isomeric pyridylethanols have been prepared by microbial (*C. macerans*) reduction of the corresponding acetyl derivatives. The absolute stereochemistry of each alcohol was determined as *S* by conversion to (+)-(*S*)-methyl *O*-acetyllactate. Reduction of 2,2′-pyridil by the same organism yielded (−)-di(2-pyridyl)ethanediol, whose configuration was established as *R,R* by conversion to (*S,S*)-dimethyl diacetyltartrate. The stereospecificity of these reductions is discussed with reference to Prelog's rule for predicting their absolute stereochemistry.

In a recent study of asymmetric cathodic reduction, Kopilov, Kariv and Miller[1] examined the reductions of 2-, 3- and 4-acetylpyridines in the presence of alkaloids known to adsorb on the cathode under the reduction conditions. Since Miller et al. obtained high optical yields (40 and 48% for **1a** and **1b**, respectively), additional studies employing this technique for the synthesis of a wide variety of medicinal compounds can be expected. Although a detailed mechanism was not proposed, it is apparent that any mechanism proposed must account for the absolute stereochemistry of the products. The configurations of (−)-**1a**, (−)-**1b**, and (−)-**1c** were assigned

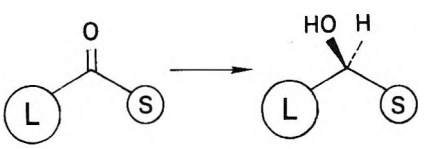

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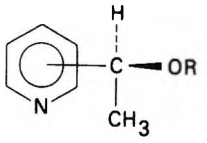
Table I. Summary of Optical Properties of 1a, 1b, 1c, and 2b and Ozonolysis Products

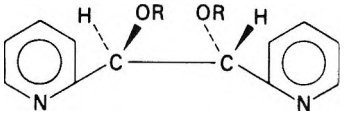
compd.	registry no.	specific rotation, deg observed	specific rotation, deg reported[2]	specific rotation of acetate	registry no.	specific rotation of ozonolysis product 3[a,b]	specific rotation of ozonolysis product 4[c,d]
1a	59042-90-9	−56.7 (*c* 3.88, EtOH)	−56.1 (*c* 0.5, EtOH)	−98 (c 2.31, EtOH)	66842-20-4	−35.7 (*c* 2.81, acetone), ee 85%	
1b	5096-11-7	−30 (*c* 4.92, EtOH)	−40.2 (*c* 0.87, MeOH)	−102 (c 3.37, EtOH)	66842-21-5	−34.5 (*c* 2.32, acetone), ee 82%	
1c	54656-96-1	−29.5 (*c* 1.60, $CHCl_3$)	−43.4 (*c* 0.5, EtOH)	−74.7 (c 5.57, EtOH)	66842-22-6	−32.0 (*c* 3.54, acetone), ee 79%	
2a	66900-45-6	−51.7 (*c* 2.44, EtOH)		−17.4 (*c* 0.78, EtOH)	66842-23-7		+19.1 (*c* 1.39, $CHCl_3$), ee 81%

[a] Authentic sample prepared from (+)-(*S*)-lactic acid has specific rotation −42 (*c* 2.13, acetone). [b] Registry no. 14031-88-0. [c] Authentic sample prepared from (−)-(*S,S*)-tartaric acid has specific rotation +23.7 (*c* = 1.52, $CHCl_3$). [d] Registry no. 6304-92-3.



1

(a) 2-pyridyl, R = H (d) 2-pyridyl, R = -$COCH_3$
(b) 3-pyridyl, R = H (e) 3-pyridyl, R = -$COCH_3$
(c) 4-pyridyl, R = H (f) 4-pyridyl, R = -$COCH_3$



2

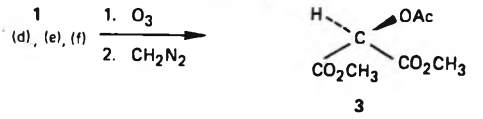
(a) R = H (b) R = -$COCH_3$

by Gottarelli and Samori[2] using Horeau's method, which is known to have exceptions.[3] Cervinka[4] independently assigned the absolute stereochemistry of the isomeric pyridylethanols; however, his assigned configuration for (−)-**1a** differed from that of Gottarelli and Samori. The latter investigators used the absorption spectra and the chiroptical properties of these compounds to interpret the spectral properties of the pyridine chromophore. Since the configurations of **1a, 1b,** and **1c** appear critical in at least two studies, we transformed optically active samples of these compounds into compounds of known absolute stereochemistry. In addition to the alcohols (+)-**1a,** (+)-**1b,** and (+)-**1c** Miller et al. also obtained dimeric reduction products from 2-acetylpyridine. In order to distinguish between *erythro-* and *threo*-1,2-di(2-pyridyl)ethanediols we have examined the microbial and chemical reduction of 2,2′-pyridil.

In addition to our interest in determining the absolute stereochemistry of the alcohols obtained from microbial reduction of the corresponding ketones, we were interested in the asymmetric syntheses of these compounds. While chiral reducing agents have recently been successfully used for asymmetric synthesis,[5] the presence of a basic nitrogen atom in the acetyl pyridines introduces many complications.[6a] In the course of examining the chiral reduction by microorganisms of several tetrahydro polycyclic ketones, we found that the chemical and optical yields in these reductions were frequently high and that the method had the distinct advantage of producing alcohols of a consistent configuration.[6b] As there were no analogous examples of the reduction of heterocyclic ketones, we were interested in determining the effect of a heteroatom, nitrogen, on the course of the reduction.

When *Cryptococcus macerans*, a microorganism which reduces acetophenone quantitatively to optically pure (*S*)-phenylethanol,[6b] is used to reduce the three isomeric acetylpyridines, the resulting alcohols are formed in good chemical and optical yields (Table I). The absolute stereochemistries of the alcohols were then determined by first acetylating the hydroxyl group, followed by ozonolysis of the pyridine derivative to a mixture of acids (Scheme I). The latter were methylated and pure methyl *O*-acetyllactate (**3**) was isolated and its specific rotation measured. The optical properties of the alcohols, acetates, and **3** formed are summarized in Table I. *These results clearly establish that C. macerans reduced each of the ketones to the S alcohol.* Thus, with the configurations of the isomeric pyridylethanols established, it is clear that Cervinka's assignment of the (*R*) configuration to (−)-2-pyridylethanol[2] was in error and that Horeau's method *correctly* predicted the absolute stereochemistry of (−)-**1a,** (−)-**1b,** and (−)-**1c.**

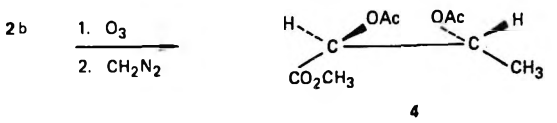
Scheme I



The configurations of **1a, 1b,** and **1c** are those expected from Prelog's rule[7] (shown in Figure 1) which states that if the ketone is placed with the larger group on the observer's left as shown, the hydroxyl group formed is closer to the observer. Thus the rule predicts that the alcohols formed from reduction of acetophenone and the isomeric acetylpyridines each have the same absolute stereochemistry, as is observed. The simplicity of predicting the configuration of alcohols formed by *C. macerans* using Prelog's rule contrasts with the difficulties associated in interpreting the weak and complex CD bands exhibited by these compounds. The latter are very difficult to use in assigning the absolute stereochemistry of a pyridine derivative whose configuration is not known.

While studying the asymmetric cathodic reduction of acetylpyridines, Kopilov, Kariv, and Miller[1] isolated small quantities of the corresponding pinacols. The pinacols were optically inactive in every case. However, the authors did not specify whether the observed pinacols were the erythro or threo isomers or mixtures. In an earlier study[8] on the reduction of a series of benzil derivatives we had shown that *C. macerans* provided optically active threo diols. Samples enriched in the erythro isomers, which are meso, were prepared by hydride reduction of the appropriate benzil. When 2,2′-pyridil was used as a substrate for *C. macerans* an optically active diol was isolated whose NMR spectrum differed from the spectrum of the major isomer formed by hydride reduction of 2,2′-pyridil. These results enable us to assign threo and erythro configurations to the microbial and chemical reduction products, respectively. The absolute stereochemistry of (−)-di(2-pyridyl)ethanediol was determined by conversion to (*S,S*)-(+)-dimethyl diacetyltartrate **4** as shown in Scheme

Scheme II



4

II. The absolute stereochemistry of (−)-di(2-pyridyl)ethanediol was thus established as (*R*,*R*).

The observation that the threo (*R*,*R*)-diol is the predominant product while the erythro isomer forms to less than 5% of the threo isomer requires some comment. Since the erythro isomer is present only to a small extent, it is apparent that the enzyme responsible for reducing the carbonyl group of the half-reduced 2,2′-pyridil distinguishes between *R* and *S* configurations, stereoselectively and preferentially reducing the former. The surprising sensitivity of the enzyme to the differences between α carbons bearing a hydrogen, a hydroxyl, and a pyridyl ring in an [*R*] or [*S*] arrangement indicates the necessity of accumulating additional experimental data before it is possible to order the effective size of substituents. The observation that the presence of a heteroatom (nitrogen) in these compounds does not alter the stereochemical course of the reduction from that of the carbon analogue is consistent with Prelog's rule, if in the half-reduced pyridil the 2-pyridyl ring is considered to be the larger substituent while $CHOHC_5H_5N$ is the smaller, which emphasizes steric effects over electronic considerations. These results strongly suggest that configurations assigned to alcohols as a result of microbial reduction have general applicability and therefore deserve more attention than they have received.

Experimental Section

Microbial Reduction. A 1-L Erlenmeyer flask containing 250 mL of a sterile solution of 6% glucose, 4% peptone, 4% yeast extract, and 4% malt extract was inoculated with a culture of *C. macerans*. The flask was shaken at 30 °C for 2 days, and 100 mg of 2,2′-pyridil was added to the optically dense culture. Shaking was continued for 7 days and the suspension was then made alkaline with 10% KOH and extracted three times with 250-mL portions of ethyl acetate. The ethyl acetate solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. No starting material was detected in the NMR spectrum of the crude extract. The threo diol (**2a**) was formed in ~80% yield along with ~5% of the erythro isomer (detected by NMR). The mixture was separated by thick-layer chromatography (silica gel, ethyl acetate:hexane (1:1)) to yield the threo diol (**2a**), 72 mg, which was recrystallized from 50% aqueous EtOH, mp 92–93 °C. The $[\alpha]^{25}_D$ data of this sample and the other optically active alcohols obtained from microbial reduction of the isomeric acetylpyridines are summarized in Table I.

Microbial reductions of the acetylpyridines were carried out in a similar manner.

Ozonolysis of (−)-*S*-1d, (−)-*S*-1e, (−)-*S*-1f, and (−)-2b. (*S*)-4-Pyridylethanol acetate **1f** was prepared by acetylating (−)-**1c** with acetic anhydride in pyridine in the usual manner. The crude acetate was purified by thick layer chromatography on silica gel (ethyl acetate:hexane (15:85)) and distilled in vacuo (colorless oil, NMR (in $CDCl_3$)): δ 1.50 (3 H, d, *J* = 6.7 Hz), 2.11 (3 H, s), 5.83 (1 H, q, *J* = 6.7 Hz), 7.24 (2 H, d, *J* = 5.7 Hz), 8.58 (2 H, d, *J* = 5.7 Hz). The $[\alpha]^{25}_D$ data of this sample and those of the other optically active acetates are summarized in Table I.

A solution of the acetate (151 mg) **1f** in 50 mL of dichloromethane was ozonized at 0 °C using a stream of ozone (2–4%) [from an Ozonator, Model 03V2]. When the ozonolysis was complete (~24 h) the solvent was removed in vacuo and 5 mL of 97% formic acid and 2 mL of 30% hydrogen peroxide were added. The solution was stirred at 50 °C for 1 h, at which time unreacted hydrogen peroxide was decomposed with sodium sulfite and the solvent was removed in vacuo. Excess saturated aqueous sodium bicarbonate was added to the residue and the solution was extracted with hexane. The aqueous layer was then acidified with hydrochloric acid, saturated with sodium chloride, and extracted several times with ether. The ether extract was washed with saturated sodium chloride, dried over sodium sulfate, and concentrated in vacuo. The NMR spectrum of the crude reaction mixture showed that **3** was produced in ~65% yield. An ether solution of this mixture was esterified with diazomethane. The solvent was removed and the residue distilled (bp 102–103 °C (99 mm)) to yield methyl (−)-(*S*)-**3**, 62 mg, 41% yield. The $[\alpha]^{25}_D$ of **3** formed from **1d** and **1e** is listed in Table I.

(−)-Methyl *O*-Acetyllactate. A solution of (+)-(*S*)-lactic acid (90 mg) in 5 mL of dry ether was esterified with diazomethane. The resulting methyl ester was treated with acetic anhydride (5 mL) and pyridine (1 mL) overnight at room temperature. The mixture was poured into water and extracted with ether and the ether solution was washed with 10% HCl and saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled (bp 102–103 °C (99 mm Hg)) to provide methyl (−)-**3** in an overall yield of 83%: 95 mg; $[\alpha]^{25}_D$ −42.0° (*c* 2.133, acetone); ^1H NMR (in $CDCl_3$) δ 1.47 (3 H, d, *J* = 7.1 Hz), 2.14 (3 H, s), 3.76 (3 H, s), 5.10 (1 H, q, *J* = 7.1 Hz). Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.85; Found: C, 49.20; H, 6.91.

Ozonolyses of **1d**, **1e**, and **2b** were carried out as described above. A sample of authentic (+)-**4** was previously prepared.[8] The $[\alpha]^{25}_D$ data and enantiomeric excess (ee) of products are given in Table I.

Registry No.—2,2′-Pyridil, 492-73-9; 2-acetylpyridine, 1122-62-9; 3-acetylpyridine, 350-03-8; 4-acetylpyridine, 1122-54-9; (+)-(*S*)-lactic acid, 79-33-4.

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Peracid Oxidation of Methylenecyclopropanes[1a]

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Several substituted methylenecyclopropanes were reacted with peracid. In general, this resulted in a direct conversion to cyclobutanones, although in the case of **18** an intermediate oxaspiropentane was characterized. Methylenecyclopropane **26** gave lactone **27** rather than a cyclobutanone product. The mechanisms of these conversions are discussed, with an emphasis on their stereochemical features.

Subsequent to our initial disclosure of the synthesis of an oxaspiropentane derivative,[2] several laboratories have described the generation of this highly strained heterocyclic system, either by the epoxidation of methylenecyclopropanes[3] or by the condensation of carbonyl compounds with cyclopropyl sulfur ylides.[4] The synthetic potential of oxaspiropentanes as intermediates has also been explored in some detail, most notably by Trost and co-workers.[5] The most commonly observed reaction of this system is a facile, acid-catalyzed transformation into an isomeric cyclobutanone.[3,4] In the present report we describe further examples of the peracid oxidation of methylenecyclopropane derivatives which reveal some unexpected complications in the oxaspiropentane–cyclobutanone rearrangement.

The oxidation of benzylidenecyclopropane (**1**) with an excess of *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 solution at 0 °C gave a 95% yield of 2-phenylcyclobutanone (**2**) (Scheme I). The presumed oxaspiropentane intermediate **3** was not observed in this reaction, although it has been prepared by the sulfur ylide method and shown to isomerize to **2**.[4] In a similar fashion diphenylmethylenecyclopropane (**4**) was converted into 2,2-diphenylcyclobutanone (**5**) (Scheme I).

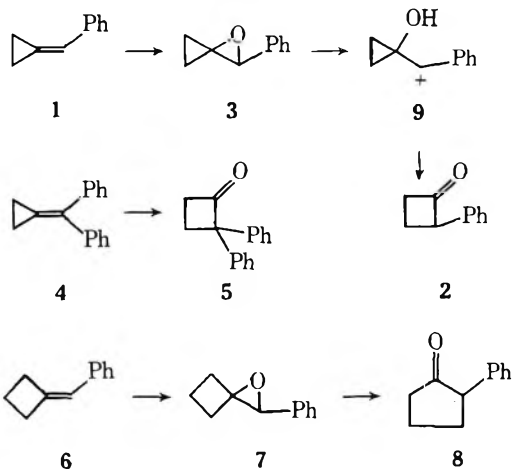
For comparison purposes, benzylidenecyclobutane (**6**) was subjected to the reaction conditions used for the oxidation of **1** (Scheme I). In this case, the spiroepoxide **7** was easily obtained. The analogous rearrangement of **7** to 2-phenylcyclopentanone (**8**) could be accomplished in high yield, but more rigorous conditions were required. For example, **8** was formed by heating a benzene solution of **7** containing *p*-toluenesulfonic acid to reflux for several hours, or by simply heating a benzene solution of **7** in a sealed tube to 150 °C.

Thus, it appears that the cyclopropyl moiety of **3** seems to greatly facilitate its rearrangement relative to that of **7**. The phenyl substituent of **3** must also contribute to its lability, since the parent oxaspiropentane has been isolated from an epoxidation reaction conducted under similar conditions to those used for **1**.[3a,b] These features are explained by protonation of the intermediate oxaspiropentane followed by ring opening to give a cyclopropylcarbinyl cation (e.g., **9**), which subsequently undergoes pinacolic rearrangement[6] to generate a cyclobutanone.[3a] Stabilization of the intermediate cation by cyclopropyl and phenyl substituents should enhance its formation.

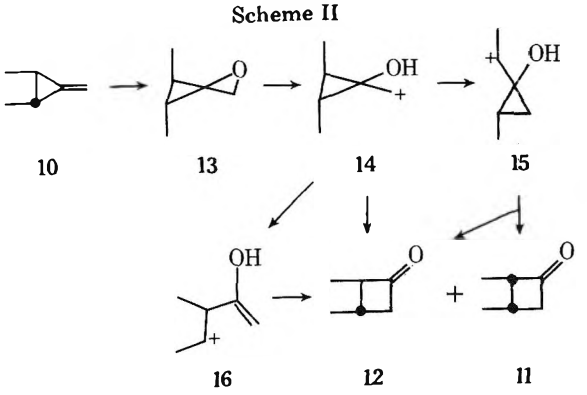
Further insight into the oxaspiropentane–cyclobutanone rearrangement is provided by the MCPBA oxidation of *trans*-2,3-dimethylmethylenecyclopropane (**10**). In this instance, a 40:60 ratio of *cis*- and *trans*-2,3-dimethylcyclobutanone (**11** and **12**, respectively) was obtained. This product ratio appears to be kinetically derived, since the two cyclobutanones did not interconvert under simulated reaction conditions. Thus, the migrating center has suffered stereochemical randomization in the transformation of oxaspiropentane **13** into product. This is not consistent with a simple alkyl migration mechanism, where retention of configuration is the rule for migrating groups.[6] However, a more elaborate form of the mechanism described above can satisfactorily account for the facts (see Scheme II). The key intermediate is again a cyclopropylcarbinyl cation. In this instance, the initially formed cation **14** (which would be expected to rearrange exclusively to the *trans*-cyclobutanone **12**) isomerizes to a secondary cyclopropylcarbinyl cation **15**. Rotation about the bond joining the cationic carbon to the cyclopropyl ring effectively randomizes the initial stereochemistry. Preferential migration of the methyl-substituted carbon of **14** now generates both cyclobutanone products.[3b] (The 2,4-dimethylcyclobutanones expected from migration of the primary cyclopropyl carbon of **15** were not observed). It is surprising that the interconversion of the cyclopropylcarbinyl cations is competitive with pinacolic ring expansion, which should be an energetically favorable process. An alternative mechanism to account for the stereochemical results involves fragmentation of **14** to the open-chain cation **16**, which then recloses efficiently to cyclobutanones **11** and **12**.

Additional complications arise with methylenecyclopropanes substituted on the ring with an ester group. Inter-

Scheme I



Scheme II



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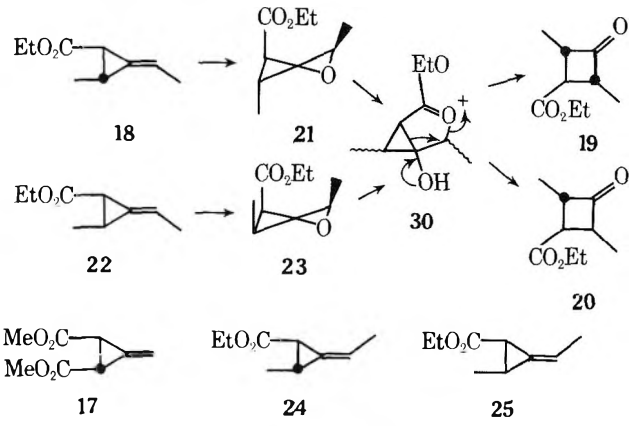
Scheme III

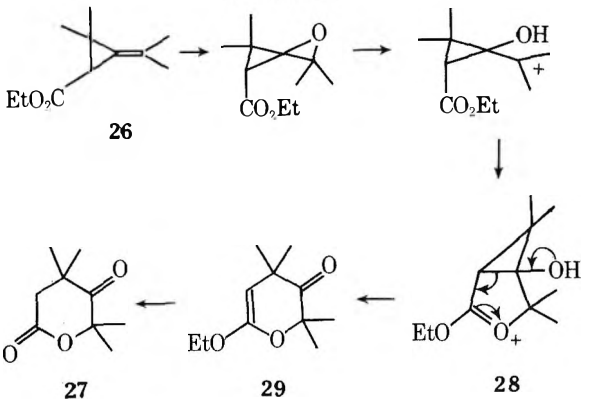


estingly, the dimethyl ester of Feist's acid (**17**; *trans*-2,3-dicarbomethoxymethylenecyclopropane) did not react with *p*-nitroperbenzoic acid (PNPBA).[3e] Apparently the neighboring ester groups greatly deactivate the double bond toward epoxidation.[7] Reaction of monoester **18** yielded a mixture of cyclobutanones **19** and **20** in a 28:72 ratio (Scheme III). These products are stable to the reaction conditions. In this case, careful workup of the reaction mixture prior to completion of the peracid oxidation revealed the formation of an intermediate. Thus, the NMR spectrum showed (among other signals) a sharp doublet at δ 1.43 (J = 5 Hz) and a quartet at δ 3.42 (J = 5 Hz). No cyclobutanone carbonyl was visible in the IR spectrum. Refluxing this material in benzene solution or simply passing it through a GLC column transformed it into a mixture of cyclobutanones **19** and **20.** This information is most readily interpreted in terms of the oxaspiropentane structure **21** for the labile intermediate. The clean NMR is consistent only with a stereoselective epoxidation. The indicated stereochemistry is assigned on the basis of peracid attack on **18** from the face of the molecule away from the carbethoxy group. This preference is expected by analogy with other rigid olefins possessing neighboring ester functions[7] and is consistent with the lack of reactivity of **17.**

Methylenecyclopropane **22** (a stereoisomer of **18**) was oxidized to essentially the same mixture of cyclobutanones **19** and **20** as obtained from **18.** The spiropentane intermediate was not pursued in this instance, but it surely possesses structure **23.** Finally, a mixture of **18, 22,** and small quantities of the other two stereoisomers **24** and **25** also gave the same mixture of cyclobutanones. The small amounts of these other compounds would not be expected to perturb product ratios appreciably, but the formation of positional isomers of **19** and **20** would have been observed. Thus, stereochemistry is lost in the rearrangement process just as it was with **10,** and common intermediates in the reactions of **21** and **23** appear likely. The most curious feature of these reactions is that the observed products can only be rationalized by preferential migration of the ester-bearing carbon to the electron-deficient center of a cyclopropylcarbinyl cation. This is not at all the expected substituent effect for such an electron-withdrawing group. (The fragmentation–cyclization mechanism mentioned above is even less appealing for similar reasons.)

A possible clue to this puzzle was provided by the peracid oxidation of methylenecyclopropane **26,** a reaction in which no cyclobutanone product was observed. Instead, a clean conversion to keto lactone **27** took place. This transformation can be understood in terms of the mechanism indicated in Scheme IV. The key feature of this explanation is intramolecular trapping of the cationic center by the neighboring ester function to give **28.** The indicated ring opening of **28** gives enol ether **29,** which must have been hydrolyzed to **27** under the reaction or workup conditions. Thus, the ester group plays an active role in this situation.

Scheme IV



A similar intermediate **30** can be proposed in Scheme III. In order to account for the loss of stereochemistry the interconversion of cyclopropylcarbinyl cations must be a competitive process as elaborated above. If, for stereoelectronic reasons, the cyclobutanes are formed directly from **30** with exclusive migration of the cyclopropyl bond that is coplanar with the bridging ester group, then migration of the carbon bearing this group follows as a natural consequence of the intervention of cation **30.** It is not at all clear why cyclobutanones are formed from **18** and **22,** whereas **26** leads to lactone **27,** although the degree of substitution at the original exocyclic olefinic carbon is probably the key difference.

Experimental Section

General. NMR spectra were recorded on a Varian HR-220 spectrometer. Infrared spectra were recorded on a Perkin-Elmer IR-7 prism spectrophotometer. Commercial *m*-chloroperbenzoic acid was recrystallized from CH_2Cl_2 and determined to be >99% peracid; *p*-nitroperbenzoic acid was used in commercial form (>97%). Anhydrous Na_2SO_4 was used as a drying agent.

Peracid Oxidation of Benzylidenecyclopropane (1).[8] A mixture 175 mg of **1** and 400 mg (1.75 equiv) of MCPBA in 5 mL of CH_2Cl_2 was stirred at 0 °C for 1 h. The solution was washed successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$ and dried. Removal of the solvent and GLC isolation gave 2-phenylcyclobutanone (**2**) (95%): IR 5.62, 6.72, 6.93, 8.56, 13.3, 14.3 μm; NMR δ 2.18 (m, 1), 2.48 (m, 1), 2.98 (m, 1), 3.11 (m, 1), 4.44 (t, 1, J = 5 Hz), 7.19 (m, 5). NMR and IR analysis of the crude product indicated only **2.**

Peracid Oxidation of Diphenylmethylenecyclopropane (4).[9] A mixture of 1.0 g of **4** and 1 g of PNPBA was stirred at 25 °C for 24 h. After addition of 20 mL of pentane and cooling to 0 °C the slurry was filtered. Removal of the solvent gave 0.96 g (88%) of 2,2-diphenylcyclobutanone (**5**) as a clear liquid: IR 5.61 μm; NMR δ 2.76 (t, 2, J = 8.5 Hz), 3.08 (t, 2, J = 8.5 Hz), 7–7.8 (m, 10). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 5.92. Found: C, 86.4; H, 5.9.

Peracid Oxidation of Benzylidenecyclobutane (6).[10] A mixture of 80 mg of **6** and 250 mg (2.5 equiv) of MCPBA in 5 mL of CH_2Cl_2 was stirred at 0 °C for 30 min, washed successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$, and dried. Removal of solvent gave 75 mg (85%) of 1-oxa-2-phenylspiro[2.3]hexane (**7**): IR 6.72, 6.85, 6.94, 7.08, 9.04, 10.3, 11.5, 13.2, 14.3 μm; NMR δ 1.61 (m, 1), 1.83 (m, 2), 2.34 (m, 2), 2.50 (m, 1), 3.65 (s, 1), 7.12 (m, 5). Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.3; H, 7.6.

Pyrolysis of 7. A 15-mg sample of **7** in 10 mL of benzene was heated in a sealed tube at 150 °C for 24 h. Removal of solvent gave 14 mg (93%) of 2-phenylcyclopentanone (**8**): IR 5.75, 6.74, 6.27, 14.4 μm.[11]

Acid-Catalyzed Rearrangement of 7. A 10-mg sample of **7** in 10 mL of benzene was refluxed with 1 mg of *p*-toluenesulfonic acid for 24 h. The solution was washed with a solution of $NaHCO_3$ and dried. Removal of the solvent gave 9.5 mg (95%) of 2-phenylcyclopentanone (**8**).

Peracid Oxidation of *trans*-2,3-Dimethylmethylenecyclopropane (10).[12] A mixture of 100 mg of **10** and 0.5 g (2.4 equiv) of MCPBA in 5 mL of CH_2Cl_2 was stirred at 25 °C for 24 h. GLC analysis indicated 50% conversion of **10** to two compounds in a 40:60 ratio. GLC isolation gave *cis*-2,3-dimethylcyclobutanone (**11**) and *trans*-2,3-dimethylcyclobutanone (**12**) (85% total yield) identified by spectral comparison.[13] Analysis of the crude reaction mixture by NMR and IR indicated the presence of starting material and the two cyclobutanones. The cyclobutanones were independently shown to be stable

to a 1:1 solution of MCPBA and *m*-chlorobenzoic acid in CH_2Cl_2 at 25 °C for 72 h and to the GLC analysis conditions.

Peracid Treatment of 17. A mixture of 1.0 g of **17** and 5.0 g of PNPBA in 20 mL of CH_2Cl_2 was refluxed for 48 h. After the addition of 20 mL of pentane and cooling to 0 °C the slurry was filtered. The solvent was removed from the filtrate to give 0.91 g (91%) of recovered **17.**

2-Methyl-3-ethylidene-1-carbethoxycyclopropane. To a stirred mixture of 65 g of 3-iodo-2-pentene[14] and 0.5 g of electrolytic copper at 100 °C was added 50 mL of ethyl diazoacetate over a 12-h period. Distillation of the resulting mixture [118–121 °C (20 mm)] gave 29 g of 3-iodo-3-ethyl-2-methyl-1-carbethoxycyclopropane. To this material in 600 mL of ether was added 24 g of a 50% oil dispersion of sodium hydride, followed by 6 mL of ethanol which caused the solution to reflux. After stirring for 2 h, a solution of 40 mL of acetic acid in 40 mL of ether was added cautiously. After 100 mL of H_2O was added slowly, the solution was washed with H_2O and $NaHCO_3$ solution and dried. Distillation gave 10 g (63%) of 2-methyl-3-ethylidene-1-carbethoxycyclopropane [90–95 °C (30 mm)]. GLC analysis indicated the presence of the four possible isomers, **24, 25, 18,** and **22,** in a 5:8:75:12 ratio. Products **18** and **22** were collected by preparative GLC.[15]

Peracid Oxidation of *trans*-2-Methyl-*anti*-3-ethylidene-1-carbethoxycyclopropane (18). A mixture of 147 mg of **18** and 183 mg (1.1 equiv) of PNPBA in 5 mL of CH_2Cl_2 was stirred at −15 °C for 24 h. The solution was washed successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$ and dried. Removal of solvent under vacuum at 0 °C gave a liquid whose NMR indicated the presence of 20% starting material and 80% of a new product assigned as *anti-trans*-3,4-dimethyl-5-carbethoxy-2-oxaspiro[2.2]pentane (**21**): NMR δ 1.25 (t, 3, J = 7 Hz), 1.26 (d, 3, J = 5 Hz), 1.43 (d, 3, J = 5 Hz), 1.70 (d, 1, J = 5 Hz), 3.42 (quart, 1, J = 5 Hz), 4.03 (m, 2). The remaining proton is not visible, but integration shows it to be in the δ 1.15–1.30 region.

GLC of this material gave a 25% yield of *trans-trans*-2,4-dimethyl-3-carbethoxycyclobutanone (**19**) and a 65% yield of *trans-cis*-2,4-dimethyl-3-carbethoxycyclobutanone (**20**). Compound **19**: IR 5.62, 5.78, 7.30, 8.28, 8.55, 9.70 μm; NMR δ 1.20 (d, 6, J = 7 Hz), 1.30 (t, 3, J = 7 Hz), 2.20 (t, 1, J = 7 Hz), 3.46 (quin, 2, J = 7 Hz), 4.18 (quart, 2, J = 7 Hz). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.2; H, 8.5. Compound **20**: IR 5.62, 5.80, 7.30, 8.50, 9.70 μm; NMR δ 1.14 (d, 3, J = 7 Hz), 1.22 (d, 3, J = 7 Hz), 2.75 (d of d, 1, J = 8 Hz, J = 7 Hz), 3.48 (m, 1), 3.69 (m, 1), 4.17 (m, 2). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.3; H, 8.4.

Independent submission of **19** and **20** to a 1:1 mixture of *p*-nitrobenzoic acid and PNPBA in CH_2Cl_2 under the above conditions gave no interconversion of isomers by GLC analysis.

Oxidation of **18** at 25 °C gave cyclobutanones **19** and **20** in a 28:72 ratio in 95% yield by GLC analysis against an internal standard.

Peracid Oxidation of 22. A 15-mg sample of **22** was oxidized with PNPBA as described above at 25 °C to **19** and **20** in a 25:75 ratio in 96% yield.

Peracid Oxidation of 2-Methyl-3-ethylidene-1-carbethoxycyclopropane. The mixture of the four stereoisomers obtained by synthesis was oxidized as above at 25 °C to give **19** and **20** in a 27:73 ratio in 92% yield by GLC.

Rearrangement of 21. The mixture of **18** and **21** obtained above was refluxed for 2 h in 2 mL of benzene. Analysis by NMR indicated conversion of **21** to **19** and **20.** GLC integration indicated 18% **18,** 21% **19,** and 53% **20.**

2,2-Dimethyl-3-isopropylidene-1-carbethoxycyclopropane (26). To a mixture of 50 g of tetramethylallene and 0.25 g of electrolytic copper at reflux was added 100 g of the ethyl diazoacetate over a 12-h period. Distillation of the crude reaction mixture gave 20 g of starting allene and 51 g (52%) of **26:** bp 93–96 °C (30 mm). GLC gave a pure sample: IR 5.83, 7.33, 7.49, 8.69 μm; NMR δ 1.25 (t, 3, J = 7 Hz), 1.25 (s, 3), 1.28 (s, 3), 1.72 (s, 3), 1.80 (s, 3), 1.86 (m, 1), 4.01 (m, 2). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.2; H, 10.0.

Peracid Oxidation of 26. A mixture of 1.0 g of **26** and 1.0 g (1 equiv) of MCPBA in 50 mL of CH_2Cl_2 was stirred at 0 °C for 2 h. Washing the mixture successively with solutions of $NaHCO_3$, $NaHSO_3$, and $NaHCO_3$ and then drying and removal of the solvent gave a mixture of starting material (3%) and 3,3,5,5-tetramethyl-4-keto-5-hydroxpentanoic acid δ-lactone (**27;** 91%): IR 5.70, 5.80, 7.30, 8.80, 9.04, 10.0 μm; NMR δ 1.18 (s, 6), 1.47 (s, 6), 2.67 (s, 2); mass spectrum *m/e* (rel intensity) 170 (6), 142 (6), 114 (10), 88 (40), 70 (13), 59 (87), 56 (100). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.5; H, 8.1.

An experiment using PNPBA at −10 °C under the above conditions also gave **27** (95%). An experiment using 10% methanol in CH_2Cl_2 as the solvent under these conditions gave **27** as the only product (90%).

Registry No.—**1,** 7555-67-1; **2,** 42436-86-2; **4,** 7632-57-7; **5,** 24104-20-9; **6,** 5244-75-7; **7,** 66826-70-8; **10,** 5070-00-8; **17,** 14750-79-9; **18,** 40897-15-2; **19,** 66826-71-9; **20,** 66826-67-3; **21,** 66826-68-4; **22,** 40897-16-3; **24,** 40897-13-0; **25,** 40897-14-1; **26,** 1131-99-3; **27,** 14744-26-4; 3-iodo-2-pentene, 40897-12-9; ethyl diazoacetate, 623-73-4; 3-iodo-3-ethyl-2-methyl-1-carbethoxycyclopropane, 66826-69-5; tetramethylallene, 1000-87-9.

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Condensation and Cyclization Catalyzed by Strong Bases. A New Route to Benzoquinolizine and Benzoquinolizinium Derivatives

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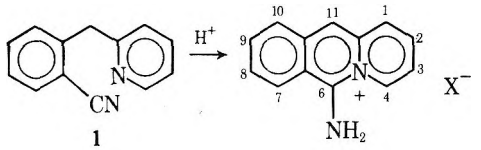
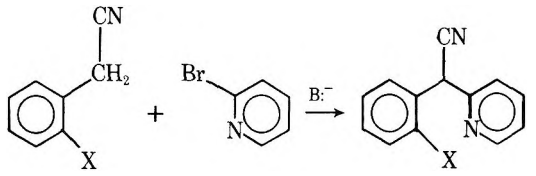
The base-catalyzed reaction of α-cyano-o-tolunitrile with 2-halopyridines (and analogues) affords 11-cyano-6*H*-benzo[*b*]quinolizin-6-one imine (**9**) and its congeners in modest yield. All of these imines are easily hydrolyzed to the corresponding quinolizinones (e.g., **10**). The action of hydrogen bromide on **9** converts it to the 6-amino-11-cyanoacridizinium ion (**11**).

Earlier research from this laboratory[1] showed that the acid-catalyzed cyclization of 2-(2-cyanobenzyl)pyridine (**1**) led to salts of the 6-aminoacridizinium (benzo[*b*]quinolizinium) ion. Unfortunately, the only known route to **1** involved ring opening of the acridizinium ion in the presence of hydroxylamine followed by dehydration of the resulting oxime. While such a reaction sequence should constitute a plausible route to derivatives of **2**, there appeared to be advantage in



1 **2**

seeking a more direct pathway. The patent literature[2-4] had reported that phenylacetonitrile (**3**) in the presence of sodium amide would undergo condensation with 2-bromopyridine in 30–58% yield. It appeared plausible that substitution of the commercially available α-cyano-o-tolunitrile (**4**) for phenylacetonitrile (**3**) would afford a 2-(2-cyanobenzyl)pyridine derivative (**6**) similar to **1** except for an extra nitrile function.



3, X = H
4, X = CN

5, X = H
6, X = CN
(not isolated)

Since the anion from α-cyano-o-tolunitrile (**4**) is known to undergo self-condensation with great ease,[5] the anion was generated in the presence of an excess of the o-bromopyridine (or o-bromopyridine analogue) by addition of the mixture of bromopyridine and nitrile **4** in glyme to a solution of sodium ethoxide in the same solvent. The initial reaction mixture was yellow-orange, but after a 12-h reflux it had become dark brown. Although the product consisted of a complex mixture, extraction and crystallization procedures afforded an orange solid with physical properties which did not correspond to those of any known self-condensation product. Consistent with our expectations for the dinitrile **6** the low-resolution mass spectrum of the product exhibited a molecular ion at a *m/e* value of 219. However the IR suggested the presence of an imine as well as a nitrile function and the UV visible spectrum indicated the presence of more conjugation than would be possible with the dinitrile **6**.

These data plus reactions to be discussed later could be explained by assuming that any of the dinitrile **6** formed would immediately be converted to its ambident anion **7**, which could cyclize to anion **8** which, upon acidification, would afford 11-cyano-6*H*-benzo[*b*]quinolizin-6-one imine (**9**). A convincing argument for the correctness of **9** as the structural formula of the product isolated can be seen in Table I, where a direct comparison is made of the electronic spectral data for our new product with those of 6*H*-benzo[*b*]quinolizin-6-one imine prepared earlier by the addition of hydroxide ion to the 6-aminoacridizinium cation. The close agreement of the electronic spectrum of the new product **9** with that of the parent compound is remarkable and provides convincing evidence that the chromophores of the two systems are very similar.

Characteristic of a compound bearing an imine group the new product **9** is readily hydrolyzed, even by aqueous acetic acid. The hydrolysis is accompanied by a color change, the imine (**9**, Scheme I) being orange while the quinolizinone (**10**) is yellow. An attempt to separate the two compounds (**9** and **10**) chromatographically on alumina gave results that indicated that even alumina served as a catalyst for the hydrolysis. This catalysis was demonstrated by heating the pure imine

Scheme I

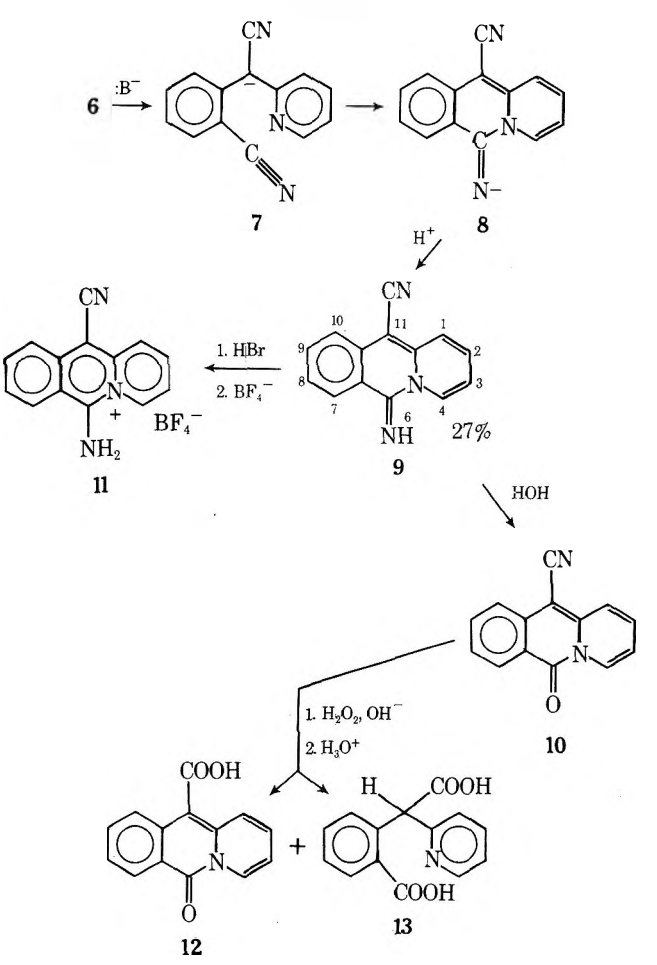


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Table I. Comparison of Electronic Spectral Data of 6*H*-Benzo[*b*]quinolizin-6-one Imine with that of Its (presumed) 11-Cyano Derivative (9) in 95% Ethanol Solution

6*H*-benzo[*b*]-quinolizin-6-one imine[a]		11-cyano derivative (9)[b]	
λ_{max}, nm	log ϵ	λ_{max}, nm	log ϵ
475	3.30	478	3.62
450	3.66	454	3.90
429	3.84	426	3.93
403	4.01	298	4.05
387	3.98	378	3.99
337	3.58		
325	3.49	322	3.81
		309	3.74
		269	4.09
260	4.12	260	4.11
241	4.45	242	4.45
235	4.48	233	4.47

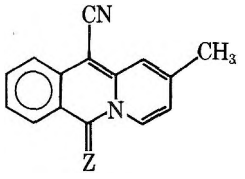
[a] Registry no.: 7561-83-3. [b] Registry no.: 66749-71-1.

9, mp 244–245 °C, in 95% ethanol with a small amount of suspended alumina. The product isolated in quantitative yield was the pure quinolizinone derivative (**10**), mp 284–285 °C.

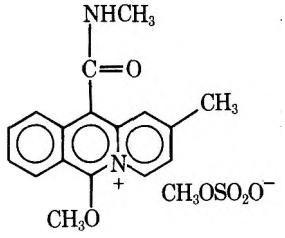
This facile hydrolysis has complicated the isolation of a pure acridizinium derivative (**11**). This could be accomplished by addition of hydrogen bromide to the imine **9** under essentially anhydrous conditions. A comparison of the electronic spectral data for **11** (as the tetrafluoroborate salt) with those obtained from 6-aminoacridizinium chloride (**2**) is shown in Table II. Again the spectral evidence appears to confirm our structural assignment.

Treatment of the cyanoquinolizinone **10** with alkaline hydrogen peroxide, followed by acidification, gave both the 11-carboxy-6*H*-benzo[*b*]quinolizine-6-one (**12**) and a dicarboxylic acid **13** formed by opening of the amide linkage. At least some of the carboxyquinolizinone **12** may be an artifact produced during the acidification process, since it is known that α-(2-pyridyl)toluic acid undergoes cyclization rapidly in the presence of a trace of mineral acid.[2]

Similar results were obtained in the condensation of α-cyano-*o*-tolunitrile (**4**) with 2-bromo-4-methylpyridine, a 29% yield of the expected imine (**14**) being obtained.



14, Z = NH
15, Z = O



16

Aside from the methyl signal at δ 2.23 the most notable feature in the proton NMR of **14** was a signal at δ 7.2–7.9 corresponding to a proton which exchanged on treatment with deuterium oxide. The unsubstituted imine **9** had an exchangeable proton at δ 8.67. There appears to be a paucity of NMR data for the imine signal in the literature: a value of δ 7.37 being reported[6] for the ketimine present in the polymer of malononitrile and δ 9.4 being listed for the imine resonance in diphenylketimine.[7] Perhaps accounting in part for the scarcity of data, Roberts[7] et al. have reported that the imine proton is rarely detectable in several common deuterated solvents. It was observed that the unsubstituted imine (**9**) underwent exchange in deuteriochloroform even in the absence of deuterium oxide, although several days were required for completion.

Table II. Comparison of Electronic Spectral Data of 6-Aminoacridizinium Ion with Those of 6-Amino-11-cyanoacridizinium Ion

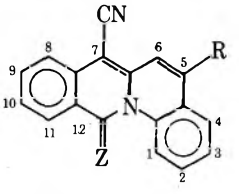
6-aminoacridizinium ion[a] (2)		11-cyano-6-aminoacridizinium ion[b] (11)	
λ_{max}, nm	log ϵ	λ_{max}, nm	log ϵ
		450	2.93
427	3.88	426	3.81
405	4.04	412	4.01
380	4.06	379	4.16
340	3.68	362	4.03
257	4.25	257	4.38
241	4.56		
235	4.55	233	5.02

[a] In 95% ethanol as the chloride. Registry no.: 7547-90-2. [b] In acetonitrile as the tetrafluoroborate. Registry no.: 66749-73-3.

The amide (**15**) obtained by hydrolysis of the methylquinolizine imine (**14**) underwent an interesting reaction when heated at 150 °C with dimethyl sulfate. On the basis of spectral data and elemental analysis the new compound has been assigned as **16**.

2-Bromopyridine analogues which have been found to undergo the condensation–cyclization reaction with α-cyano-*o*-tolunitrile include 2-chloro-3-methylpyrazine, yielding **17** (7%), and 2-chloroquinoline and 2-chloro-4-methylquinoline, yielding **19** and **21** in yields of 44 and 49%, respectively.

17, Z = NH
18, Z = O



19, Z = NH; R = H
20, Z = O; R = H
21, Z = NH; R = CH_3
22, Z = O; R = CH_3

After completion of this project, but before completion of the manuscript, Douglass and Hunt[8] described an alternate route to 7-cyano-12*H*-dibenzo[*b*,*f*]quinolizin-12-one imine (**19**) via the reaction of quinoline 1-oxide with α-cyano-*o*-tolunitrile in the presence of acetic anhydride and triethylamine. Interestingly, the related dibenzoquinolizine derivative (**20**) which they obtained by hydrolysis of **19** had been prepared earlier[9] by a method similar to ours except that methyl α-cyano-*o*-toluate had been used instead of α-cyano-*o*-tolunitrile.

As a route to benzoquinolizine derivatives our method offers the advantages of being general yet requiring only a single operation using commercially available starting materials, advantages which may outweigh the modest yields obtained.

Experimental Section

The elemental analyses were carried out by M-H-W Laboratories, Garden City, Michigan. Melting points were determined in capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet absorption spectra were determined with a Beckman Model DB-G spectrometer and infrared spectra were taken in KBr disks with a Perkin-Elmer Model 237 spectrometer. ^{1}H NMR spectra were obtained at 60 MHz on a Varian T-60 spectrometer using tetramethylsilane as the internal standard.

Generalized Condensation–Cyclization Procedure. A three-neck flask is fitted with two reflux condensers, a glass-covered magnetic stir bar, and a glass stopper, all previously dried in an oven. Atop

one reflux condenser is placed a dropping funnel, and the entire system is protected with calcium chloride drying tubes and maintained under a static N_2 atmosphere.

The flask is charged with 1.1–1.2 equiv of NaH and about 100 mL of glyme freshly distilled from $LiAlH_4$. An excess of absolute ethanol was added dropwise to the NaH suspension ultimately resulting in a clear solution.

Commercial grade α-cyano-o-tolunitrile, purified by vacuum distillation and recrystallization from methanol (1 equiv), and 2 equiv of the 2-halopyridine (or analogue) were dissolved in dry glyme and added dropwise to the rapidly stirred mixture. Initially an orange solution is generated which turns to a brown suspension. After addition is complete the mixture, still under N_2 atmosphere, was refluxed for 12–24 h.

The reaction mixture was cooled to room temperature and poured into five volumes of water containing 1 equiv of NH_4Cl and a weighed amount of filter-aid. An immediate precipitation occurred. The precipitate was collected, washed with water, and dried in a vacuum oven at 50 °C. The dried solid was extracted in a Soxhlet extractor for 15 h with 200 mL of ethyl acetate. Concentration of the yellow or orange solution afforded the cyclized product, which frequently needed purification by column chromatography on alumina in addition to crystallization.

11-Cyano-6*H*-benzo[*b*]quinolizin-6-one Imine (9). Starting with 2-bromopyridine and following the standard procedure **9** was obtained, mp 237–242 °C, in 27% yield after an 18-h reflux. Without chromatography, but after recrystallization from 1-butanol, the analytical sample was obtained as long orange needles: mp 244–245 °C; UV_{max} (95% ethanol) 478 (sh) (log ε 3.62), 454 sh (3.90), 426 (3.93), 398 (4.05), 378 sh (3.99), 322 (3.81), 309 (3.74) 269 (4.09), 260 (4.11), 242 sh (4.45), 233 nm (4.47); IR (KBr) 3340 (C=NH), 2209 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 6.70 (m, 1), 7.15–8.05 (m, 6), 8.67 (br s, 1, C=NH), 9.24 (d, 1, J = 8 Hz, C-4); mass spectrum m/e (rel intensity) 219 (70), 192 (10), 164 (6). Anal. ($C_{14}H_9N_3$) C, H, N.

6-Amino-11-cyanoacridizinium Tetrafluoroborate (11). Dry HBr was bubbled through a solution of 0.44 g of the imine **9** in 40 mL of dry glyme. The yellow precipitate was collected and dissolved in 15 mL of hot water. After filtration to remove a small amount of undissolved solid a concentrated aqueous solution of sodium tetrafluoroborate was added, precipitating 0.40 g (65%) of the expected salt **11**. The salt crystallized from acetonitrile as yellow needles: mp 247–249 °C; UV_{max} (CH_3CN) 450 sh (log ε 2.93), 426 (3.81), 412 (4.01), 379 (4.16), 362 sh (4.03), 268 sh (4.34), 257 sh (4.38), 233 nm (5.02); IR (KBr) 3355–3215 (NH_2), 2225 (CN), 1080 cm^{-1} (BF_4). Anal. ($C_{14}H_{10}BF_4N_3$) C, H, N.

11-Cyano-6*H*-benzo[*b*]quinolizin-6-one (10). To 5 mL of water in 45 mL of acetic acid 1.25 g of the imine **9** was added and the mixture was refluxed for 1 h. The solution was concentrated to 20 mL. The addition of 20 mL of water immediately precipitated 1.25 g (99%) of yellow solid, mp 283–285 °C. The analytical sample was obtained as long yellow needles: mp 284–285 °C; UV_{max} (95% ethanol) 452 (log ε 3.70), 427 (3.93), 394 sh (4.04), 384 (4.17), 363 sh (4.06), 309 (3.78), 296 (3.73), 265 (4.21) 238 (4.52), 235 nm (4.51); IR (KBr) 2208 (CN), 1690 cm^{-1} (C=O, amide); NMR (CF_3COOH) δ 7.10 (m, 1), 7.33–8.07 (m, 5), 8.30 (d, 1, J = 7 Hz), 8.98 (d, 1, J = 7 Hz). Anal. ($C_{14}H_8N_2O$) C, H, N.

Since the amide (**10**) is easily formed by hydrolysis of the imine (**9**) it appears as a byproduct in its preparation. When the preparation of 11-cyano-6*H*-benzo[*b*]quinolizin-6-one imine (**9**) was carried out essentially as described except that the unrecrystallized product was subjected to column chromatography on alumina, elution of the yellow band (amide) and orange band (imine) followed by hydrolysis with dilute acetic acid afforded the amide **10** in 32% yield, mp 283–285 °C.

A similar experiment carried out with 2-chloro instead of 2-bromopyridine afforded only a 21% yield of amide **10**.

11-Carboxy-6*H*-benzo[*b*]quinolizin-6-one (12). To a suspension of 0.2 g of amide **10** in 15 mL of 95% ethanol, 5 mL of 2 N NaOH was added along with 5 mL of 30% H_2O_2. After the mixture was stirred for 4 h at room temperature it was refluxed for an additional 2 h. The cooled mixture was acidified and diluted with water. Extraction with methylene chloride and evaporation of the solvent afforded 0.09 g (40%) of a dull yellow solid, which recrystallized to afford yellow microcrystals: mp 205–210 °C; IR (KBr) 2690–2490, (COOH, H-bonded), 1702–1680 (C=O, acid, amide), 1285 cm^{-1} (COOH). Anal. ($C_{14}H_9NO_3 \cdot \frac{1}{2}H_2O$) C, H, N.

α-(2-Pyridyl)-o-carboxyphenylacetic Acid (13). The hydrolysis was carried out as for **12** except that refluxing was continued for 18 h and the reaction mixture was carefully neutralized. The residue obtained by extraction with CH_2Cl_2 and evaporation of the solvent afforded 0.18 g (32%) of the diacid **13**. Pure **13** was obtained from ethanol as colorless needles: mp 217–222 °C; UV_{max} (95% ethanol) 266, 231 sh, 227 nm; IR (KBr) 2670–2470 (H-bonded COOH), 1705–1680 (C=O), 1280 cm^{-1} (COOH); ^1H NMR [$(D_3C)_2SO$] δ 7.41–8.27 (m, 7), 8.50–8.67 (m, 1). Anal. ($C_{14}H_{11}NO_4 \cdot \frac{1}{4}H_2O$) C, H, N.

11-Cyano-2-methyl-6*H*-benzo[*b*]quinolizin-6-one Imine (14). The standard procedure was used with 2-bromo-4-methylpyridine and the orange chromatographic band was collected separately and the solvent was removed, affording 0.63 g (5.4%) of the imine **14**, mp 227–229 °C. Recrystallization from 1-butanol afforded orange platelets: mp 229–230; UV_{max} (95% ethanol) 473 sh (log ε 3.48), 443 sh (3.78), 394 (4.01), 322 (3.71), 309 (3.62), 269 sh (3.95), 256 sh (3.96), 236 sh (4.41), 232 nm (4.43); IR (KBr) 3310 (C=NH), 2210 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 2.33 (s, 3, 2-Me), 6.47 (m, 1), 7.23–7.93 (m, 6, one H exchangeable with D_2O), 8.86 (d, 1, J = 8 Hz). Anal. ($C_{15}H_{11}N_3$) C, H, N.

11-Cyano-2-methyl-6*H*-benzo[*b*]quinolizin-6-one (15). The remaining orange-yellow and yellow chromatographic fractions from the preceding experiment were combined and the solute was subjected to hydrolysis in dilute acetic acid, affording 2.73 g (23.3%) of **15**, mp 263–265 °C. Recrystallization from acetic acid afforded yellow needles: mp 264.5–265 °C; UV_{max} (95% ethanol) 452 sh (log ε 3.76), 420 sh (3.87), 382 (4.21), 364 sh (4.18), 309 (3.72), 297 (3.67), 262 sh (4.24), 232 nm (4.57); IR (KBr) 2210 (CN), 1685 cm^{-1} (C=O, amide); ^1H NMR (CF_3COOH) δ 2.39 (s, 3, 2-Me), 6.78 (d, 1, J = 7 Hz), 6.96–8.06 (m, 5) and 8.52 (d, 1, J = 7 Hz). Anal. ($C_{15}H_{10}N_2O$) C, H, N.

6-Methoxy-11-(*N*-methylcarbamoyl)-2-methylacridizinium Methylsulfate (16). A suspension of 0.86 g of the amide (**15**) in 10 mL of dimethyl sulfate was heated for 5 h at 150 °C and the cooled reaction mixture was poured into anhydrous ether. The ether layer was decanted from an oil which was fractionally crystallized from ethanol. From the more soluble fraction 0.25 g (18%) of a yellow solid, mp 255–259 °C, was obtained. The analytical sample was recrystallized from acetonitrile: mp 259–262 °C; UV_{max} (95% ethanol) 426 sh, 342, 312, 242 sh, 222 nm; IR (KBr) 1657 cm^{-1} (C=O, amide); ^1H NMR (CF_3COOH) δ 2.58 (s, 3, 2-Me), 3.86 (s, 3, CONHMe), 3.95 (s, 3, $MeSO_2O^-$), 4.25 (s, 3, OMe), 7.03–7.37 (m, 1), 7.70–8.27 (m, 4), 8.47–9.00 (m, 2). Anal. ($C_{18}H_{20}N_2O_6S$) C, H, N.

11-Cyano-1-methyl-2-aza-6*H*-benzo[*b*]quinolizin-6-one Imine (17). Using 2-chloro-3-methylpyrazine in the general procedure there was obtained from the ethyl acetate extract a solid which did not completely dissolve in methylene chloride. Recrystallization of this residue from 1-butanol yielded 2.8% of the imine **17** as deep orange needles: mp 240–242 °C; UV_{max} (95% ethanol) 458 sh (log ε 3.98), 437 (3.90), 392 (3.91), 373 (3.88), 303 sh (3.71), 291 sh (3.77), 237 nm (4.44); IR (KBr) 3325 (C=NH), 2198 cm^{-1} (CN); ^1H NMR (CF_3COOH) δ 3.63 (s, 3, 1-Me), 7.90–9.10 (m, 7). Anal. ($C_{14}H_{10}N_4$) C, H, N.

11-Cyano-1-methyl-2-aza-6*H*-benzo[*b*]quinolizin-6-one (18). Chromatography of the methylene chloride solution and slow elution with benzene afforded a yellow solid which once recrystallized from 10:1 acetic acid/water afforded 0.51 g (4.35%) of **18**: mp 270–272 °C dec; UV_{max} (95% ethanol) 438 sh (log ε 3.88), 424 sh (3.97), 383 (405), 364 sh (4.00), 270 sh (4.08), 236 nm (4.44); IR (KBr) 2208 (CN), 1690 cm^{-1} (C=O, amide); ^1H NMR (CF_3COOH) δ 3.67 (s, 3, 1-Me), 7.68 (d, 1, J = 6 Hz, C-4), 8.01–8.64 (m, 3), 8.86 (m, 1), 9.27 (d, 1, J = 6 Hz, C-3). Anal. ($C_{14}H_9N_3O$) C, H, N.

Condensation–Cyclization with 2-Chloroquinoline and 2-Chloro-4-methylquinoline. The standard procedure was followed.

For imine **19** the yield was 44% of yellow solid, mp 208–212 °C, which was recrystallized from 1-butanol: mp 210–212 °C [lit.[8] 214–215 °C]; UV_{max} (95% ethanol) 464 (log ε 3.77), 438 (4.04), 417 (4.03), 398 (3.95), 314 (4.09), 301 (4.01), 279 (4.07), 238 nm (4.50); IR (KBr) 3250 (C=NH), 2198 cm^{-1} (CN). Anal. ($C_{18}H_{11}N_3$) C, H, N.

Imine **21** was obtained (before chromatography) as a yellow solid, mp 215–218 °C, in 49% yield, but this was probably contaminated with the higher melting amide **22**. A sample was purified by chromatography and recrystallization from 1-butanol: mp 211–212 °C; UV_{max} (95% ethanol) 464 sh (log ε 3.84), 438 (4.08), 414 (4.08), 392 sh (4.02), 311 (4.16), 301 (4.17), 279 sh (4.12), 236 nm (4.51); IR (KBr) 3245 (C=NH), 2203 cm^{-1} (CN); ^1H NMR δ 2.81 (s, 3, Me), 7.67–9.30 (m, 10).

7-Cyano-12*H*-dibenzo[*b*,*f*]quinolizin-12-one (20) and its 5-Methyl Derivative (22). As reported by Douglass and Hunt[8] the imine **19** undergoes hydrolysis to the amide **20**, mp 191–192 °C (lit.[8,9] 189–190, 190 °C). Anal. ($C_{18}H_{10}N_2O$) C, H, N.

The hydrolysis of the homologous imine **21** gave the expected amide **22**, which crystallized from acetic acid: mp 231–232 °C; UV_{max} (95% ethanol) 420 (4.05), 404 (4.26), 386 (4.24), 306 (4.08), 295 (4.11), 279 sh (4.12), 236 (4.55), 232 nm sh (4.54); IR (KBr) 2213 (CN), 1676 cm^{-1}

(C=O, amide); ^{1}H NMR (CF_3COOH) δ 2.19 (s, 3, Me), 6.76 (s, 1), 7.03–7.63 (m, 6), 7.88–8.02 (m, 1), 8.70 (m, 1). Anal. ($C_{19}H_{12}N_2O$) C, H, N.

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Registry No.—**4**, 3759-28-2; **10**, 66749-74-4; **12**, 66749-75-5; **13**, 66749-76-6; **14**, 66749-77-7; **15**, 66749-78-8; **16**, 66749-80-2; **17**, 66749-81-3; **18**, 66749-82-4; **19**, 63702-24-9; **20**, 63702-25-0; **21**, 66749-83-5; **22**, 66749-84-6; 2-bromopyridine, 109-04-6; 2-bromo-4-methylpyridine, 4926-28-7; 2-chloro-3-methylpyrazine, 95-58-9; 2-chloroquinoline, 612-62-4; 2-chloro-4-methylquinoline, 634-47-9.

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A Convenient Synthesis of Azidothiophenes and Some of Their Reactions

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Several azidothiophenes have been prepared by treatment of lithium thiophene derivatives with *p*-toluenesulfonyl azide and subsequent fragmentation of the intermediate triazene–lithium salts. High yields have been obtained for all 3-azido compounds; conversely, yields are low in the case of 2-azido derivatives. 2-Azido- and 3-azidothiophene have been converted to the corresponding 1-(thienyl)-1,2,3-triazoles by reaction with acetylene or dimethyl acetylenedicarboxylate. Thermal decomposition of 3-azidothiophene and 3-azidobenzo[*b*]thiophene in acetic anhydride or in a mixture of acetic and polyphosphoric acids has been investigated as a possible route to thienooxazoles.

The azido group represents a very attractive starting group in organic synthesis.[1] Heteroaromatic azides derived from five- and six-membered rings containing nitrogen can be obtained by nucleophilic displacement of a suitable leaving group by azide ion.[1,2] Heteroaromatic azides derived from five-membered rings containing sulfur and oxygen have received only scant attention. For example, Gronowitz and coworkers[3] reported the preparation of 3-azido-2-formylfurano and -thiophen by nucleophilic displacement of the corresponding 3-bromo derivatives with azide ion. However, no azides could be obtained from 2- and 4-bromo-3-formylthiophene, 5-bromo-2-formylthiophene, and bromothiophenes carrying electron withdrawing groups thus limiting the scope of this reaction. Moreover this method is unsuited for the preparation of the parent azides or those carrying electron releasing groups.

We wish to report a convenient synthesis of azidothiophenes and some of their reactions. We have found that azidothiophenes can be obtained by treatment of the corresponding lithium derivatives with *p*-toluenesulfonyl azide and subsequent fragmentation of the resulting triazene salts.[4] Thus, treatment of an ethereal solution of 3-lithium thiophene with tosylazide at −70 °C for 4–5 h and decomposition of the resulting triazene salt with an aqueous solution of tetrasodium pyrophosphate at room temperature afforded 3-azidothiophene (**1**) in 85% yield.

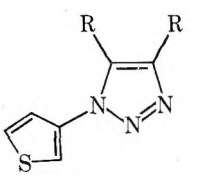
The azides **2–6**, **9**, and **10** reported in Table I were prepared analogously; 3-azido-2-formylthiophene (**7**) and 4-azido-3-formylthiophene (**8**) were obtained by hydrolysis with 2 N HCl of the corresponding acetals (**3** and **4**).

All 3-azidothiophenes (**1** and **3–8**) and 3-azidobenzo[*b*]thiophene (**10**) are stable compounds which showed no sign of decomposition on standing in the dark at room temperature for several days; 2-azidothiophene (**2**) and 2-azidobenzo[*b*]thiophene (**9**) are somewhat unstable at room temperature but can be stored in the dark at low temperature for some days. The low yields obtained in the preparation of these two latter azides are attributed in part to some decomposition taking place during the fragmentation of the intermediate triazene salt and workup of the reaction mixture.[6]

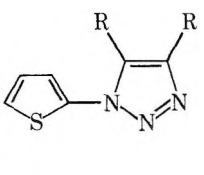
All azido compounds prepared in this work were characterized by spectra (IR, NMR, MS) and, when possible, elemental analysis.

The IR spectra showed the expected N_3 asymmetric stretching absorption in the region 2080–2100 cm^{-1}. The mass spectra showed, in addition to the parent ion, the expected peaks corresponding to loss of a nitrogen molecule [M − 28] and peaks due to subsequent loss of HCN. In particular, in the mass spectra of 2-azidothiophene (**2**) and 2-azidobenzo[*b*]thiophene (**9**), the molecular ion peaks were noticeably less intense than the corresponding peaks of the 3-azido derivatives; this trend is in line with the reduced stability observed with 2-azido compounds.

Azides **1** and **2** were allowed to react with acetylene and dimethyl acetylenedicarboxylate at room temperature for 48–56 h affording the 1-(3-thienyl)-1,2,3-triazoles, **11** and **12**,



11, R = H
12, R = $COOCH_3$



13, R = H
14, R = $COOCH_3$

and 1-(2-thienyl)-1,2,3-triazoles, **13** and **14**, respectively, in almost quantitative yield.

On the other hand reaction of 3-azidothiophene (**1**) with acetic anhydride under reflux gave 3-diacetylamino-2-acetoxythiophene (**16**) in 52% yield as the only identifiable product. The formation of compound **16** is not unexpected

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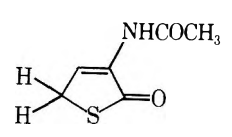
Table I. Yields and Physical, IR, and Analytical Data of Azidothiophenes (1–10)

compd	registry no.	yield, %	mp or bp (mm), °C	N_3, cm^{-1}
3-azidothiophene (1)	66768-57-8	85	55–56 (15)	2080
2-azidothiophene[d] (2)	66768-58-9	10	a	2100
3-azido-2-formylthiophene ethylene acetal (3)	66768-59-0	65	36–37	2085
4-azido-3-formylthiophene ethylene acetal (4)	66768-60-3	70	100–102 (15)	2095
3-azido-2-methylthiothiophene (5)	66768-61-4	68	103–107 (15)	2090
3-azido-4-methylthiothiophene (6)	66768-62-5	70	33–34	2100
3-azido-2-formylthiophene (7)	56473-97-3	88[b]	57–58[c]	2095
4-azido-3-formylthiophene (8)	66768-63-6	85[b]	50–52	2090
2-azidobenzo[b]thiophene[d] (9)	66768-64-7	7	38–40	2085
3-azidobenzo[b]thiophene (10)	66768-65-8	83	54–55	2090

[a] It was obtained as an oil whose bp could not be determined due to its decomposition on heating. [b] Obtained by hydrolysis from the corresponding acetal. [c] Lit.[3] mp 56.6–57.2 °C. [d] Satisfactory analytical data (±0.4% for C, H, N, S) were reported for all compounds except those noted.

since thermolysis of aryl azides under similar reaction conditions is known to lead to the formation of *o*-acetamidoaryl and *o*-diacetylaminoaryl acetates presumably via rearrangement of the intermediate *O,N*-diacylarylhydroxylamines.[7]

Under the same conditions 2-azidothiophene (2) did not give any identifiable products and 3-azidobenzo[*b*]thiophene (10) gave small amounts (18%) of 3-diacetylamino-2-acetoxybenzo[*b*]thiophene (17) together with a solid which has been tentatively assigned the 3-acetamido-2-acetoxybenzo[*b*]thiophene (18) structure.



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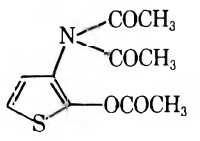

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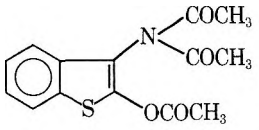

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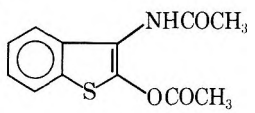

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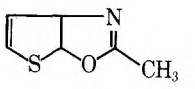

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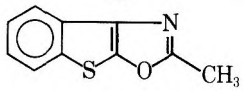

20

Attempts to obtain 2-methylthieno[3,2,*d*]oxazole (19) and 2-methyl[1]benzothieno[3,2-*d*]oxazole (20) by heating compounds 16 and 17, respectively, at 250–350 °C, in the absence or presence of phosphorus pentoxide,[8] were unsuccessful. Thermolysis of 3-azidothiophene (1) and 3-azidobenzo[*b*]thiophene (10) in a mixture of polyphosphoric and acetic acids[9] was likewise unsuccessful; in these instances 3-acetamidothiophen-2(5*H*)-one (15) (64%) was formed from azide 1 and compound 18 (34%) from azide 10 (cf. a previous report[10c] of the failure of this method for the synthesis of the 8,8-dioxide of 2-methyl[1]benzothieno[3,2-*d*]oxazole from 3-azidobenzo[*b*]thiophen 1,1-dioxide).

In summary, azidothiophenes are obtained in fair to good yields by treatment of lithium thiophene derivatives with *p*-toluenesulfonyl azide and subsequent fragmentation of the intermediate triazene–lithium salts. This procedure offers a convenient general route to the synthesis of azidothiophenes, thus allowing an extensive investigation of their chemical reactivity.

Experimental Section

All melting points are uncorrected. 2-Bromothiophene,[11] 3-bromothiophene,[12] 2-formyl-3-bromothiophene ethylene acetal,[13] 3-formyl-4-iodothiophene ethylene acetal,[14] 3-bromo-4-methylthiothiophene,[14] 3-bromo-2-methylthiothiophene,[15] and 3-bromobenzo[*b*]thiophene[16] were prepared as described in the literature. IR spectra are for solutions in carbon disulfide unless otherwise stated; NMR spectra were recorded in carbon disulfide at 60 MHz on a JEOL C 60 HL using Me_4Si as internal standard; mass spectra were recorded on a JEOL DMS 100 instrument.

Preparation of Azidothiophenes (1–6) and Azidobenzo[*b*]thiophenes (9 and 10). General Procedure. A solution of the appropriate bromothiophene derivative or 3-bromobenzo[*b*]thiophene (0.05 mol) in 20 mL of dry ether was added dropwise with stirring at −70 °C to *n*-butyllithium, 35 mL, 1.6 N in ether. The reaction mixture was stirred for 45 min at −70 °C, after which an ethereal solution of tosylazide[17] (0.055 mol) was added dropwise. After the addition was complete the resulting mixture was stirred for 5 h at −70 °C and the yellow triazene salt which had formed was rapidly filtered off and washed several times with dry ether. This material was then suspended in 150 mL of dry ether and treated at 0 °C with a solution of 22.5 g (0.05 mol) of tetrasodium pyrophosphate decahydrate in 250 mL of water. After stirring overnight at room temperature the ether layer was separated and the aqueous solution was extracted twice with pentane. The combined organic layers were washed with water and dried. The solvent was evaporated and the residue was chromatographed on a Florisil column using petroleum ether (bp 30–60 °C) as eluant.

2-Azidobenzo[*b*]thiophene was prepared by the same procedure except that direct metalation of benzo[*b*]thiophene was effected with a refluxing ether solution of *n*-butyllithium.

3-Azido-2-formylthiophene (7) and 4-azido-3-formylthiophene (8) were obtained from the corresponding ethylene acetals (3 and 4) by hydrolysis with 2 N HCl solution at room temperature.

Yields and physical, IR, and analytical data are collected in Table I.

1-(2-Thienyl)- and 1-(3-Thienyl)-1,2,3-triazoles (11–14). General Procedure. About 2 molar equiv of acetylene or dimethyl acetylenedicarboxylate were added to 20 mL of an acetone or benzene solution respectively of azides 1 and 2 (500 mg). The reaction mixture was allowed to stand at room temperature for 24–56 h until TLC showed the absence of azide. The excess solvent was removed and the residue was chromatographed on a silica gel column using 10% ether–pentane as eluant.

1-(2-Thienyl)-1,2,3-triazole (13) was obtained in 95% yield as white plates: mp 58–60 °C; NMR δ 7.04 (3 H, m), 7.59, and 7.78 (AB q, J = 1.2 Hz); mass spectrum, *m/e* 151 [M^+], 123, 122, 96, 70. Anal. Calcd for $C_6H_5N_3S$: C, 47.66; H, 3.33; N, 27.78; S, 21.20. Found: C, 47.68; H, 3.32; N, 27.85; S, 21.35.

1-(3-Thienyl)-1,2,3-triazole (11) was obtained in 96% yield as white needles: mp 70–72 °C; NMR δ 7.50 (3 H, m), 7.70 and 7.92 (AB q, J = 1.2 Hz); mass spectrum, *m/e* 151 [M^+], 123, 122, 96, 83. Anal. Found: C, 47.75; H, 3.37; N, 27.85; S, 21.15.

4,5-Dimethoxycarbonyl-1-(2-thienyl)-1,2,3-triazole (14). This product was obtained in 95% yield as white needles: mp 56–57 °C; NMR δ 3.80 (6 H, s), 7.20 (3 H, m); mass spectrum, *m/e* 267 [M^+], 239, 208, 207, 149. Anal. Calcd for $C_{10}H_9N_3O_4S$: C, 44.94; H, 3.39; H, 15.72; S, 11.99. Found: C, 45.05; H, 3.38; N, 15.65; S, 12.03.

4,5-Dimethoxycarbonyl-1-(3-thienyl)-1,2,3-triazole (12). This product was obtained in 92% yield: mp 91–92 °C; NMR δ 3.98 (6 H, s), 7.40 (3 H, m); mass spectrum, *m/e* 267 [M^+], 239, 208, 207, 149, 83. Anal. Found: C, 44.98; H, 3.35; N, 15.81; S, 11.86.

Thermal Decomposition of 3-Azidothiophene (1) in Acetic Acid–Polyphosphoric Acid. A mixture of the 3-azidothiophene (0.5

g), polyphosphoric acid (4 g), and acetic acid (10 mL) was stirred and heated at 100 °C for 1 h and then poured on ice. Extraction with chloroform gave a solid which was chromatographed on silica gel. Elution with 20% ether–pentane furnished 3-acetamidothiophen-2(5*H*)-one (**15**) (0.4 g, 64%): mp 153–155 °C; IR ν_{max} 3380 (NH), 1705 (amide C=O), and 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.21 (3 H, s), 4.03 (2 H, d, J = 3.1 Hz), and 7.87 (1 H, t, J = 3.1 Hz); mass spectrum, m/e 157 [M^+], 115, 86. Anal. Calcd for $C_6H_7NO_2S$: C, 45.85; H, 4.49; N, 8.92; S, 20.39. Found: C, 45.90; H, 4.50; N, 8.89; S, 20.30.

Thermal Decomposition of 3-Azidothiophene (1) in Acetic Anhydride. A solution of 3-azidothiophenone (0.4 g) in 6 mL of acetic anhydride was refluxed for 6 h (until TLC showed that no starting material was left). The reaction mixture was poured into water and extracted with chloroform. The combined extracts were washed with water, dried, and evaporated to give an oily residue which was chromatographed on silica gel. Elution with pentane afforded 3-diacetylamino-2-acetoxythiophene (**16**) (0.4 g, 52%) as a yellow oil: bp 118–120 °C (1 mm); IR ν_{max} 1780 (ester C=O) and 1720 cm^{-1} (amide C=O); NMR δ 2.20 (6 H, s), 2.24 (3 H, s), 6.47 and 6.77 (AB q, J = 5.6 Hz); mass spectrum, m/e 241 [M^+], 199, 157, 139. Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.80; H, 4.56; N, 5.80; S, 13.27. Found: C, 49.85; H, 4.54; N, 5.86; S, 13.21.

The same compound (**16**) was obtained in quantitative yield from 3-acetamidothiophene-2(5*H*)-one (**15**) in refluxing acetic anhydride.

Thermal Decomposition of 3-Azidobenzo[*b*]thiophene in Acetic Anhydride and in an Acetic Acid–Polyphosphoric Acid Mixture. Decomposition of 3-azidobenzo[*b*]thiophene (**10**) (0.5 g) in boiling acetic anhydride (10 mL) as described above for 3-azidothiophene led, after column chromatography, to (i) trace amounts of an unidentified yellow oil, (ii) 3-diacetylamino-2-acetoxybenzo[*b*]thiophene (**17**) (0.15 g, 18%) as white plates, and (iii) a solid material (**18**) (0.25 g). **17** had: mp 117–118 °C; IR ($CHCl_3$) ν_{max} 1775 (ester C=O) and 1720 cm^{-1} (amide C=O); NMR δ 2.4 (9 H, s), 7.4 (4 H, m); mass spectrum, m/e 291 [M^+], 249, 207, 189, 165. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.00. Found: C, 57.78; H, 4.48; N, 4.89; S, 10.93. **18** had: mp 148–152 °C; IR ($CHCl_3$) ν_{max} 3410 (NH), 1775 (ester C=O), and 1690 cm^{-1} (amide C=O); NMR 2.1 (3 H, s), 2.28 (3 H, s), 7.3 (4 H, m); mass spectrum, m/e 249 [M^+], 207, 165, 164, 136, 86, 84.

A satisfactory elemental analysis could not be obtained for **18**.

Thermolysis of azide **10** (0.5 g) in a mixture of polyphosphoric acid (4 g) and acetic acid (10 mL) at 100 °C gave, after chromatography: (a) a solid material (0.1 g), mp 140–150 °C, whose spectral analysis showed it to be a mixture of products, the major component being compound (**18**); and (b) a complex mixture of unidentifiable products (0.3 g).

Acknowledgment. The authors thank C.N.R. for a research grant.

Registry No.—**11**, 66768-66-9; **12**, 66768-67-0; **13**, 66768-68-1; **14**, 66768-69-2; **15**, 66768-70-5; **16**, 66768-71-6; **17**, 66768-72-7; **18**, 66768-73-8; 2-bromothiophene, 1003-09-4; 3-bromothiophene, 872-31-1; 2-formyl-3-bromothiophene ethylene acetal, 56857-02-4; 3-formyl-4-iodothiophene ethylene acetal, 66768-74-9; 3-bromo-4-methylthiothiophene, 58414-59-8; 3-bromo-2-methylthiothiophene, 66768-75-0; 3-bromobenzo[*b*]thiophene, 7342-82-7; 2-bromobenzo[*b*]thiophene, 5394-13-8; tosylazide, 941-55-9; acetylene, 74-86-2; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available: Full NMR and mass spectral data for compounds 1–10 (2 pages). Ordering information is given on any current masthead page.

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Syntheses of Indoles and Carbolines via Aminoacetaldehyde Acetals[1]

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Aminoacetaldehyde dimethyl acetal has been condensed with 1,3-cyclohexanediones and cyclized with acid to 4-oxo-4,5,6,7-tetrahydroindoles. These oxoindoles have, in turn, been condensed with formaldehyde and methylaminoacetaldehyde dimethyl acetal and cyclized with acid to octahydro-β-carboline derivatives. Indole has been condensed with formaldehyde and methylaminoacetaldehyde dimethyl acetal and cyclized with acid to a tetrahydro-γ-carboline derivative.

For several years, we have used aminoacetaldehyde acetals in the synthesis of isoquinoline derivatives.[2] In this paper, we would like to present a modified experimental procedure for the use of these versatile acetals for the synthesis of 4-oxo-4,5,6,7-tetrahydroindoles[3] and to extend the work to β- and γ-carboline systems.

4-Oxo-4,5,6,7-tetrahydroindoles, prepared by an alternate route,[4] have been developed[5,6] as synthetic intermediates. In a preliminary communication,[3] we described the preparation of these compounds (**1** → **3**, Scheme I) by an extremely simple process. The synthesis involves a remarkably stable enamine **2**, which undergoes an intramolecular condensation to yield

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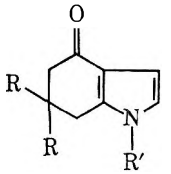
Table I. 4-Oxo-4,5,6,7-tetrahydroindoles



3

Compd	Registry no.	R	R′	Yield, %	Mp, °C
3a	13754-86-4	H	H	33	184–186[a]
3b	20955-75-3	CH_3	H	33	182–183[b]
3c	13671-74-4	H	$C_6H_5C-H_2$	61	81–82[c]
3d	66842-60-2	CH_3	$C_6H_5C-H_2$	57	Viscous liquid
3e	51471-08-0	H	CH_3	60	84–86[d]
3f	20955-76-4	CH_3	CH_3	65	109–110[b]

[a] Lit.[12] mp 188–190 °C. [b] Analytical data were within ±0.3% for C, H, N. [c] Lit.[4] mp 80–81.5 °C. [d] Lit.[12] mp 85–86 °C.

the 4-oxotetrahydroindole **3**. The synthesis is similar to one described by Gomez Sanchez and co-workers,[7,8] involving the reactions between D-glucosamine (as the aminoaldehyde) and 1,3-diketones. The compounds prepared are described in Table I. The proton NMR spectra of these indoles showed characteristic peaks at δ 6.7 (t, J = 3 Hz, 1, H-2) and 6.5 (t, J = 3 Hz, 1, H-3) for **3a**, and similar peaks were observed for **3b**. For compounds **3c**, **3d**, **3e**, and **3f** these protons (H-2 and H-3) appear as single peaks in the region of δ 6.5–6.7.

The precise experimental procedures for the preparation of **3a**, **3b**, **3c**, and **3d** have been changed from the original publication[3] (see ref 9). In more recent papers, similar ring closures of enamine acids[10] and methylaminovinyl compounds[11] have been described.

Scheme I

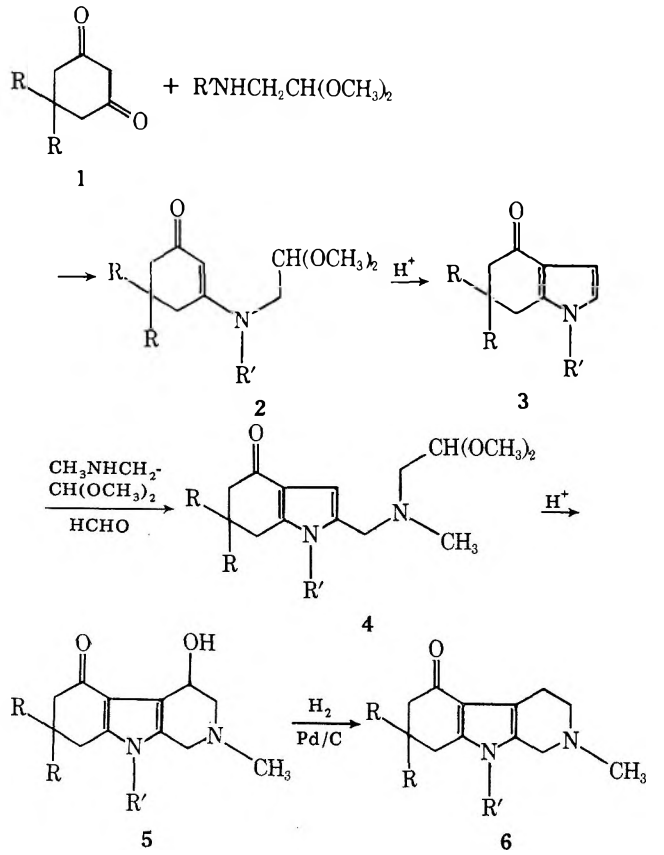
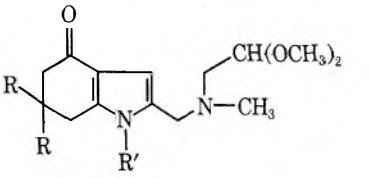


Table II. Condensation Products from 3, Methylaminoacetaldehyde Dimethyl Acetal, and Formaldehyde



4

Compd	Registry no.	R	R′	Yield, %
4a	66842-61-3	H	H	59
4b	66842-62-4	CH_3	H	88
4c	66842-63-5	H	$C_6H_5CH_2$	73 (crude)
4d	66842-64-6	CH_3	$C_6H_5CH_2$	34 (45 crude)
4e	66842-65-7	H	CH_3	61 (92 crude)
4f[a]	66842-66-8	CH_3	CH_3	65

[a] This compound was crystalline and melted at 71–72 °C. The others were viscous oils.

The general method involving Mannich reactions with aminoacetals[13] was applied to the oxoindoles **3** and indole itself to yield β-carboline derivatives (Scheme I) and a γ-carboline derivative (Scheme II), respectively. The oxoindoles **3** described in Table I were allowed to react with formaldehyde and methylaminoacetaldehyde dimethyl acetal in glacial acetic acid[14] to yield the condensation products **4** listed in Table II. These materials were mostly viscous liquids and were not completely characterized. Their NMR spectra exhibited the expected peaks. Evidence for the fact that the Mannich reaction takes place at C-2 rather than C-3 of the oxoindoles is derived from the ^{13}C NMR spectra of the products **4**. Carbons 2 and 3 of **3f** were shown to appear at 124.3 and 105.7 ppm (downfield from Me_4Si), respectively, by correlation with known spectra of pyrrole[15] and indole[16] and their derivatives. After the addition of the side chain (as shown in **4f**), these carbons appeared at 132.4 and 103.4 ppm, a shift of +8.1 for carbon 2 and −2.3 for carbon 3. For pyrrole[15] these shifts are +9.4 and −1.9, respectively. For indole they are +10.5 and −2.2.[16] Indole gave the corresponding Mannich base **7** as anticipated.[14]

Ring closure of the Mannich bases **4a–f** and **7** to the corresponding hydroxy compounds was carried out by treatment with dilute HCl.[17,18] 4-Hydroxy-*N*-methyl-1,2,3,4-tetrahydro-γ-carboline (**8**) was obtained in 62% yield. The products

Scheme II

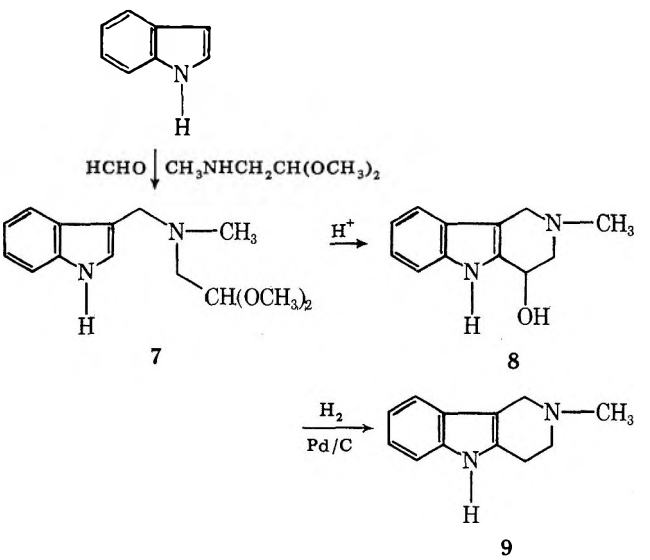
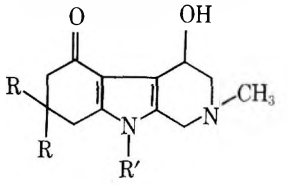


Table III. 2-Methyl-4-hydroxy-5-oxo-1,2,3,4,5,6,7,8-octahydro-β-carbolines[a]

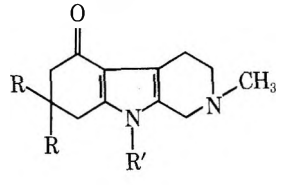


5

Compd	Registry no.	R	R′	Yield, %	Mp, °C
5a	66842-67-9	H	H	20	173–175
5b	66842-68-0	CH_3	H	56	178–180
5c	66842-69-1	H	$C_6H_5CH_2$	86	154–156
5d	66842-70-4	CH_3	$C_6H_5CH_2$	57	135–136
5e	66842-71-5	H	CH_3	63	157–159
5f	66842-72-6	CH_3	CH_3	77	159–160

[a] Analytical data were within ±0.4% for C, H, N.

Table IV. 2-Methyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-β-carbolines[a]



6

Compd	Registry no.	R	R′	Yield, %	Mp, °C
6a	66842-73-7	H	H	59	193–195
6b	66842-74-8	CH_3	H	57	227–229
6c	66842-75-9	H	$C_6H_5CH_2$	55	124–125
6d	66842-76-0	CH_3	$C_6H_5CH_2$	50	131–133
6e	66842-77-1	H	CH_3	45	166–168
6f	66842-78-2	CH_3	CH_3	74	130–131

[a] Analytical data were within ±0.35% for C, H, N for all new compounds in the table except for **6a**, where they were C, +0.75, H, +0.60, and N, −0.35.

derived from **4a–f** are described as **5a–f** in Table III. The proton NMR spectra of these compounds showed a characteristic broad triplet (J = 4–6 Hz) for H-4 in the δ 4.75–5.1 region. However, this proton (H-4) was buried beneath the benzyl protons in compounds **5c** and **5d**.

The hydrogenolysis of the various hydroxy compounds, **5a–f** and **8**, was accomplished with some difficulty over palladium on carbon.[19] The time and temperature of the hydrogenolysis were varied to accomplish the desired results. In no case was an N-benzyl group removed by hydrogenolysis. The known compound N-methyl-1,2,3,4-tetrahydro-γ-carboline (**9**)[20] was obtained in 66% yield. The various β-carboline derivatives (**6a–f**) are described in Table IV.

Experimental Section

Melting points were measured on a Thomas-Hoover capillary melting point apparatus or on a Reichert hot stage apparatus and are uncorrected. Proton NMR spectra were determined in $CDCl_3$ with a Me_4Si standard on a Varian A-60 instrument. The proton noise-decoupled ^{13}C NMR spectra were measured in $CDCl_3$ on a Bruker WP-60 FT spectrometer with 8K computer memory using a 10 mm sample tube. Spectra were recorded on a 4000 Hz sweep width at 15.08 MHz using the fast Fourier transform technique. All solvent evaporations were carried out on a Büchi rotary vacuum evaporator. Analyses were carried out by Baron Consulting Co., Orange, Conn.

4-Oxo-4,5,6,7-tetrahydroindoles 3a, 3b, 3e, and 3f. A mixture of 4.48 g (0.04 mol) of 1,3-cyclohexanedione, 6.4 g (0.06 mol) of aminoacetaldehyde dimethyl acetal, and 0.2 g of p-toluenesulfonic acid in 150 mL of benzene was heated to reflux for 24 h with continuous removal of H_2O through a Dean-Stark tube. The benzene was evaporated, and the orange residue was treated with an ice-cold mixture of 60 mL of 3 N HCl and 50 mL of $CHCl_3$. The mixture was stirred for a few minutes at room temperature, and the aqueous acidic layer was separated and transferred to a continuous extraction apparatus designed for extraction with heavier-than-H_2O liquids. The mixture was extracted with $CHCl_3$ overnight or until no more material was extracted. A few chips of $CaCO_3$ were placed in the $CHCl_3$ reservoir to neutralize any acid which might be extracted.[21] After removal of the solvent from the extract, the residue was dissolved in 10 mL of benzene/acetone (4:1) and placed on top of a short column (2.4 × 11 cm) of silica gel[22] and eluted with benzene/acetone (4:1). Fractions of 75 mL were taken. The product, **3a** (1.8 g), obtained from fractions 2, 3, and 4, was crystallized from benzene/hexane. Compounds **3b, 3e,** and **3f** were prepared in the same manner. Compound **3f** had the following spectral properties: ^1H NMR ($CDCl_3$) δ 6.57 (s, 2, H-2 and H-3); ^{13}C NMR ($CDCl_3$) (downfield from Me_4Si) 124.3 (C-2) and 105.7 (C-3) ppm.

4-Oxo-4,5,6,7-tetrahydroindoles 3c and 3d. A mixture of 2.24 g (0.02 mol) of 1,3-cyclohexanedione, 5.85 g (0.03 mol) of N-benzylaminoacetaldehyde dimethyl acetal, 70 mL of benzene, and 0.1 g of p-toluenesulfonic acid was heated to reflux for 24 h with continuous removal of H_2O with a Dean-Stark tube. The benzene was removed, and the residue was heated to 45–50 °C with 30 mL of 3 N HCl for 4 h. A gummy material separated. The mixture, gum and all, was extracted with $CHCl_3$, washed (H_2O), dried (Na_2SO_4), and concentrated to give 3.75 g of dark red viscous material. This was dissolved in 10 mL of benzene/acetone (4:1) and chromatographed over silica gel as described for **3a** to give 2.75 g of **3c** which was crystallized from benzene/hexane. Compound **3d** was prepared in the same manner.

Mannich Bases Derived from Compounds 3. A solution of 0.01 mol of the 4-oxo-4,5,6,7-tetrahydroindole in 5 mL of acetic acid was treated with 0.012 mol of methylaminoacetaldehyde dimethyl acetal. The mixture was heated to 70–75 °C for 2 h, cooled, diluted with about 50 mL of H_2O, and extracted with ether to remove any nonbasic material. The aqueous acidic layer was basified (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), concentrated to a residue, dissolved in 15 mL of benzene/acetone (4:1), and chromatographed over a silica gel column as described for **3a**. The eluents were concentrated to give the Mannich bases which, except for **4f**, were viscous oils. Compound **4f** melted at 71–72 °C and had the following spectral properties: ^1H NMR ($CDCl_3$) δ 6.5 (s, 1, H-3) and 4.54 (t, 1, $-CH(OCH_3)_2$); ^{13}C NMR ($CDCl_3$) (downfield from Me_4Si) 132.4 (C-2) and 103.4 (C-3) ppm.

4-Hydroxy-1,2,3,4,5,6,7,8-octahydro-5-oxo-β-carbolines 5. General Procedure. A solution of the appropriate Mannich base 4 (0.005 mol) in 15 mL of 8 N HCl was warmed to 60–70 °C for 5 min. After cooling, the mixture was washed ($CHCl_3$), basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), concentrated to a residue, and crystallized to yield the product (**5a** from chloroform/hexane; **5b** from acetone/hexane; and **5c, 5d, 5e,** and **5f** from benzene/hexane).

5-Oxo-1,2,3,4,5,6,7,8-octahydro-β-carbolines 6. A mixture of the hydroxycarboline **5** and an equal weight of 5% Pd/C, 8 N HCl (5 mL per 0.1 g of carboline), and ethanol (5 mL per 0.1 g of carboline) was hydrogenated in a Paar apparatus at 16 psi until no more hydrogen was absorbed. The hydrogenations of **5a, 5b, 5e,** and **5f** were carried out at room temperature, and those of **5c** and **5d** were carried out at 60–65 °C. The catalyst was removed by filtration, and the filtrate was concentrated to a small volume, basified (NH_4OH), and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried (Na_2SO_4), and concentrated to a residue which was crystallized to give the product (**6a** from ether; **6b** and **6e** from chloroform/hexane; and **6c, 6d,** and **6f** from benzene/hexane).

Mannich Base 7. This compound was prepared from indole by a method identical with that described above for **3** except that the formaldehyde was added dropwise and the solution was not heated but was allowed to stir for 1 h. The product, 4 g (80%), was obtained by triturating the crude final residue (see procedure for **4**) with hexane. The compound melted at 79–80 °C. Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.97; H, 8.05; N, 11.22.

4-Hydroxy-2-methyl-1,2,3,4-tetrahydro-γ-carboline (8). Compound **7** (2 g, 0.01 mol) was added to 60 mL of 6 N HCl which had been previously cooled to 0 °C. The solution was stirred at 0 °C for 1 h and at room temperature for 3.5 h and then basified (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed (H_2O), dried

(Na_2SO_4), and evaporated to give 1 g (62%) of 8 which was recrystallized from $CHCl_3$ to give the product, mp 205–207 °C. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.76; H, 6.98; N, 13.85. Found: C, 70.99; H, 6.89; N, 13.87.

2-Methyl-1,2,3,4-tetrahydro-γ-carboline (9). A mixture of 0.202 g of 8, 0.2 g of 5% Pd/C, 10 mL of 6 N HCl, and 10 mL of ethanol was hydrogenated at 17 psi for 16 h at room temperature. The product was isolated as described above for **6**. The final residue was triturated with benzene to give 0.123 g (66%) of crystalline **9** with mp 163–165 °C. After recrystallization from acetone/benzene, the compound melted at 172–173 °C (lit.[20] mp 171–172 °C).

Acknowledgment. In addition to the financial support previously mentioned, we would like to thank Professor A. Makriyannis of the College of Pharmacy of the University of Connecticut for measuring the ^{13}C NMR spectra.

Registry No.—**1a**, 504-02-9; **1b**, 126-81-8; **7**, 66842-79-3; **8**, 66842-80-6; **9**, 5094-12-2; $H_2NCH_2CH(OMe)_2$, 22483-09-6; $PhCH_2NHCH_2CH(OMe)_2$, 54879-88-8; $MeNHCH_2CH(OMe)_2$, 122-07-6; indole, 120-72-9; formaldehyde, 50-00-0.

References and Notes

(1) This work was sponsored in part by Contract DA-49-193-MD-2948 from the U.S. Army Medical Research and Development Command, publication 1500 from the Army Research Program on Maleria, and in part by Research Grant CA-10494 from the Cancer Institute of the National Institutes of Health.
(2) J. M. Bobbitt and S. Shibuya, *J. Org. Chem.*, **35**, 1181 (1970), and preceding papers of the series.
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(9) Dr. J. A. Joule of the University of Manchester in England has informed us that he was unable to repeat our original procedure[3] for the preparation of **3a**. We have been able to repeat it, but the extraction procedure described in this paper is more reliable. A third procedure has been described to us in a private communication by Dr. James Cook of the University of Wisconsin in Milwaukee, Wis.
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(21) The basis of this procedure is that the Schiff base **2** is basic and soluble in dilute HCl, whereas the product **3** is no longer basic and is extracted as it is formed.
(22) Silica gel M was obtained from Herrmann Brothers, Cologne, Ger.

Azaindolizines. 5. Nucleophilic Substitution on Chloro-6- and -8-azaindolizines

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Received November 8, 1977

Cyclization of the products of reaction between phenacyl bromide and 4,6-dimethyl-2-pyrimidone and 2-methyl-4-pyrimidone gave the 6- and 8-azaindolizinones **7** and **9**, which on reaction with phosphoryl chloride gave the corresponding 5- and 7-chloro-6- and -8-azaindolizines **2** and **5**, respectively. The substitution of chlorine from **2** and **5** by hydroxide, methoxide, and amide was investigated; displacement of chlorine by all these nucleophiles occurred with the 5-chloro-6-azaindolizine **2**, whereas only methoxylation occurred with the 7-chloro-8-azainolizine **5**. Reaction of **2** with phosphoryl chloride gave the peri condensed structure **13**. Formylation of the product of ammonolysis of **2** gave the 1,7-diazacyclo[3.2.2]azine **16**.

Both 6- and 8-azaindolizines can be formally classified as π-excessive[1] heteroaromatic systems and as such would be expected to show a propensity toward electrophilic rather than nucleophilic substitution processes. Electrophilic substitution of both 6- and 8-azaindolizines has been shown[2,3] to occur preferentially at C-3 and then at C-1, findings which are broadly in agreement with theoretical MO calculations.[4,5] Although the 6- and 8-azaindolizines are π excessive, the MO calculations indicate both systems to have sites of considerable electron deficiency. The sites of minimum electron density, as might be expected, occur within the pyrimidine moiety specifically at C-5 and C-7, the C-5 site being the most deficient for the 6-aza- and the C-7 site for the 8-azaindolizine system.

Although nucleophilic displacement from pyrimide and other π-deficient[1] heteroaromatic systems is common, even hydride ion displacement being possible,[6] no instances of successful nucleophilic displacement from the indolizine nucleus have been reported, and of the seven possible azaindolizines only the 1-azaindolizine system has been shown to undergo nucleophilic displacement of chlorine.[7-9] In this paper we describe the reactivity of the chlorine in 5-chloro-7-methyl-2-phenyl-6-azaindolizine (**2**) and 7-chloro-2-phenyl-8-azaindolizine (**5**). Attempts to effect direct nucleophilic subtitution on 7-methyl-2-phenyl-6-azaindolizine (**1**) by treatment with sodamide or sodium methoxide at temperatures up to 180 °C merely resulted in decomposition or at lower temperatures in the recovery of starting material.

The chloro-6- and 8-azaindolizines **2** and **5** were prepared by heating the corresponding 6- and 8-azaindolizinones **7** and **9** with phosphoryl chloride. 7-Methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (**7**) and 2-phenyl-8-azaindolizine-7(8*H*)-one (**9**) were each obtained by reacting 4,6-dimethyl-2-pyrimidone and 2-methyl-4-pyrimidone, respectively, with phenacyl bromide. In each reaction the minor product was the corresponding azaindolizinone **7** and **9** and the major product the corresponding *N*-phenacylpyrimidones **11** and **12** which were readily cyclized to the 6- and 8-azaindolizinones **7** and **9** by heating at 180 °C. While the reaction of 4,6-dimethyl-2-pyrimidone with phenacyl bromide can only lead, on cyclization, to the 6-azaindolizin-5(6*H*)-one **7**, 2-methyl-4-pyrimidone could give either the 2-phenyl-8-azaindolizin-7(8*H*)-one **9** or

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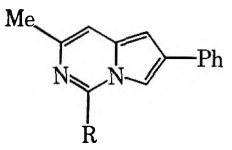
the 8-azaindolizin-5(8*H*)-one **10**. That the former 8-azaindolizin-7(8*H*)-one **9**, the product expected from quaternization at the more accessible nitrogen, was obtained was confirmed by its alternative formation by the demethylation of 7-methoxy-2-phenyl-8-azaindolizine (**6**).[3] The IR and ^{1}H NMR spectra of both the 6- and 8-azaindolizinones **7** and **9** show these compounds to exist in the keto forms. The conversion of the 6- and 8-azaindolizinones **7** and **9** to the corresponding chloroazaindolizines **2** and **5** by treatment with phosphoryl chloride occurred in good yield and presumably substitution occurs in a manner analogous to that postulated for the conversion of pyridones to chloropyridines.[10]

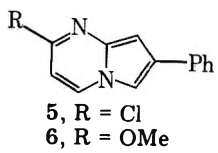
The chloroazaindolizines **2** and **5** were each treated with sodium hydroxide, sodium methoxide, and ammonia or sodamide. Hydrolysis of 5-chloro-7-methyl-2-phenyl-6-azaindolizine (**2**) with aqueous sodium hydroxide was slow and after refluxing for several hours only a 9% yield of the azaindolizinone **7** was obtained. The 7-chloro-2-phenyl-8-azaindolizine **5** when similarly treated with sodium hydroxide gave only unchanged starting material. In contrast methoxylation of either the 5-chloro-6-azaindolizine **2** or the 7-chloro-8-azaindolizine **5** occurred readily by refluxing each with sodium methoxide in boiling methanol to give the corresponding 5- and 7-methoxyazaindolizines **3** and **6** in high yield. Cleavage of the ether linkage of both **3** and **6** with hydrochloric acid gave the 6- and 8-azaindolizinones **7** and **9**. Replacement of chlorine by amino occurred when the 5-chloro-6-azaindolizine **2** was treated with a solution of anhydrous ammonia in ethanol in a sealed tube at 130–150 °C. The IR spectrum of the resulting 5-amino-7-methyl-2-phenyl-6-azaindolizine **4** showed the presence of the amino group by absorptions at 3480, 3340, and 1655 cm^{-1} and the ^{1}H NMR spectrum showed a broad 2 H signal at δ 7.14. No analgous replacement of chlorine by amino occurred when 7-chloro-2-phenyl-8-azaindolizine (**5**) was treated with either ammonia or with sodamide in liquid ammonia.

Refluxing 5-chloro-7-methyl-2-phenyl-6-azaindolizine (**2**) with phosphoryl chloride gave a dark red product whose mass spectrum showed a molecular ion at *m/e* 412 corresponding to the *m/e* value expected for a molecule constructed from two units of the percursor **2** less two molecules of hydrogen chloride. The ^{1}H NMR spectrum of this dark red compound was simple and apart from methyl and phenyl absorptions at δ 1.93 and δ 7.20–7.88 showed only two other singlets at δ 5.96 and 6.08. This suggests the compound to have the centrosymmetric structure **13**. Irradiation at the frequency of the methyl signal resulted in sharpening of the 2 H singlet at δ 6.08; this singlet was therefore assigned to H-3 and H-8 and that at δ 5.96 to H-2 and H-7. The bridging between the two 6-azaindolizine units leading to **13** can be envisaged to occur by the interaction of the electron rich C-3 site of one 6-azaindolizine molecule with the electron deficient C-5 site of another, accompanied by the elimination of hydrogen chloride. Small quantities of **13** were also isolated when the 6-azaindolizin-5(6*H*)-one **7** was treated with phosphoryl chloride, in its conversion to **2**. Formylation and protonation studies on **13**, which has 16 peripheral π electrons, suggest it to behave essentially as two separate 6-azaindolizine units. Thus formylation gave the 2,7-diformyl derivative **14** and the ^{1}H NMR spectrum of **13** in trifluoroacetic acid indicated the formation of the nitrogen protonated dication **15**. The spectrum of the dication was similar in pattern to that of the free base **13** showing no midfield methylene or methine signals. Slow deuterium exchange[12] of the H-2 and H-7 protons was observed when the spectrum of **13** was recorded in deuteriotrifluoroacetic acid.

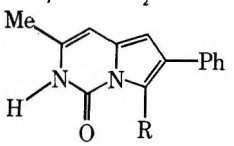
Previous work on both 5-methyl-6-azaindolizines[2] and aminoindoles[13] suggested that formylation of 5-aminoazaindolizines may serve as a convenient route to diazacycl[3.2.2]-azines. Accordingly treatment of 5-amino-7-methyl-2-phenyl-6-azaindolizine (**4**) with a preformed solution of the Vilsmeier complex[14] at room temperature gave **16** as the sole product of reaction in 31% yield; significantly no 3-formyl derivative of **4** was isolated suggesting the attack of the Vilsmeier electrophile to occur only at the exocyclic 5-amino group.[2] The diazacyclazine **16** did not ring open on treatment with acid[15] nor did it undergo formylation. In contrast to the formylation of the 5-amino-6-azaindolizine **5** the 6-azaindolizin-5(6*H*)-one **7** and the 5-chloro-6-azaindolizine **2** gave formyl products resulting from attack at the electron rich C-3 and/or C-1 sites. Thus **7** gave 3-formyl-7-methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (**8**) whose formyl proton occurred at particularly low field (δ 10.82) due to the anisotropic deshielding effect of the nearby 5-keto group. Formylation of the 5-chloro-6-azaindolizine **2** gave in addition to **8** the three formyl-6-azaindolizines **17**, **18**, and **19**, all in low yield. The H-8 absorption of aldehydes **17** and **18** showed, when compared to the H-8 absorption position of their percursor **2**, peri shifts of 110 and 78 Hz, respectively; such shifts can only arise by formylation at C-1; aldehyde **19** showed no such per shift. Formation of the 5-dimethylamino-6-azaindolizine aldehydes **18** and **19** presumably arises by nucleophilic displacement of the 5-chloro group of **2** by dimethylamino during the course of formylation.



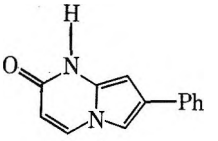
1, R = H
2, R = Cl
3, R = OMe
4, R = NH_2



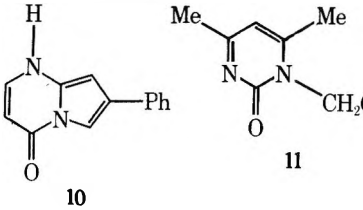
5, R = Cl
6, R = OMe



7, R = H
8, R = CHO

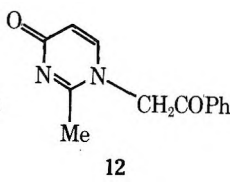


9

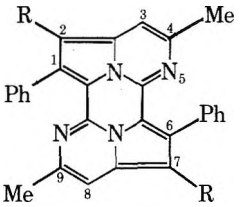


10

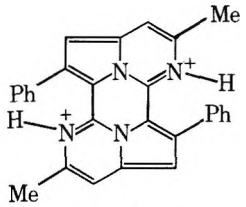
11



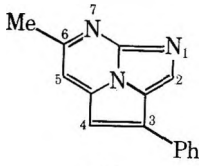
12



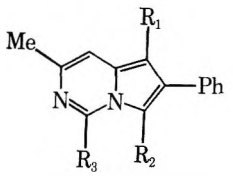
13, R = H
14, R = CHO



15



16



17, R_1 = CHO; R_2 = H; R_3 = Cl
18, R_1 = CHO; R_2 = H; R_3 = $N(Me)_2$
19, R_1 = H; R_2 = CHO; R_3 = $N(Me)_2$

Experimental Section

The instruments used and general procedures are as given in ref 3. ^{1}H NMR signal assignments were made on the basis of the relative

proximity of the protons to nitrogen and by the assistance of double resonance; weakly coupled signals are marked by asterisks.

Attempted Reaction between 7-Methyl-2-phenyl-6-azaindolizine (1) and (a) Sodamide and (b) Sodium methoxide. (a) 7-Methyl-2-phenyl-6-azaindolizine[2] (1) (500 mg, 2.4 mmol) was added to a suspension of $NaNH_2$ (0.5 g, 12.8 mmol) in dry *N,N*-dimethylaniline[16] (20 cm^3) and the mixture was heated at 110 °C for 4 h under N_2. Water was added and the resulting mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to remove $CHCl_3$ and *N,N*-dimethylaniline. The residual solid was subjected to TLC which gave only starting material (177 mg, 35%). Raising the reaction temperature to 180 °C resulted in complete decomposition of the starting material.

(b) 7-Methyl-2-phenyl-6-azaindolizine (1) (1 g, 4.8 mmol) was added to a solution of NaOMe prepared from MeOH (20 cm^3) and Na (1 g, 43.5 mmol) and the resultant was refluxed for 8 h. The solvent was removed and the residue was treated with water and extracted with $CHCl_3$. The extract gave only unchanged starting material (0.93 g, 93%).

Reaction between 2-Hydroxy-4,6-dimethylpyridine and Phenacyl Bromide. A solution of 2-hydroxy-4,6-dimethylpyrimidine[17] (17.5 g, 0.14 mol) and phenacyl bromide (28.1 g, 0.14 mol) in EtOH (200 cm^3) was refluxed on a water bath for 1.5 h. The solid which separated was filtered from the hot solution, washed with a little boiling EtOH, and dried under vacuum to give **2-hydroxy-4,6-dimethylpyrimidine hydrobromide** (9.1 g, 31%) as a pale orange solid which did not melt below 300 °C: λ_{max} 305 nm (log ϵ 3.79); IR 847, 1627, 1735, 2500–3300 cm^{-1}; NMR [$(CD_3)_2SO$] 2.44 (6 H, Me-4 and Me-6), 6.74 (H-5).

Anal. Calcd for $C_6H_9N_2BrO$: C, 35.14; H, 4.42; N, 13.66; Br, 38.97. Found: C, 35.4; H, 4.5; N, 13.8; Br, 39.0.

The ethanolic solution was refluxed for a further 1.5 h and the EtOH was removed. The brown solid obtained was dissolved in water (400 cm^3) and the solution was extracted with ether (4 × 100 cm^3). $NaHCO_3$ (25 g) was added to the aqueous part and the solution was heated for 15 min on a boiling water bath. The solid (4.4 g) which separated was collected and dried. The UV and NMR spectra of this solid indicated it to be a 1:4 mixture of 7-methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (7) and 4,6-dimethyl-1-phenacylpyrimid-2(1*H*)-one (11).

The residual aqueous bicarbonate phase was extracted with $CHCl_3$ (5 × 200 cm^3) and the $CHCl_3$ extract was dried and evaporated to give a pale yellow solid which was recrystallized from $CHCl_3$ to give **4,6-dimethyl-1-phenacylpyrimid-2(1*H*)-one** (11) (1.17 g, 3%) as needles: mp 166.5 °C; λ_{max} *243*, 305 nm (log ϵ 4.17, 3.89); IR 760, 1225, 1608, 1655, 1690 cm^{-1}; NMR ($CDCl_3$) 2.11 (3 H, Me), 2.35 (3 H, Me), 5.51 (2 H, methylene), 6.16 (H-5), 7.33–8.13 (m, 5 H, Ph); mass spectrum *m/e* 242 (M^+, 40% base peak).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.83; N, 11.56. Found: C, 69.2; H, 5.7; N, 11.8.

7-Methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (7). The pyrimidone 11 (50 mg) was heated at 180 °C under vacuum (10 mm) for 15 min to give 7 (44 mg, 96%) as a buff colored solid: mp 275 °C dec; λ_{max} *253*, (277), (305) nm (log ϵ 4.69; 4.09; 3.72); IR 832, 1200, 1410, 1640, 1693, 3100, 3210, cm^{-1}; NMR [$(CD_3)_2SO$] 2.13* (3 H, Me-7), 6.23* (H-8), 6.58 (H-1), 7.20–7.78 (m, 5 H, Ph), 7.83 (H-3), 10.88 (broad, NH); mass spectrum *m/e* 224 (M^+, base peak).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.1; H, 5.3; N, 12.8.

2-Methyl-1-phenacylpyrimid-4(1*H*)-one (12). 4-Hydroxy-2-methylpyrimidine[18] (5.5 g, 50 mmol) and phenacyl bromide (10 g, 50 mmol) were heated together at 60 °C for 8 h in dimethylformamide (10 cm^3). The dark red product was dissolved in water (150 cm^3) and washed with $CHCl_3$ (3 × 100 cm^3). $NaHCO_3$ (5 g) was added to the aqueous part and the needles which separated were collected, washed with a little water, and dried at 50 °C (0.01 mm) to give hydrated 12 (3.2 g, 27%): λ_{max} *248* (log ϵ 4.47); IR 750, 1210, 1520, 1590, 1639, 1690, 3430 (broad) cm^{-1}; NMR [$(CD_3)_2SO$] 2.22 (3 H, Me), 5.72 (2 H, methylene), 5.97 (d, J = 7.5 Hz, H-5), 7.40–8.20 (m, 5 H, Ph), 7.59 (d, J = 7.5 Hz, H-6).

Anal. Calcd for $C_{13}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$: C, 65.81; H, 5.62. Found: C, 65.7; H, 5.6. Heating the hydrated pyrimidone 12 at 110 °C (0.01 mm) for 30 min gave the anhydrous pyrimidone; mp 172–182 °C, followed by the formation of new crystals at 184 °C which decomposed at 270 °C; λ_{max} *248* nm (log ϵ 4.48); IR 759, 1228, 1528, 1627, 1643, 1692 cm^{-1}; NMR ($CDCl_3$) 2.25 (3 H, Me), 5.50 (2 H, methylene), 6.05 (d, J = 7.5 Hz), 7.32 (d, J = 7.5 Hz, H-6), 7.40–8.17 (m, 5 H, Ph), the NMR spectrum in $(CD_3)_2SO$ was identical to that of the above hydrated derivative; mass spectrum *m/e* 228 (M^+, 1% base peak), 210 (M^+ − 18, base peak).

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found C, 68.1; H, 5.4; N, 12.3.

2-Phenyl-8-azaindolizin-7(8*H*)-one (9). (a) A solution of 7-methoxy-2-phenyl-8-azaindolizine[3] (6) (100 mg) in concentrated hydrochloric acid (20 cm^3) was heated on a boiling water bath for 30 min and evaporated to dryness. The solid obtained was dissolved in water (20 cm^3) and the solution was made basic by the addition of $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and evaporated and the residue was sublimed at 200 °C (0.01 mm) to give 9 (80 mg, 85%) as a pale yellow solid which decomposed at 270 °C: λ_{max} *243*, (249) 290, 299, (329) nm (log ϵ 4.50, 4.47, 4.12, 4.13, 3.54); IR 728, 760, 811, 968, 1219, 1440, 1680, 2800, 3140 cm^{-1}; NMR [$(CD_3)_2SO$] 5.78 (d, J = 8.0 Hz, H-6), 5.89 (d, J = 1.5 Hz, H-1), 7.06–7.70 (m, 5 H, Ph), 7.36 (H-3), 8.17 (d, J = 8.0 Hz, H-5), 11.52 (broad, NH, disappears on addition of D_2O); mass spectrum *m/e* 210 (M^+, base peak).

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found; C, 74.0; H, 5.0; N, 13.3.

(b) The pyrimidone 12 (100 mg) was heated at 180 °C under vacuum (15 mm) for 30 min and the product sublimed at 200 °C (0.01 mm) to give 9 (90 mg, 98%) with identical spectral characteristics to the sample obtained above.

Reaction between 7-Methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (7) and Phosphoryl Chloride. A solution of the 6-azaindolizinone 7 (300 mg) in $POCl_3$ (45 cm^3) was refluxed for 4 h and the bulk of the $POCl_3$ was then removed at 60 °C (10 mm). The dark colored residue was poured onto crushed ice (30 g), basified by the addition of 2 M NaOH, and extracted with $CHCl_3$ (4 × 50 cm^3). The $CHCl_3$ extract was dried and evaporated and the gum obtained was subjected to TLC with benzene. Two main bands developed. The material from the fast moving orange colored band was extracted with $CHCl_3$ and the extract concentrated to approximately 5 cm^3 and cooled in ice. **4,9-Dimethyl-1,6-diphenyldi(6-azaindolizino)-[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (13)** (8 mg, 3.1%) separated as dark red prisms: mp 262.5–265 °C dec; λ_{max} (CH_2Cl_2) *268*, (288), (410), (438), 460, 486 nm (log ϵ 4.80, 4.55, 3.47, 3.87, 4.09, 4.17); IR 698, 760, 839, 1387, 1541, 1615 cm^{-1}; NMR ($CDCl_3$) 1.93* (6 H, Me-4 and Me-9), 5.96 (2 H, H-2 and H-7), 6.08* (2 H, H-3 and H-8), 7.20–7.88 (m, 10 H, Ph-1 and Ph-6); NMR (CF_3COOH) 2.20* (6 H, Me-4 and Me-9), 6.69* (2 H, H-3 and H-8), 6.78 (2 H, H-2 and H-7), 7.70 (10 H, Ph-1 and Ph-6); mass spectrum *m/e* 412 (M^+, base peak).

Anal. Calcd for $C_{28}H_{20}N_4$: C, 81.53; H, 4.89; N, 13.58. Found C, 81.7; H, 4.7; N, 13.8.

The material from the slower moving band which gave a green Ehrlich's test was extracted and recrystallized from petroleum ether to give **5-chloro-7-methyl-2-phenyl-6-azaindolizine (2)** (243 mg, 75%) as white flakes: mp 144.5–145 °C; λ_{max} *254*, (256), (283), (300), 358 (broad) nm (log ϵ 4.71, 4.71, 3.95, 3.57, 3.45); IR 728, 768, 1245, 1407, 1620 cm^{-1}; NMR ($CDCl_3$) 2.39* (3 H, Me-7), 6.70 (H-1), 7.00* (h-8), 7.10–7.75 (m, 5 H, Ph), 7.70 (H-3); mass spectrum (^{35}Cl) *m/e* 242 (M^+, base peak).

Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.3; H, 4.3; N, 11.5; Cl, 14.9.

7-Chloro-2-phenyl-8-azaindolizine (5). A solution of the 8-azaindolizinone 9 (100 mg) in $POCl_3$ (10 cm^3) was gently refluxed for 4 h and the product was worked up as in the reaction between the 6-azaindolizinone 7 and $POCl_3$. TLC with benzene/ethyl acetate (20:1) gave a fast-moving yellow band. The material from this band was extracted and recrystallized from benzene to give 5 (82 mg, 75%): mp 212 °C dec; λ_{max} *254*, 325, 370 (broad) nm (log ϵ 4.60, 3.88, 3.47); IR 737, 770, 1090, 1132, 1510, 1609 cm^{-1}; NMR ($CDCl_3$) 6.50 (d, J = 7.0 Hz, H-6), 6.84 (H-1), 7.26 (H-3), 7.30–7.76 (m, 5 H, Ph), 8.07 (d, J = 7.0 Hz, H-5); mass spectrum (^{35}Cl) *m/e* 228 (M^+, base peak).

Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.28; H, 3.97; N, 12.25; Cl, 15.50. Found: C, 68.5; H, 4.1; N, 12.0; Cl, 15.4.

Reaction between 5-Chloro-7-methyl-2-phenyl-6-azaindolizine (2) and (a) Hydroxide ion, (b) Methoxide, and (c) Ammonia. (a) A suspension of 2 (20 mg) in aqueous $NaHCO_3$ was heated on a boiling water bath for 30 min, cooled, and extracted with $CHCl_3$. The extract was dried and evaporated and the residue was subjected to TLC with benzene and then with benzene/ethyl acetate (4:1). The fast-moving band gave unchanged 2 (12 mg, 60%). TLC indicated the crude hydrolysis product to contain only traces of the azaindolizinone 7.

A suspension of 2 (35 mg) in 2 M aqueous NaOH was heated on a boiling water bath for 6 h and the hydrolysis product was worked up as in the attempted hydrolysis using $NaHCO_3$. The fast-moving band gave unchanged 2 (15 mg, 43%). The slower-moving band gave (7), (3 mg, 9%).

(b) A suspension of 2 (40 mg, 0.16 mmol) in a methanolic solution of NaOMe obtained from MeOH (20 cm^3) and Na (0.3 g) was refluxed for 30 min. The MeOH was evaporated and the residue was dissolved

in water, dried, and evaporated and the residue obtained was subjected to TLC with benzene. Only one band developed; the material from this band was recrystallized from petroleum ether to give **5-methoxy-7-methyl-2-phenyl-6-azaindolizine (3)** (32 mg, 81%) as pale green needles: mp 87 °C; λ_{max} *253*, (276), (289), 322 nm (log ϵ 4.67, 4.02, 3.78, 3.46); IR 700, 758, 1570, 1630 cm^{-1}; NMR ($CDCl_3$) 2.30* (3 H, Me-7), 4.13 (3 H, OMe), 6.47 (H-1), 6.65* (H-8), 7.20–7.80 (m, 5 H, Ph), 7.55 (H-3).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.8; H, 5.8; N, 11.8.

Demethylation of **3** (10 mg) with hydrochloric acid gave **7** in quantitative yield.

(c) The 6-azaindolizine **2** (100 mg) was heated at 140 °C for 4 h in a sealed glass tube containing EtOH (10 cm^3) saturated with anhydrous NH_3 at 0 °C. After cooling the tube was opened and the solvent was evaporated. The residue was subjected to TLC with benzene/ethyl acetate (2:1) and gave one main band. The material from this band was recrystallized from benzene containing a small percentage of EtOH to give **5-amino-7-methyl-2-phenyl-6-azaindolizine (4)** (65 mg, 71%) as small white crystals which decomposed at temperatures greater than 215 °C: λ_{max} 257, 301, 331 (broad) nm (log ϵ 4.61, 3.82, 3.49; IR 699, 765, 1540, 1610, 1655, 3050, 3340, 3450 cm^{-1}; NMR [$(CD_3)_2SO$] 2.17* (3 H, Me), 6.50 (2 H, H-1 and H-8), 7.14 (2 H, broad, NH_2), 7.20–7.78 (m, 5 H, Ph), 7.89 (H-3); NMR ($CDCl_3$) 2.32 (3 H, Me), 6.52 (H-1), 6.65* (H-8), 7.12–7.74 (m, 5 H, Ph), 7.22 (H-3); mass spectrum *m/e* 223 (M^+, base peak).

Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.3; H, 5.9; N, 18.6.

Attempted Reaction between 7-Chloro-2-phenyl-8-azaindolizine (5) and (a) Hydroxide Ion, (b) Amide Ion, and (c) Ammonia. (a) A suspension of **5** (10 mg) in 2 M aqueous NaOH (5 cm^3) was heated on a boiling water bath for 6 h, cooled, and extracted with $CHCl_3$. The extract was dried and evaporated to give unchanged **5** in quantitative yield.

The same procedure was repeated with the suspension contained in a sealed tube at a reaction temperature of 130 °C. The crude product was subjected to TLC using benzene and benzene/ethanol (10:1); this gave only unchanged **5** (6.3 mg, 63%).

(b) The azaindolizine **5** (20 mg, 0.08 mmol) was added to a stirred suspension of $NaNH_2$ (100 mg, 2.6 mmol) in liquid NH_3 (10 cm^3) at −33 °C. The suspension gradually darkened and after 30 min the NH_3 was allowed to evaporate and the residue was treated with water and extracted with $CHCl_3$. The extract was evaporated to give a brown amorphous solid from which no crystalline material could be obtained.

(c) The azaindolizine **5** (30 mg) was heated at 140 °C and also at 200 °C for 4 h in a sealed glass tube containing EtOH (10 cm^3) which had been saturated with anhydrous NH_3 at 0 °C. In each case only unchanged **5** was recovered.

Reaction between 7-Chloro-2-phenyl-8-azaindolizine (5) and Methoxide Ion. The chloro-8-azaindolizine **5** (14 mg, 0.06 mmol) in MeOH (2 cm^3) was added to a solution of NaOMe, obtained from MeOH (4 cm^3) and Na (50 mg, 2.2 mmol), and refluxed for 2 h. The solvent was removed, water (25 cm^3) was added, and the mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to yield **6** (13 mg, 97%) as a yellow crystalline solid, mp 139–143 °C, with spectral characteristics identical with those previously reported.[3]

4,9-Dimethyl-1,6-diphenyldi(6-azaindolizino)[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (13). A solution of the chloro-6-azaindolizine **2** (5 mg) in $POCl_3$ (10 cm^3) was refluxed for 4 h. The excess $POCl_3$ was removed at 60 °C (10 mm) and ice (5 g) was added to the residue which was then basified with 2 M NaOH. Extraction with $CHCl_3$ and evaporation of the solvent gave **13** (3 mg, 70%) with identical mp and IR spectrum to that of the sample obtained from **7** with $POCl_3$.

Formylation of 4,9-Dimethyl-1,6-diphenyldi(6-azaindolizino)[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (13). Formylation[2] of **13** (20 mg) gave a product which was subjected to TLC with benzene/ethyl acetate (10:1). The material from the slow moving orange band was extracted to give **2,7-diformyl-4,9-dimethyl-1,6-diphenyldi(6-azaindolizino)[3,4,5-*af*:3′,4′,5′-*dc*]pyrazine (14)** (22 mg, 97%): mp >350 °C; λ_{max} (CH_2Cl_2) *274*, 370, (452), 467 nm (log ϵ 4.72, 4.12, 4.19, 4.28); IR 702, 830, 1200, 1500, 1545, 1608, 1645 cm^{-1}; NMR (CF_3COOH) 2.28* (6 H, Me-4 and Me-9), 7.58* (2 H, H-3 and H-8), 7.72 (10 H, Ph-1 and Ph-6), 9.72 (2 H, CHO-2 and CHO-7). Calcd mass for $C_{30}H_{20}N_4O_2$: 468.1586. Found M^+ (base beak): 468.1585.

6-Methyl-3-phenyl-1,7-diazacyclo[3.2.2]azine (16). Formylation[2] of the amino-6-azaindolizine **4** (50 mg) yielded a product which after TLC with petroleum ether/ethyl acetate (1:1) gave two bands. The material from the faster moving band gave unchanged **4** (6 mg). The material from the following yellow band on extraction and recrystallization from benzene/petroleum ether gave **16** (16 mg, 31%) as yellow needles: mp 155–157 °C; λ_{max} (238), *247*, 332, 404, 416 nm (log ϵ 4.34, 4.43, 4.30, 3.72, 3.69); IR 700, 778, 1133, 1540, 1595 cm^{-1}; NMR ($CDCl_3$) 3.00* (3 H, Me), 7.33–8.11 (m, 5 H, Ph), 7.40 (H-1), 7.65* (H-7), 8.83 (H-3). Calcd mass for $C_{15}H_{11}N_3$: 233.0952. Found M^+ (base peak): 233.0952.

An attempted formylation[2] of **16** (5 mg, 0.02 mmol) gave only unchanged starting material (3 mg).

Attempted Ring Opening of 6-Methyl-3-phenyl-1,7-diazacyclo[3.2.2]azine (16). A solution of **16** (5 mg) in MeOH (2 cm^3) containing concentrated hydrochloric acid (0.2 cm^3) was left at room temperature for 24 h. The solution was concentrated under reduced pressure, basified with 2 M aqueous sodium hydroxide, and extracted with ether. The extract gave unchanged **16** (5 mg).

3-Formyl-7-methyl-2-phenyl-6-azaindolizin-5(6*H*)-one (8). Formylation[2] of the azaindolizin-5(6*H*)-one **7** (100 mg) gave **8** (58 mg, 52%) as yellow crystals from $CHCl_3$: mp 258 °C dec; λ_{max} 225, *272*, (293), 365 nm (log ϵ 4.12, 4.28, 3.86, 4.19); IR 791, 838, 1360, 1638, 1690, 3110, 3250 cm^{-1}; NMR [$(CD_3)_2SO$] 2.22* (3 H, Me), 6.46* (H-8), 6.49 (H-1), 7.28–7.74 (m, 5 H, Ph), 10.82 (CHO); mass spectrum *m/e* 252 (M^+, base peak).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79. Found: C, 71.3; H, 4.9.

Formylation of 5-Chloro-7-methyl-2-phenyl-6-azaindolizine (2). Formylation[2] of **2** (58 mg) gave four products which were separated by TLC using benzene–ethyl acetate (3:1). The material from the fastest moving band gave **5-chloro-1-formyl-7-methyl-2-phenyl-6-azaindolizine (17)** (2 mg, 3%): mp 169.5–170 °C: λ_{max} (243), *249*, (276), 339 nm (log ϵ 4.27, 4.29, 3.71, 3.92); IR 700, 728, 1220, 1420, 1609, 1650 cm^{-1}; NMR ($CDCl_3$) 2.55* (3 H, Me), 7.47 (H-3), 7.50 (5 H, Ph), 8.10* (H-8), 10.04 (CHO). Calcd mass for $C_{15}H_{11}{}^{35}ClN_2O$: 270.0559. Found M^+ (79% base peak): 270.0555.

The next band gave a product which crystallized from benzene/petroleum ether to give **5-(*N*,*N*-dimethylamino)-1-formyl-7-methyl-2-phenyl-6-azaindolizine (18)** (4 mg, 6.0%) as needles: mp 208.5 °C; λ_{max} 240, 367 nm (log ϵ 4.54, 424);IR 757, 850, 1410, 1510, 1648 cm^{-1}; NMR ($CDCl_3$) 2.47* (3 H, Me-7), 3.07 (6 H, NMe_2), 7.22 (H-3), 7.32–7.64 (m, 5 H, Ph), 7.78* (H-8), 9.98 (CHO). Calcd mass for $C_{17}H_{17}N_3O$: 279.1371. Found M^+ (base peak): 279.1369.

The material from the next yellow band was extracted and recrystallized from benzene/petroleum ether to give **5-(*N*,*N*-dimethylamino)-3-formyl-7-methyl-2-phenyl-6-azaindolizine (19)** (17 mg, 25%) as yellow crystals: mp 178 °C; λ_{max} *246*, 272, 330 (broad), 407 nm (log ϵ 4.48, 4.16, 3.70, 4.05); IR 702, 795, 1170, 1352, 1530, 1610, 1645 cm^{-1}; NMR ($CDCl_3$) 2.38* (Me-7), 3.05 (6 H, NMe_2), 6.37 (H-1), 6.68* (H-8), 7.30–7.72 (m, 5 H, Ph), 9.80 (CHO). Calcd mass for $C_{17}H_{17}N_3O$: 279.1371. Found M^+ (35% base peak): 279.1369. The slowest moving band gave **8** (17 mg, 28%).

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Registry No.—**1**, 57139-15-8; **2**, 66653-02-9; **3**, 66653-03-0; **4**, 66653-04-1; **5**, 66653-05-2; **6**, 61900-73-0; **7**, 66653-06-3; **8**, 66653-07-4; **9**, 66653-08-5; **11**, 66653-09-6; **12**, 66653-10-9; **13**, 66653-11-0; **14**, 66653-12-1; **6**, 66653-13-2; **17**, 66653-14-3; **18**, 66653-15-4; **19**, 66653-16-5; 2-hydroxy-4,6-dimethylpyrimidine, 108-79-2; phenacyl bromide, 70-11-1; 2-hydroxy-4,6-dimethylpyrimidine hydrobromide, 66653-17-6; 4-hydroxy-2-methylpyrimidine, 19875-04-8.

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Use of (Thio)Acetal Esters as Reagents for the Protection of Alcohols. Synthesis of 2-Tetrahydrothienyl Ethers[1]

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Primary and secondary alcohols can be converted in high yields into their 2-tetrahydrothienyl (THT) ethers by an acid-catalyzed exchange reaction with 2-tetrahydrothienyl diphenylacetate. The characteristics of the THT group as a protecting group for alcohols are discussed. Conditions for quantitative removal under neutral conditions are described. This acetal exchange reaction also provides an excellent method for the preparation of other mixed acetals, in particular THP and THF ethers.

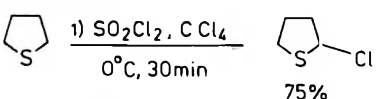
The protection of hydroxyl groups, often as mixed acetals, is an extensively used technique in the synthesis of polyfunctional compounds.[2] Recently, several new protecting groups have been introduced, which can be removed with a highly specific reagent.[3]

The methylthiomethyl (MTM) group has been recommended in this respect because of its stability toward both basic and mildly acidic conditions and its easy cleavage under neutral conditions with certain metal ions.[3b,4,5] In the acetal series, protecting groups with a cyclic structure, in particular 2-tetrahydropyranyl (THP) ethers, have been employed frequently. We have focused our attention on the synthesis of 2-tetrahydrothienyl (THT) ethers. Previously, two THT ethers have been prepared in moderate yield by reaction of alcohols with 2,3-dihydrothiophene,[5] but this procedure is not suitable for the introduction of a THT protecting group. In this study we describe an efficient method for the protection of primary and secondary alcohols with a THT group. This method appears to be also very suitable for the introduction of THP and THF groups. The possibility of selective cleavage of THT ethers in the presence of THF ethers and vice versa is discussed.

Results and Discussion

Synthesis of 2-Chlorotetrahydrothiophene (2-Cl-THT). In view of the favorable results obtained with the reaction of 2-chlorotetrahydrofuran with alcohols,[3d] our initial objective was to use 2-Cl-THT as a reagent for introducing the THT group. Various reports in the literature deal with the chlorination of THT.[6,7] 2-Cl-THT has not been isolated in a pure state because of its lack of stability.[6b]

Conversion of THT into 2-Cl-THT could be accomplished in apolar solvents [*N*-chlorosuccinimide in benzene at 25 °C (50% conversion)[6b] or chlorine in carbon tetrachloride at 40 °C (80% conversion)[6c]]. By contrast, sulfuryl chloride in refluxing pentane was reported to cause extensive polymerization.[6a] Because of the successful application of sulfuryl chloride to the chlorination of tetrahydrofuran[3d] and 1,3-dithiane,[8] we have reexamined its reaction with THT. It appeared that THT could be converted into 2-Cl-THT in 75% yield by a simple and fast procedure.[9]



Polymerization was effectively retarded by addition of triethylamine. In more polar solvents, mixtures of 2-Cl-THT and 2,3-diCl-THT were formed and the yield of chlorinated products decreased (see Table I). The reaction exhibits the same characteristics as the reaction with chlorine which was studied by Wilson and Albert.[7]

It is generally accepted[10] that upon reaction of sulfides with chlorinating agents, sulfonium salts are formed in the first step. In general, two structures are possible.[11] To our knowledge no spectroscopic data are available on sulfonium salts formed with chlorine or sulfuryl chloride.[12] Upon addition of sulfuryl chloride to a solution of THT in $CDCl_3$, the signals of the original NMR spectrum shifted downfield appreciably (α protons, 1.4 ppm; β protons, 0.8 ppm).[13] Interestingly, exactly the same spectrum was obtained when *thionyl chloride* (1.0 equiv) was added at −65 °C to a $CDCl_3$ solution of *THT sulfoxide*.[10e] When $CDCl_3$ solutions of THT and chlorine (1.0 equiv each) were mixed at −75 °C, the NMR spectrum revealed the presence of both THT and the chlorosulfonium chloride **2** (δ 4.2 and 2.7) in about equal quantities. Comparison with data obtained for the 1:1 adduct of THT and bromine (**2a**) (α and β protons shifted 0.8 and 0.3 ppm)[12] leads to the conclusion that the charge separation in the adduct with chlorine is more pronounced, and therefore structure **2** seems most likely. Also, these data indicate that chlorosulfonium salts **1** and **2** have the same cation since their spectra are identical and a different anion. Only **2** is in equilibrium with its components because of the better nucleophilicity of chloride ion.

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Table I. Product Composition from Reactions of THT with Sulfuryl Chloride in Various Solvents[a]

Molar ratio THT/SO_2Cl_2	Solvent	Molar ratio 2-Cl-THT/ 2,3-diCl-THT	Yield (%) of methoxylated derivatives
5:1	CH_2Cl_2	3:2	35
5:1	THF	9:1	35
5:1	Benzene	20:1	60
1:1	Benzene	20:1	35
1:1	CCl_4	20:1	75

[a] See Experimental Section.

Table II. Protection of Primary and Secondary Alcohols as THT Ethers via THT Diphenylacetate

Substrate	Method[a]	Yield, %	δ (2′-H)	$n^{23}D$
1-Hexanol	a	99	5.19	1.4728
2-Phenylethanol	a	95	5.18	1.5496
Benzyl alcohol	a	98	5.21	1.5582
Geraniol	a	99	5.22	1.5123
2-Pentanol	b	85	5.36	1.4711
Cyclohexanol	b	90	5.39	1.5104

[a] Method a: room temperature, 5 h. Method b: 40–50 °C, 16 h.

Reaction of 2-Cl-THT with Alcohols. A solution of 2-Cl-THT in carbon tetrachloride, prepared as depicted above, reacted only sluggishly with alcohols. The best conversions were obtained by reaction with 2 equiv of the THT–sulfuryl chloride reaction mixture in carbon tetrachloride–acetonitrile (1:1) at 25 °C in the presence of triethylamine.[14] However, use of 2-Cl-THT has no advantage over dihydrothiophene.[5] Both suffer from (i) a lack of quantitative conversion of the alcohol and (ii) contamination of the crude product with 4-(2-tetrahydrothienyl)-2,3-dihydrothiophene (**3**), which could only be removed by extensive chromatography (Scheme I). A possible explanation for this deviation from the results obtained with 2-Cl-THF, which reacts rapidly with alcohols at room temperature,[3d] becomes clear by inspection of Scheme I.

Compared with the THF series,[15] the equilibrium between **4** and **5** is shifted toward **4** and the side reaction leading to 2,3-dihydrothiophene and subsequently to **3** becomes important.

Synthesis of THT Ethers by Reaction with THT Diphenylacetate. An excellent preparation of THT ethers could be realized by a (thio)acetal exchange reaction. The reagent

Scheme I

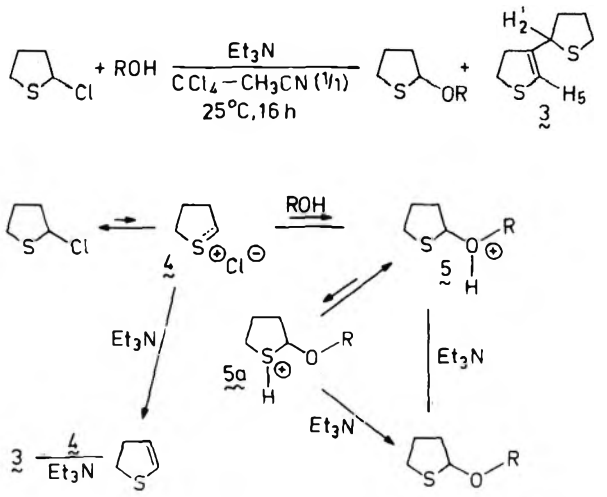
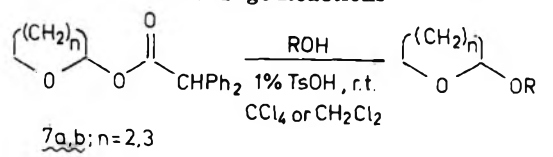


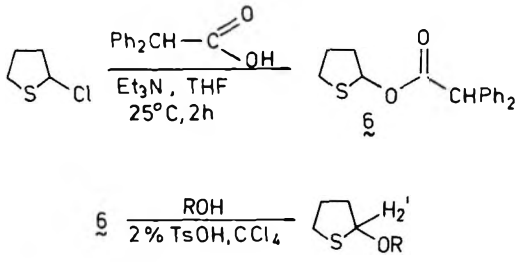
Table III. Synthesis of THF and THP Ethers by Acetal Exchange Reactions



Substrate	Yield (%) of THF ether (n = 2)[a]	Yield (%) of THP ether (n = 3)[b]
1-Hexanol	99	96
2-Phenylethanol	99	94
2-Pentanol	90	85, 96[a]
Cyclohexanol	91	90, 96[a]

[a] CCl_4, 30 min. [b] CH_2Cl_2, 5 min.

2-tetrahydrothienyl diphenylacetate (**6**) is a stable crystalline solid, easily obtainable in 60–65% yield by reaction of diphenylacetic acid with 2-Cl-THT. The procedure for the reaction of (thio)acetal ester **6** with primary alcohols is ex-



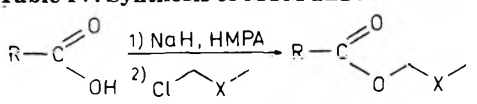
ceedingly simple. Stirring in carbon tetrachloride with a catalytic amount of *p*-toluenesulfonic acid at room temperature for 5 h results in quantitative precipitation of diphenylacetic acid. After addition of some sodium carbonate, the mixture is filtered and concentrated, affording THT ethers of better than 95% purity in the yields indicated in Table II. Optimum yields for THT ethers of secondary alcohols were obtained by reaction at 40–50 °C for 16 h.

By contrast, reaction of **6** with tertiary alcohols and phenols produced mixtures of the expected THT ethers and dimer **3**. This was also observed when the reactions with primary alcohols were conducted in the presence of more than 5% of *p*-toluenesulfonic acid or when more polar solvents were employed.[16] Protection of a primary alcohol in the presence of a tertiary alcohol proceeds with better than 90% selectivity. Comparing tertiary with primary alcohols, the concentration of thiacarbenium ion intermediate **4** will be increased, both because of the lower reaction rate of **4** with tertiary alcohols and because of the faster protonation of THT ethers from tertiary alcohols to give **5**.[17] The use of more polar solvents will also lead to a higher concentration of **4**.[18] As a consequence, the irreversible formation of dimer **3** is favored.

Introduction of Other Protecting Groups by (Thio)-Acetal Exchange Reactions. The appropriate reagents for the protection of alcohols as THF and THP ethers (**7a,b**; see Table III) could be synthesized conveniently by reaction of diphenylacetic acid with 2-Cl-THT and 2,3-dihydropyran in yields of 82 and 64%, respectively. The acid-catalyzed reaction of alcohols with these acetal esters proceeded even faster than with (thio)acetal ester **6**. Applying the same conditions (carbon tetrachloride, 2% *p*-toluenesulfonic acid, and room temperature), quantitative formation of 1-hexanol THF and THT ethers required 10 min and 5 h, respectively.

Thus, by using reagents **7a,b** nearly quantitative conversion of primary and secondary alcohols into THF and THP ethers under mild conditions (carbon tetrachloride, 1% *p*-toluene-

Table IV. Synthesis of MTM and MM Esters



	R	X	Yield, %[a]	Mp, °C
8a	Ph_2CH	S	90	31–32
8b	4-NO_2Ph	S	95	55–56
8c	2,4-diNO_2Ph	S	99	25
8d	4-NO_2Ph	O	90	74–75
8e	2,4-diNO_2Ph	O	85	60–61.5

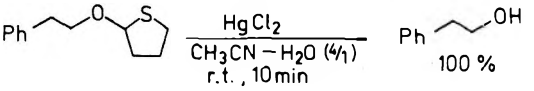
[a] Yields are based on products of better than 95% purity (NMR).

sulfonic acid, and room temperature for 30 min) could be achieved.[19] In more polar solvents, these reactions were still faster but an equilibrium resulted which contained 5–15% of the alcohol. The results are summarized in Table III.

THF- and THP-protected tertiary alcohols were only formed in moderate yields (40 and 75%, respectively) due to their sensitivity to acid. In view of the pronounced advantages of these acetal exchange reactions, we recommend compounds **7a,b** as standard reagents for the protection of alcohols with THF and THP groups.[19]

The suitability of (thio)acetal esters for the introduction of MTM and methoxymethyl (MM) groups was also studied (Table IV).[20] The requisite esters could be synthesized in excellent yields using the conditions described for the formation of phenolic MTM ethers.[21,22] It appeared that the transfer of MTM groups from methylthiomethyl diphenylacetate (**8a**) to 1-hexanol required rather drastic conditions (carbon tetrachloride, 5% *p*-toluenesulfonic acid, and reflux for 2 h). Under these conditions the MTM ether engaged in a disproportionation reaction to form acetal **10** and (dithio)acetal **11a**.[23a] Attempts to circumvent this problem by using (thio)acetal esters **8b–e**, containing better leaving groups, were not successful (see Table V). The MM ether of 1-hexanol was formed in reasonable yields by reaction with **8d,e**, but the formation of disproportionation products **10** and **11b** could not be retarded satisfactorily (see Table V).[23b] It can be concluded that the (thio)acetal exchange reaction is only successful for the protection of alcohols when an appreciable difference in acid sensitivity exists between the (thio)acetal ester and the corresponding ether.

Cleavage of the THT Ethers. The THT group can be removed by a fast reaction under mild conditions. When 2-phenylethanol THT ether was treated with mercuric chloride (1.5 equiv) in acetonitrile–water (4:1; 10 mL per mmol) at 25 °C for 10 min, 2-phenylethanol could be isolated quantitatively. Using standard conditions,[3b] the THT group was removed appreciably faster than the MTM group (see Experimental Section), clearly indicating the possibility of selective removal. Likewise, THT ethers are more sensitive toward acid-catalyzed hydrolysis than MTM ethers, which are fairly resistant to the conditions employed for the removal of THP groups.[3b] In acetic acid–water–THF (3:1:1) at 25 °C, the THT group was 90% cleaved in 3h, a rate comparable to that of the THP group but appreciably slower than that of the THF group.



Also, conditions were elaborated for the selective cleavage of THT ethers in the presence of the highly acid-sensitive THF ethers.[24] These consisted of treatment with (i) mercuric chloride (1.5 equiv) buffered with calcium carbonate (3.0 equiv) in acetonitrile–water (4:1) at 25 °C for 10 min (MTM ethers are unaffected under these conditions[3b]) or with (ii) silver nitrate (2.0 equiv) buffered with 2,6-lutidine (2.0 equiv) in THF–water (4:1) at 25 °C for 90 min. THP, MEM, and $TBMe_2Si$ groups are also unaffected under these conditions. Conversely, THF and THP groups could be removed selectively in the presence of a THT group by reaction with methanol at reflux temperature during 1 h.[3d] Under these conditions, THT ethers are unaffected, while cleavage is rapid in the presence of 5% *p*-toluenesulfonic acid. These results are schematically represented in Table VI.

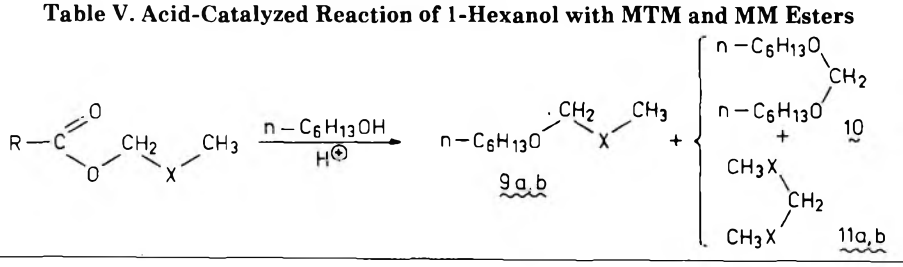
Further work concerning the reactions of 2-Cl-THT and acetal ester **6** with nucleophiles is in progress.

Experimental Section

General. All melting points are uncorrected. IR spectra were recorded on a Unicam SP-100 spectrophotometer. NMR spectra (δ expressed in parts per million) were taken on a Jeol PS-100 instrument. Elemental analyses of the crystalline products were performed by Mr. W. J. Buys, TNO Laboratory of Organic Chemistry, Utrecht, Neth. For analytical and preparative GC analyses, a 2 m, 3% SE-30 on Chromosorb W (80–100 mesh) column and a 6 m, 20% SE-30 on Chromosorb W (60–80 mesh) column were employed, respectively. Column chromatography was performed with silica gel (MN, 70–270 mesh).

Materials. Commercial tetrahydrothiophene (Aldrich) was distilled and stored over calcium chloride. Solvents were purified and dried according to standard procedures. Sulfuryl chloride was distilled in a nitrogen atmosphere before use. Commercial chloromethyl methyl ether was freshly distilled from sodium carbonate. Chloromethyl methyl sulfide[24] and tetrahydrothiophene sulfoxide[25] were prepared

Table V. Acid-Catalyzed Reaction of 1-Hexanol with MTM and MM Esters



(Thio)acetal ester No.	R	X	Conditions for 95% conversion of 1-hexanol	Product distribution[a]
8a	Ph_2CH	S	CCl_4–5% TsOH; reflux (2 h)	**9a** (30%); **10** + **11a** (70%)
8b	4-NO_2Ph	S	Benzene–5% MsOH; 45 °C (6 h)	**9a** (50%); **10** + **11a** (50%)
8c	2,4-diNO_2Ph	S	Benzene–10% MsOH; 20 °C (7 h)	**9a** (25%); **10** + **11a** (75%)
8d	4-NO_2Ph	O	Ether–10% MsOH; 20 °C (16 h)	**9b** (80%); **10** + **11b** (20%)
8e	2,4-diNO_2Ph	O	Benzene–5% MsOH; 20 °C (1.5 h)	**9b** (75%); **10** + **11b** (25%)

[a] GC analysis.

Table VI. Removal of Some (Thio)Acetal Protecting Groups by Selected Reagents

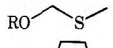
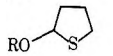
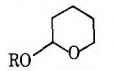
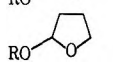
Protecting group	$HgCl_2$	$HgCl_2$–$CaCO_3$	AcOH–H_2O–THF	MeOH
	+	–	–	–
	++	+	+	–
	–	–	+	+
	–	–	++	++

Table VII. Product Composition from Reactions of THT with Sulfuryl Chloride in Chloroform

Volume % THT	Molar ratio THT/SO_2Cl_2	Molar ratio 2-Cl-THT/ 2,3-diCl-THT
7	1:1	3:5
15	2:1	1:1
35	5:1	2:1
20	5:1	3:1
40	10:1	2:1

by known procedures. All reagents were used as high grade commercial products.

2-Chlorotetrahydrothiophene (2-Cl-THT). A solution of sulfuryl chloride (6.75 g, 50 mmol) in carbon tetrachloride (25 mL) was added dropwise with efficient stirring to a chilled solution of THT (4.4 g, 50 mmol) in carbon tetrachloride (100 mL) in an atmosphere of dry nitrogen. A fluffy white precipitate was formed. The ice bath was removed after stirring at 0 °C for 30 min. Upon warming to room temperature, the precipitate dissolved and evolution of hydrogen chloride was observed. Triethylamine (4.0 g, 40 mmol) was added over a 2-min period, and a white precipitate formed. Stirring was continued at room temperature for 30 min. The resulting reaction mixture was cooled to −16 °C to attain complete precipitation of triethylammonium chloride, which was removed by filtration in a nitrogen atmosphere. A slightly yellow colored solution of 2-Cl-THT was obtained which was used directly for subsequent reactions either as such or after evaporation of the solvent to a volume of ca. 25 mL.

Chlorination of THT with Sulfuryl Chloride in Various Solvents (Table I). The chlorinations were carried out under nitrogen by addition of sulfuryl chloride (10 mmol) to well-stirred solutions of THT (30 mL of solvent) at 0 °C. Triethylamine (10 mmol) was added and stirring was continued at 0 °C for 30 min and at room temperature for 1 h. Relative amounts of 2-Cl-THT and 2,3-diCl-THT were determined by NMR spectroscopy after filtration and evaporation of the solvent [($CDCl_3$) 2-H at δ 5.77 (m) and 5.63 (s), respectively]. The yield of chlorinated products was determined by reaction with methanol (20 mmol) in the presence of pyridine (10 mmol), as described by Wilson and Albert.[6c,7] In polar solvents like chloroform, the molar ratio of 2-Cl-THT and 2,3-diCl-THT was dependent upon both the concentration of THT and the molar ratio of the reactants (see Table VII).[7]

Reactions of 2-Cl-THT with Alcohols (Scheme I). To a stirred solution of the alcohol (10 mmol) and triethylamine (15 mmol) in acetonitrile (40 mL) was added at room temperature in two portions a solution of 2-Cl-THT (2 equiv based on THT) in carbon tetrachloride (40 mL). Stirring at room temperature was continued for 16 h. The precipitate was filtered off, and ether was added to the filtrate. The resulting solution was washed with water and brine and dried ($MgSO_4$). After evaporation of the volatile components, the crude product was purified by column chromatography (20 g; 3:1 benzene–hexane). The pure THT ethers were obtained in yields of 60 and 55% for 1-hexanol and cyclohexanol, respectively. In another experiment, a partially evaporated solution of 2-Cl-THT (5 equiv) in carbon tetrachloride (20 mL) was mixed with acetonitrile (50 mL), and the resulting solution was added dropwise to a stirred solution of 1-hexanol (10 mmol) and triethylamine (15 mmol) in acetonitrile (50 mL). After stirring for 16 h and workup as described above, a mixture was obtained of about equal amounts of 1-hexanol THT ether (60% yield) and dimer **3** [NMR ($CDCl_3$) δ 5.9 (s, 1 H, 5-H) and 4.1 (t, 1 H, 2′-H)].

2-Tetrahydrothienyl Diphenylacetate (6). A solution of 2-Cl-THT in carbon tetrachloride (from a 0.1-mol scale chlorination) was concentrated to a volume of ca. 30 mL and diluted with THF (50 mL). This mixture was added to a stirred solution of diphenylacetic acid (10.6 g, 0.05 mol) and triethylamine (10.1 g, 0.10 mol) in THF (100 mL). Precipitation of triethylammonium chloride started almost immediately. The suspension was stirred at room temperature for 2 h. The reaction mixture was kept at −16 °C for 1 h, filtered, diluted with ether (150 mL), and washed with sodium carbonate solution, water, and brine. After drying with a mixture of $MgSO_4$ and MgO (to remove the last traces of triethylammonium chloride) and evaporation of the solvents, an oil was obtained which was dissolved in a minimal amount of dry ether (ca. 20 mL). Upon cooling to −16 °C, **6** crystallized as white needles which were collected by filtration, yield 60–65% (9–10 g). An analytical sample was obtained by crystallization from benzene–hexane: mp 82–83 °C; IR 3050 and 2950 (C–H), 1730 (C–O), 1180, 1145, and 1110 (C–O), and 750 and 700 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.24 (s, 10 H, phenyl), 6.20 (m, 1 H, 2-H), 4.97 (s, 1 H, Ph_2C–H), and two broad multiplets at δ 2.6–2.9 (2 H, 5-H) and 1.7–2.2 (4 H, 3- and 4-H).

Anal. Calcd for $C_{18}H_{18}O_2S$: C, 72.46; H, 6.08; S, 10.72. Found: C, 72.41; H, 6.11; S, 10.89.

General Procedure for the Protection of Alcohols with a THT Group (Table II). For primary alcohols, a solution of the alcohol (5 mmol), (thio)acetal ester **6** (5 mmol, 1.5 g), and *p*-toluenesulfonic acid (0.02 equiv, 19 mg) in carbon tetrachloride (25 mL) was stirred for a minimum of 5 h at room temperature. For secondary alcohols, 1.3 equiv of **6** was employed and the reaction temperature was maintained at 40–50 °C for 16 h. In both cases diphenylacetic acid separated quantitatively. Sodium carbonate (1.0 g) was added, and stirring was continued for 30 min. The reaction mixture was filtered and the solvent evaporated. The residue was treated with hexane (10 mL), and the THT ether could be isolated after filtration and evaporation. Alternatively, aqueous workup was possible by filtering, diluting with ether, washing with sodium carbonate solution and brine, drying ($MgSO_4$), and evaporating the solvents. The yields are given in Table II. THT ethers isolated in this way were of better than 95% purity. The last traces of impurities could be removed by chromatography. The THT ethers are colorless oils which are stable for months when stored at −16 °C with some MgO. Distillation is only convenient with the lower boiling compounds because THT ethers slowly decompose when heated above 100 °C. Also, GC analyses of solutions of THT ethers (temperatures up to 170 °C) could be performed, but purification by preparative GC was not successful. IR spectra of all THT ethers exhibited an absorption at ca. 710 cm^{-1} with medium intensity. In the NMR spectra the signal for the 2′-H is characteristic. It was found at δ 5.2 for protected primary alcohols and at δ 5.35–5.4 for secondary alcohols. Two broad multiplets are found at δ 2.7–2.9 (5′-H) and δ 1.8–2.2 (3′- and 4′-H).

1-Hexanol THT Ether: bp 52 °C (0.025 mm); $n^{23}D$ 1.4728; IR 2980 and 2900 (C–H), 1075 (C–O), and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.19 (m, 1 H, 2′-H, ΣJ = 6 Hz), 3.56 and 3.22 (t of AB, 2 H, 1-H, J_{AB} = 9 Hz and $J_{1\text{-}H,2\text{-}H}$ = 6.5 Hz), 1.5 (m, 2 H, 2-H), 1.25 (m, 6 H, CH_2), and 0.86 (t, 3 H, CH_3).

2-Phenylethanol THT Ether: $n^{23}D$ 1.5496; IR 3080, 2980, and 2900 (C–H), 1075 (C–O), 750 and 695 (phenyl), and 710 cm^{-1}; NMR ($CDCl_3$) δ 7.16 (s, 5 H, phenyl), 5.18 (m, 1 H, 2′-H, ΣJ = 6 Hz), 3.80 and 3.40 (t of AB, 2 H, 1-H, J_{AB} = 9 Hz and $J_{1\text{-}H,2\text{-}H}$ = 7 Hz), and 2.82 (t, 2 H, 2-H, J = 7 Hz).

Benzyl Alcohol THT Ether: $n^{23}D$ 1.5582; IR 3100, 2980, and 2900 (C–H), 1055 (C–O), 740 and 690 (phenyl), and 710 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 5 H, phenyl), 5.21 (m, 1 H, 2′-H, ΣJ = 6 Hz), and 4.63 and 4.26 (AB, 2 H, 1-H, J_{AB} = 11.5 Hz).

Geraniol THT Ether: $n^{23}D$ 1.5123; IR 2950 and 2900 (C–H), 1660 (C=C), 1050 (C–O), and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.30 and 5.08 (m, 2 H, =CH), 5.22 (m, 1 H, 2′-H, ΣJ = 6 Hz), 4.08 and 3.85 (d of AB, 2 H, 1-H, J_{AB} = 11.5 Hz and $J_{1\text{-}H,2\text{-}H}$ = 7 Hz), 2.02 (m, 4 H, CH_2), 1.63 (s, 6 H, CH_3), and 1.57 (s, 3 H, CH_3).

Pentanol-2 THT Ether: bp 39 °C (0.025 mm); $n^{23}D$ 1.4711; IR 2980 and 2900 (C–H), 1050 (C–O), and 710 cm^{-1}; NMR ($CDCl_3$) δ 5.36 (m, 1 H, 2′-H), 3.57 (p, 1 H, 1-H, J = 6 Hz), 1.3–1.4 (m, 4 H, CH_2), 1.13 and 1.06 (d, 3 H, CH_3, J = 6 Hz), and 0.88 (m, 3 H, CH_3).

Cyclohexanol THT Ether: bp 70 °C (0.015 mm); $n^{23}D$ 1.5104; IR 2980 and 2920 (C–H), 1065 (C–O), and 715 cm^{-1}; NMR ($CDCl_3$) δ 5.39 (m, 1 H, 2′-H, ΣJ = 6 Hz), 3.4 (m, 1 H, 1-H), and 1.2–1.8 (m, 10 H, CH_2).

2-Tetrahydrofuranyl Diphenylacetate (7a). This compound was obtained by reaction of diphenylacetic acid and triethylamine with 2-Cl-THF in 82% yield as described in ref 1.

2-Tetrahydropyranyl Diphenylacetate (7b). A solution of diphenylacetic acid (20 mmol, 4.24 g) and 2,3-dihydropyran (18 mmol,

1.50 g) in benzene (25 mL) was refluxed for 16 h. The reaction mixture was washed twice with sodium carbonate solution and with brine. Acetal ester **7b** was isolated after drying ($MgSO_4$), evaporation, and crystallization of the oily residue from hexane as white crystals: 3.4 g (64%); mp 59–60 °C; IR 3050, 2950, and 2900 (C–H), 1740 (C=O), 1200, 1160, 1110, and 1025 (C–O), and 745 and 695 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.24 (s, 10 H, phenyl), 6.06 (m, 1 H, 2-H), 5.04 (s, 1 H, Ph_2C–H), 3.55 (m, 2 H, 6-H), and 1.3–1.7 (m, 6 H, 3-, 4-, and 5-H).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.82; H, 6.93.

General Procedure for the Protection of Alcohols with THF and THP Groups (Table III). To a stirred solution of the alcohol (2 mmol) and *p*-toluenesulfonic acid (0.01 equiv, 4 mg) in carbon tetrachloride (10 mL) was added acetal ester **7** (primary alcohols, 2.1 mmol, and secondary alcohols, 2.2 mmol). Within 5 min precipitation of diphenylacetic acid started. Stirring was continued at room temperature for 30 min, and the reaction mixture was then diluted and washed twice with sodium carbonate solution and with brine. After drying ($MgSO_4$) and evaporation, THF and THP ethers were obtained as products of better than 95% purity. Spectra (GC, IR, and NMR) and refractive indexes were identical with those of products synthesized by literature procedures.[3d,20]

General Procedure for the Preparation of MTM and MM Esters (8a–e) (Table IV). Under an atmosphere of dry nitrogen, sodium hydride (55% dispersion in oil; 2.32 g, 55 mmol) was washed twice with dry pentane (10 mL) and HMPA (5 mL) was added. To this stirred suspension was added dropwise, while cooling with a water bath, a solution of the acid (50 mmol) in HMPA (50 mL). When the addition was completed (ca. 30 min) and hydrogen evolution had ceased, the water bath was removed and the clear solution was stirred for another 30 min. Addition of chloromethyl methyl (thio)ether in one portion caused a slightly exothermic reaction. After stirring for 3 h at room temperature, the mixture was poured into a saturated sodium hydrogen carbonate solution (250 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL) and brine. After drying ($MgSO_4$) and evaporation of the solvent, (thio)acetal esters **8a–e** were isolated in the yields indicated in Table IV. Compounds **8a,c,e** crystallized only with difficulty.

Methylthiomethyl Diphenylacetate (8a): white (hexane); mp 31–32 °C; IR 3150 and 2920 (C–H), 1730 (C=O), 1120 (C–O), 960 (S–C–O), and 740 and 690 (phenyl) cm^{-1}; NMR ($CDCl_3$) δ 7.25 (s, 10 H, phenyl), 5.07 (s, 2 H, S–CH_2–O), 5.02 (s, 1 H, Ph_2C–H), and 1.95 (s, 3 H, CH_3).

Methylthiomethyl 4-Nitrobenzoate (8b): white needles (1:1 ether–pentane); mp 55–56 °C; IR 3080 and 2900 (C–H), 1720 (C=O), 1520 and 1330 (NO_2), and 1240 and 1080 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.28 (s, 4 H, phenyl), 5.44 (s, 2 H, S–CH_2–O), and 2.31 (s, 3 H, CH_3).

Anal. Calcd for $C_9H_9NO_4S$: C, 47.58; H, 3.99; N, 6.17; S, 14.09. Found: C, 47.70; H, 4.12; N, 6.15; S, 14.12.

Methylthiomethyl 2,4-Dinitrobenzoate (8c): solidifies slowly at −16 °C; mp 25 °C; IR 3080 and 2900 (C–H), 1740 (C=O), 1530 and 1330 (NO_2), and 1250 and 1080 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.76 (d, 1 H, 3-H, J = 2.0 Hz), 8.57 (d of d, 1 H, 5-H, J = 2.0 and 8.0 Hz), 8.01 (d, 1 H, 6-H, J = 8.0 Hz), 5.42 (s, 2 H, S–CH_2–O), and 2.30 (s, 3 H, CH_3).

Methoxymethyl 4-Nitrobenzoate (8d): white needles (1:5 benzene–hexane); mp 74–75 °C; IR 3080 and 2940 (C–H), 1720 (C=O), 1520 and 1340 (NO_2), and 1280, 1160, and 1080 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.26 (s, 4 H, phenyl), 5.54 (s, 2 H, O–CH_2–O), and 3.58 (s, 3 H, CH_3).

Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.22; H, 4.27; N, 6.64.

Methoxymethyl 2,4-Dinitrobenzoate (8e): pale yellow (1:1 benzene–hexane); mp 60–61.5 °C; IR 3080 and 2940 (C–H), 1740 (C=O), 1530 and 1330 (NO_2), and 1270, 1167, and 1040 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 8.79 (d, 1 H, 3-H, J = 2.0 Hz), 8.59 (d of d, 1 H, 5-H, J = 2.0 and 8.0 Hz), 8.02 (d, 1 H, 6-H, J = 8.0 Hz), 5.51 (s, 2 H, O–CH_2–O), and 3.57 (s, 3 H, CH_3).

Reactions of 8a–e with 1-Hexanol (Table V). Applying the conditions depicted in Table V, reactions were carried out with equimolar amounts of 1-hexanol and esters **8a–e** (ca. 30 mL of solvent per 10 mmol). The disappearance of **8a–e** and the conversion of 1-hexanol were followed by TLC and GC (120 °C), respectively. Esters **8b–e** were insoluble in carbon tetrachloride. In general, the best conversions were obtained with methanesulfonic acid as a catalyst. The reactions were worked up following the precedure described above for THT, THF, and THP ethers. Products **9a,b**, **10**, and **11a** were isolated as pure compounds by preparative GC (190 °C).

1-Hexanol MTM Ether (9a): n^{22}_D 1.4524; IR 2940 and 2880 (C–H), 1070 (C–O), 725, and 675 cm^{-1}; NMR ($CDCl_3$) δ 4.56 (s, 2 H, O–CH_2–S), 3.48 (t, 2 H, O–CH_2, J = 6.5 Hz), 2.04 (s, 3 H, S–CH_3), 1.55 and 1.25 (m, 8 H, CH_2), and 0.87 (t, 3 H, CH_3).

1-Hexanol MM Ether (9b): n^{20}_D 1.4043 (lit.[26] n^{20}_D 1.4045); IR 2960 and 2900 (C–H), and 1140, 1100, and 1040 (O–C–O) cm^{-1}; NMR ($CDCl_3$) δ 4.58 (s, 2 H, O–CH_2–O), 3.50 (t, 2 H, O–CH_2, J = 6.5 Hz), 3.30 (s, 3 H, OCH_3), 1.55 and 1.25 (m, 8 H, CH_2), and 0.89 (t, 3 H, CH_3).

Di-1-hexyloxymethane (10): n^{22}_D 1.4264; IR 2940 and 2880 (C–H), and 1100, 1060, and 1030 (O–C–O) cm^{-1}; NMR ($CDCl_3$) δ 4.59 (s, 2 H, O–CH_2–O). 3.46 (t, 4 H, O–CH_2, J = 6.5 Hz), 1.55 and 1.25 (m, 16 H, CH_2), and 0.88 (t, 6 H, CH_3).

Dimethylthiomethane (11a): NMR ($CDCl_3$) δ 3.56 (s, 2 H, CH_2) and 2.07 (s, 6 H, CH_3) [lit.[27] (CCl_4) δ 3.45 and 2.05].

Cleavage of THT Ethers. General. Mercuric chloride (812 mg, 3 mmol) was added to a stirred solution of 2-phenylethanol THT ether (416 mg, 2 mmol) in a mixture of acetonitrile and water (4:1; 20 mL). After 10 min the reaction mixture was filtered through Celite, which was eluted with ether (2 × 10 mL). The resulting mixture was washed with a 10% ammonium acetate solution, water, and brine and dried with magnesium sulfate. Evaporation of the solvents gave a colorless oil, 248 mg (100%), with spectra identical with an analytical sample of 2-phenylethanol.

Selectivity. The experiments concerning selective cleavage of the THT group were carried out with 1-hexanol THT ether (1 mmol per 25 mL of solvent). The reactions were followed by GC (150 °C) with naphthalene as an internal standard. Disappearance of the THT ether occurred simultaneously with the formation of 1-hexanol; other products were not detected.

Standard conditions for the cleavage of MTM ethers are the following:[3b] (i) mercuric chloride (1.5 equiv) in acetonitrile–water (4:1) at 25 °C for 4 h (THT ether: 0 °C, 5 min) and (ii) silver nitrate (5 equiv) and 2,6-lutidine (3 equiv) in THF–water (4:1) at 25 °C for 45 min (THT ether: 5 min). However, by employing methyl iodide (3 equiv) and sodium hydrogen carbonate (3 equiv) in moist acetone at 25 °C,[3b] the THT ether hydrolyzed at a comparable rate (90% conversion in 6 days).

Registry No.—**3**, 13042-82-5; **7b**, 66675-13-6; **8a**, 31280-16-7; **8b**, 5388-04-5; **8c**, 66675-02-3; **8d**, 66675-03-4; **8e**, 66675-04-5; **9a**, 66675-05-6; **9b**, 66675-06-7; **10**, 54815-12-2; **11a**, 1618-26-4; THT, 110-01-0; sulfuryl chloride, 7791-25-5; 2-Cl-THT, 22432-03-6; THT diphenylacetate, 66675-01-2; 1-hexanol, 111-27-0; 2-phenylethanol, 60-12-8; benzyl alcohol, 100-51-6; geraniol, 106-24-1; 2-pentanol, 6032-29-7; cyclohexanol, 108-93-0; 1-hexanol THT ether, 66675-07-8; 2-phenylethanol THT ether, 66675-08-9; benzylalcohol THT ether, 66675-09-0; geraniol THT ether, 66675-10-3; 2-pentanol THT ether, 66675-11-4; cyclohexanol THT ether, 66675-12-5; 2,3-dihydropyran, 110-87-2.

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(11) In the case of *N*-chlorosuccinimide, arguments for both structures have been put forward; see ref 10d and E. Vilsmaier and W. Sprügel, *Justus Liebigs Ann. Chem.*, **747**, 151 (1971).
(12) On the other hand, the structure of the relatively stable 1:1 adduct of THT and bromine has been studied by NMR spectroscopy and X-ray diffraction: G. Allegra, G. E. Wilson, Jr., C. Pedone, E. Benedeth, and R. Albert, *J. Am. Chem. Soc.*, **92**, 4002 (1970).
(13) When a similar experiment was done with THF and sulfuryl chloride, no change in the spectrum was observed. The enhanced reactivity of THT toward sulfuryl chloride s also apparent from Table I, where THF is used as a solvent for the chlorination of THT.
(14) Yields were not improved by the addition of 2 equiv of sodium iodide or by reaction at 50 °C.
(15) For a discussion of the mechanism of the reaction of 2-Cl-THF with alcohols, see ref 3d.
(16) Some data for 1-hexanol: in acetonitrile the product contains 35% of dimer **3**, and the yield of THT ether is 35%; in benzene these values are 5 and 75%, respectively; and in carbon tetrachloride no dimer is detectable with GC and NMR spectroscopy.
(17) A discussion of the relative reaction rates of tertiary and primary alcohols with 2-Cl-THF can be found in ref 3d.
(18) Thiacarbenium ion **4** is also an intermediate in the chlorination of THT (ref 7). In apolar solvents it reacts immediately with chloride ion, but in polar solvents this reaction is reversible and the formation of 2,3-dihydrothiophene, which reacts with chloride to form 2,3-dichloro-THT, is favored.
(19) The introduction of THP groups with 2,3-dihydropyran, which is a standard technique, requires considerably less subtile conditions; see, for instance, ref 2, p 105.
(20) Chloromethyl methyl ether has been used for the introduction of MM groups, but a new reagent is desirable because (i) it is a powerful carcinogen and (ii) for a convenient reaction, alcoholate anions are needed. The use of dimethoxymethane as a reagent is restricted to phenols: J. P. Yardley and H. Fletcher, *Synthesis*, 244 (1976).
(21) R. A. Holton and R. G. Davies, *Tetrahedron Lett.*, 533 (1977); see also T. L. Ho and C. M. Wong, *J. Chem. Soc., Chem. Commun.*, 244 (1973), for the synthesis of MTM esters by reaction with chlorodimethyl sulfide and triethylamine in refluxing acetonitrile.
(22) L.G. Wade, J. M. Gerdes, and R. P. Wirth, *Tetrahedron Lett.*, 732 (1978).
(23) (a) When hexanol MTM ether was refluxed in carbon tetrachloride containing 5% *p*-toluenesulfonic acid, a 90% conversion into **10** and **11a** occurred within 120 min. (b) Using the conditions from ref 23a, hexanol MM ether was transformed in 50% conversion into **10** and **11b** within 100 min.
(24) W. E. Truce, G. H. Girum, and E. T. McBee, *J. Am. Chem. Soc.*, **74**, 3594 (1952).
(25) R. M. Carlson and P. M. Helquist, *J. Org. Chem.*, **33**, 2596 (1968).
(26) M. H. Palomaa and K. K. Kantola, *Chem. Ber.*, **65**, 1593 (1932).
(27) G. R. Petit, I. B. Douglass, and R. A. Hill, *Can. J. Chem.*, **42**, 2357 (1964).

Reaction of Isocyanides with Divalent Sulfur-Containing Heterocycles[1]

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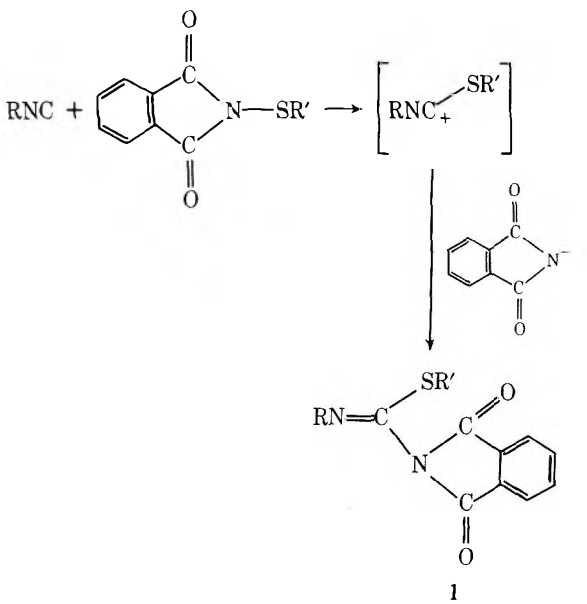
Reaction of *N*-(substituted thio)phthalimides with organic isocyanides results in sulfur–nitrogen bond cleavage and formation of new α adducts **1**. In addition to **1**, 2-alkylthio-5-aminooxazoles (**2**) were prepared for the first time by this method from 2-isocyanoacetamides. Likewise, when sulfur transfer reagents such as 2-alkyldithiobenzimidazoles and benzothiazoles are reacted with isocyanides, sulfur–sulfur fission results in the formation of α adducts possessing attachment of the heterocycle through nitrogen (**4**, **6**) or sulfur (**5**) to the isocyanide carbon. Product structure, isomer distribution, and reaction scope are discussed. Reactions of the parent heterocycles with isocyanides are also found to give α adducts **7**, **8**, **9**, and **10** formed by nitrogen–hydrogen heterolysis.

Reaction of sulfenamides with organic isocyanides (Scheme I) has been found to give α adducts **1** (Table I). The reaction is visualized as proceeding through a polar intermediate, much in keeping with the generally accepted mechanism encountered with a number of other well-known α additions to isocyanides,[2] including certain sulfur compounds.[3-5]

Moreover, sulfenamides have been shown to serve as effective sulfur transfer agents,[6-8] with the products therefrom indicative of sulfur transfer via a positive sulfenium intermediate.

Scheme I



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The reaction appears fairly general, although with certain isocyanides possessing an active methylene group, an alternative reaction is also possible (Scheme II). Although the corresponding α adduct can be isolated, significant amounts of the novel 2-alkylthio-5-aminooxazoles **2** are also formed. Since oxazole formation has been postulated in certain instances to proceed through a nitrile ylid,[9] especially during the Cornforth rearrangement, its intermediacy is suggested here. Curiously, present evidence indicates that the α adduct in Scheme II cannot be transformed to the substituted oxazole, but rather the two products are formed simultaneously and apparently independently regardless of whether the reaction is carried out at room temperature or in refluxing acetonitrile.

To further define the reaction scope, other types of divalent sulfur compounds were reacted with organic isocyanides, with the results diagrammed in Scheme III.

From the examples given in Schemes I–III it becomes apparent that the α additions depicted require facile cleavage of the sulfenamides or mixed disulfides to give relatively stable sulfenium cation and mercaptide or amine anions. A case in point is disulfides derived from benzothiazoline-2-thione which behave analogously to *N*-alkylthiophthalimides, except that while the sulfenamides derived from imides and amines cleave to give a nitrogen anion and sulfenium cation, the mixed disulfides give the latter ion and resonance stabilized mercaptide anion as addends.

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Table I. Products[a] From Reaction of Isocyanides with Sulfenamides and Disulfides

Material	registry no.	R	R′	R″	% yield	mp, °C	pertinent spectral data[b-d]
1a	66858-78-4	2,6-$(CH_3)_2C_6H_3$	$CH(CH_3)_2$		75	109–110	IR 5.6, 5.8–5.9 (C=O), 6.25 μm (C=N); NMR δ 1.35 (d, 6, $CH(CH_3)_2$), 2.28 (s, 6, $ArCH_3$), 3.42 (m, 1, $CH(CH_3)_2$)
b	66858-79-5	$(CH_3)_3C$	$CH(CH_3)_2$		54	140–142	IR 5.65, 5.8 (C=O), 6.08–6.2 μm (C=N); NMR δ 1.20 (s, 9, $C(CH_3)_3$), 1.30 (d, 6, $CH(CH_3)_2$), 3.6 (m, 1, $SCH(CH_3)_2$)
c	66858-80-8	$C_6H_5CH(CH_3)$	$CH(CH_3)_2$		77	105–106	IR 5.60, 5.8 (C=O), 6.18 μm (C=N); NMR δ 1.1–1.3 (multiple doublets, unequal intensity, syn/anti and chiral $CH(CH_3)_2$), 3.2 and 3.9 (minor and major heptet, syn/anti $CH(CH_3)_2$), 4.6 and 5.05 (major and minor quartet, syn/anti $CH(CH_3)_2$), 7.2 (m, 5, ArH)
d	66858-81-9	$C_6H_5CH_2CH(C_6H_5)$	$CH(CH_3)_2$		50	98–100	IR 5.6, 5.8 (C=O), 6.2 μm (C=N); NMR δ 1.1 (d, fractional $(CH(CH_3)_2)$, 1.4 (2d, fractional chiral $CH(CH_3)_2$), total at 1.1 and 1.4 (6 protons), 3.15 (m, 2, chiral CH_2CH), 3.85 (heptet, 1, $CH(CH_3)_2$), 4.6 and 5.1 (unequal triplet, syn/anti $ArCHCH_2$), 7 (m, 10, ArH)
e		$C_2H_5OC(O)CH_2$	$CH(CH_3)_2$		51	89–91	IR 5.65, 5.8 (C=O), 6.2 μm (C=N); NMR δ 1.20 (t, 3, CH_3CH_2), 1.35 (d, 6, $(CH_3)_2C$), 4.07 (heptet, 1, SCH), 4.12 (s, ca. 1.6, NCH_2), 4.13 (quartet, 2, CH_2CH_3), 4.30 (s, ca. 0.5, NCH_2, remaining syn/anti isomer)
f[e]		$C_6H_5N(i\text{-}Pr)C(O)CH_2$	$CH(CH_3)_2$		<10	140–145	IR 5.65, 5.8 (C=O), 6.05 (C=O), 6.2–6.3 μm (C=N); NMR δ 1–1.16 (multiple doublets, 12, syn/anti $CH(CH_3)_2$), 3.8 and 3.97 (2s, 2, syn/anti CH_2N), 4.95 (heptet, 1, $NCH(CH_3)_2$)
g	66858-82-0	2,6-$(CH_3)_2C_6H_3$	$n\text{-}C_3H_7$		71	130–132	IR 5.7, 5.8–5.9 (C=O), 6.2–6.3 μm (C=N); NMR δ 0.82 (t, 3, CH_2CH_3), 1.5 (m, 2, CH_2CH_3), 2.20 (s, 6, $ArCH_3$), 2.8 (t, 3, SCH_2)
h	66858-83-1	2,6-$(CH_3)_2C_6H_3$	C_6H_5		62	169–171	IR 5.65, 5.8 (C=O), 6.2 μm (C=N); NMR δ 2.4 (s, 6, $ArCH_3$), 6.9–7.5 (m, 5, ArH)
i	66858-84-2	2,6-$(CH_3)_2C_6H_3$	$C(CH_3)_3$		43	160–162	IR 5.68, 5.85 (C=O), 6.2 μm (C=N); NMR δ 1.6 (s, 9, $C(CH_3)_3$) 2.22 (s, 6, $ArCH_3$)
2a	*66858-85-3*	$(CH_3)_2CH$	$(CH_3)_2CH$	C_6H_5	31	oil	IR 6.2, 6.3 μm (oxazole and phenyl ring); NMR δ 1.23 (d, 6, $CH(CH_3)_2$), 1.43 (d, 6, $CH(CH_3)_2$), 3.82 (heptet, 1, $CH(CH_3)_2$), 4.20 (heptet, 1, $CH(CH_3)_2$), 6.75 (s, 1,4-oxazole H)
2b	66858-86-4	cyclohexyl	$(CH_3)_2CH$	C_6H_5	63	oil	IR 6.18, 6.3 μm (oxazole and phenyl ring); NMR δ 1.2 [d, 6, $(CH_3)_2C$], 1–2.3 (m, 10, cyclohexyl H), 3.6 (m, 1, CHS), 4.1 (heptet, 1, NCH), 6.42 (s, 1, 4-oxazole H)

Table I (*continued*)

Material	registry no.	R	R′	R″	% yield	mp, °C	pertinent spectral data[b-d]
3	66858-87-5				59	oil	IR 6.2–6.35 μm (C=N); NMR δ 1.1 (d, 6, $OCHCH_3$), 0.8–1.8 (m, 10, cyclohexyl **H**), 1.95 (s, 6, $ArCH_3$), 2.3–2.7 (m, 4, NCH_3), 3.3–4.2 (m, 3, OCH and SCH)
4	66858-88-6	2,6-$(CH_3)_2C_6H_3$	cyclohexyl	H		136–138	NMR δ 1.0–1.9 (m, 10, cyclohexyl **H**), 2.40 (s, 6, $ArCH_3$), 3.05 (m, 1, SCH), 7.0 (m, 3, ArH), 7.4 (m, 4, heterocyclic **H**); ^{13}C=N 152.5, ^{13}C=S 188.6
5a	66858-89-7	2,6-$(CH_3)_2C_6H_3$	cyclohexyl	H		50–60	NMR δ 1.1–1.9 (m, 10, cyclohexyl **H**), 2.2 (s, 6, ArH), 3.8 (m, 1, CHS), 7.2–8.2 (m, 4, heterocyclic **H**); ^{13}C=N 152.6, 155.6
b	66858-90-0	2,6-$(CH_3)_2C_6H_3$	cyclohexyl	Cl	76	140–141	IR 6.3 (C=N), 6.4 μm (hetero ring); NMR δ 1.05–1.9 (m, 10, cyclohexyl **H**), 2.20 (s, 6, $ArCH_3$), 3.8 (m, 1, SCH), 8.07 (d, J = 2 Hz, 1,4-heterocyclic **H**); ^{13}C=N 153.2, 155.1; single-crystal X-ray
6a	66858-91-1	2,6-$(CH_3)_2C_6H_3$	cyclohexyl		64	160–162	IR 6.2 (C=N), 6.35 μm (heteroaromatic); NMR δ 0.9–1.9 (m, 20, cyclohexyl **H**), 2.40 (s, 12, $ArCH_3$), 3.05 (m, 2, SCH), 7.3 (AB quartet, 4, hetero **H**), ^{13}C=N 151.7, ^{13}C=S 169.1
b	66858-92-2	2,6-$(CH_3)_2C_6H_3$	*n*-C_3H_7		65	201–203	IR 6.2 (C=N), 6.35 μm (heteroaromatic); NMR δ 0.88 (t, 6, $CH_2CH_2CH_3$), 1.55 (m, 4, $CH_2CH_2CH_3$), 2.48 (s, 12, $ArCH_3$), 2.80 (t, 4, $SCH_2CH_3CH_3$), 7.04 (m, 6, ArH), 7.4 (AB quartet, 4, hetero **H**); ^{13}C=S 168.0

[a] Elemental analyses [C, H(S), N] consistent with structure. [b] IR ($CHCl_3$), NMR ($CDCl_3$). [c] All materials possessing 2,6-xylyl and/or phthaloyl moieties display respectively ca. δ 2.2–2.4 (s, $ArCH_3$), ca. 7.0 (s, 3, ArH), and ca. 7.8 (A_2B_2 quartet, 4, ArH). [d] ^{13}C NMR resonances in ppm from Me_4Si. [e] Per general formula **1**, Scheme I.

Addition products with attachment at nitrogen (**4**) or sulfur (**5**) have been isolated. In one instance these pure isomers were separately shown to be convertible in refluxing acetonitrile to an equilibrium mixture of ca. 42% **4** and 58% **5a**. This observation is in accord with previous studies of S vs. N attachments of benzothiazole-2-thione derivatives,[10] although in the present case the S derivative is predominate. In fact, **5b** was isolated without evidence for nitrogen attachment and further completely resisted isomerization to **4** in refluxing acetonitrile, suggesting a steric influence on equilibrium.

In Scheme III reaction occurs only at both heteronitrogens, leading to bisadduct **6**. Attachment of the isocyanide carbon to heteronitrogens rather than mercapto exo-sulfur does not, however, necessarily preclude initial attack of isocyanide at this latter atom, followed by rearrangement. The propensity for final nitrogen rather than sulfur alkylation and acylation in these heterocyclic ring systems has previously been studied by Halasa.[11]

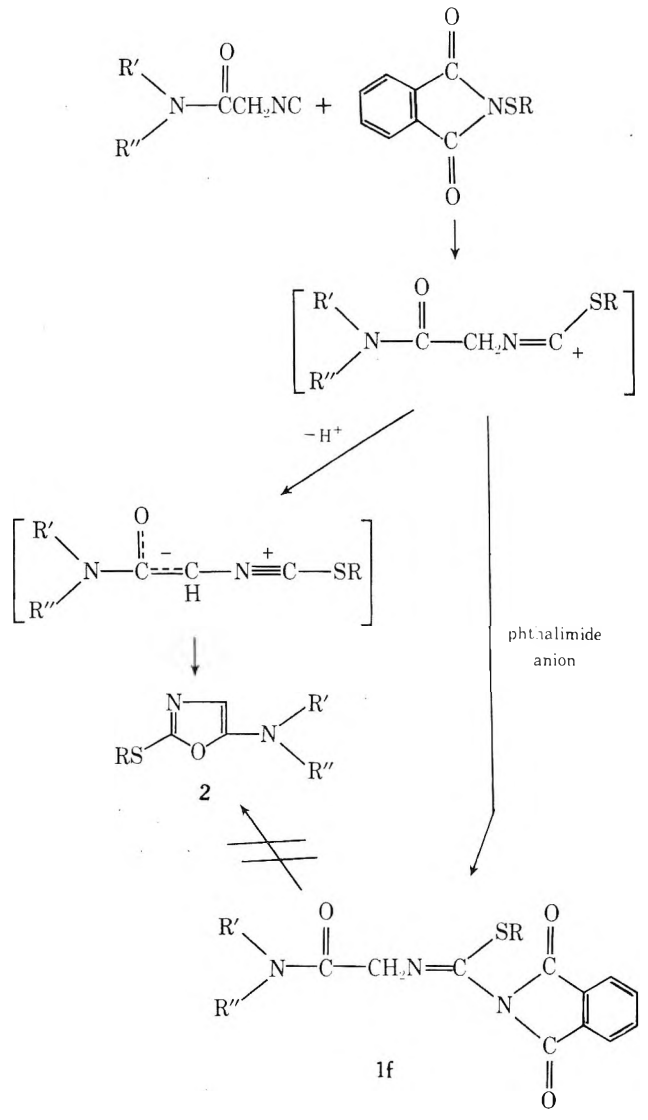
Nitrogen attachment is exclusively found with simple uncatalyzed α addition of isocyanides to benzothiazole-2-thione and other heterocyclic thiones (Scheme IV). The preparation of such adducts appears new[12] and a limited scope expansion is presented in Table II. Although benzothiazoline-2-thione and certain of its nuclear substituted derivatives react with isocyanide in a few hours or less in refluxing toluene, other ring systems require more stringent conditions. Refluxing dimethylformamide was found to effect reaction between sluggish benzimidazoline-2-thione rings and isocyanide. Certain closely related ring systems underwent addition to give materials **7**, **8** and **9**.

The formations of **7–10**, like **5** and **6**, are sensitive to steric influences. Benzothiazoline-2-thione reacted a good deal faster than the more acidic 5-chloro isomer with 2,6-xylyl isocyanide. 5-Methylbenzimidazole-2-thione, unlike the unsubstituted homologue, when permitted to react with 2 mol of 2,6-xylyl isocyanide produced only the monoadduct, and from the downfield shift of the 7-proton multiplet (coupled to the adjacent 6 proton), reaction occurred only at the 1-nitrogen to give **7h**, with no formation of 2:1 adduct.

Structure proofs for the new products arising from organic isocyanides and divalent sulfur compounds as listed in Tables I and II are based on methods of preparation, elemental analyses, and spectral interpretations with pertinent absorptions listed in the tables.

Thus materials **1** and **3–10** are characterized by strong imino IR bands at 6.2–6.3 μm. Compounds **1e** and **1f** are the only materials that seemingly display syn/anti forms as indicated by multiple absorptions for the $N-CH_2$ and $CH(CH_3)_2$.

Scheme II



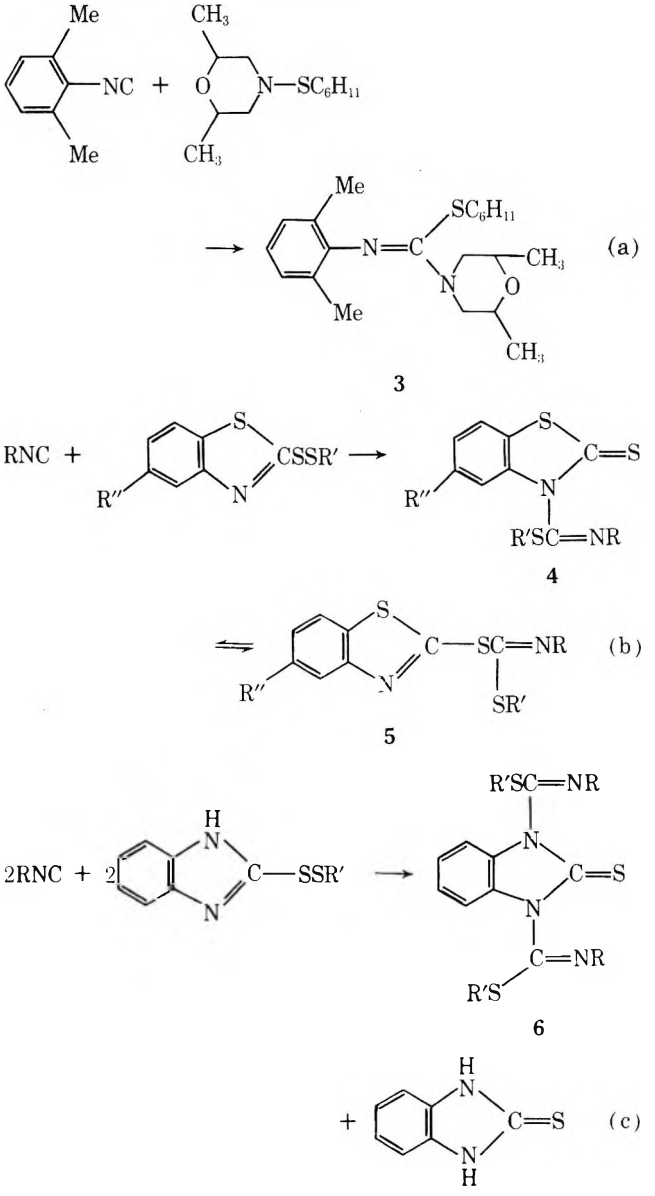
Spectra of the oxazoles **2** are quite consistent with those found for such ring systems.[13] Additionally, simple acid hydrolysis of **2a** furnishes the expected degradation product, namely 2-(isopropylthiocarbamoyl)-*N*-isopropylacetanilide.

Compounds **6** possess one sharp xylyl methyl peak (12 protons) (^{1}H NMR) and by ^{13}C display the predicted maximum decoupled absorptions for the requisite different carbon atoms. If **6** were unsymmetrical, with one imino moiety linked through sulfur, the ^{1}H and ^{13}C spectra would entail more complexities. Similarly, only one kind of aromatic methyl and formyl proton respectively could be observed for the symmetrical adduct **10**.

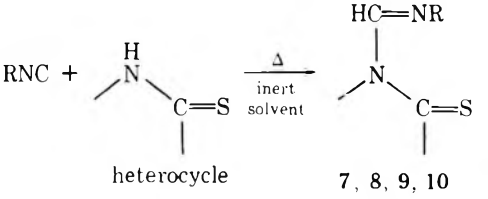
^{13}C NMR analysis is especially valuable in verifying the presence of a thiocarbonyl moiety in materials **4** and **6–10**. The ^{13}C=S absorption, particularly those derived from thiazole or oxazole ring systems (**4**, **7a–f**), is prominent with its downfield position between 178 and 200 ppm, in keeping with this resonance as found in the parent heterocycles such as benzothiazole-2-thione.[14] The absence of such thiocarbonyl absorptions immediately suggests derivatization through sulfur as in **5** rather than nitrogen (single-crystal X-ray crystallography of **5b** confirms this assignment, see Experimental Section).

The iminoformyl groups (HC=N) in materials **7–10** are also confirmed by ^{13}C off-resonance experiments, where the single proton coupling serves to locate this resonance among the other sp^2 carbon–heteroatom absorptions. In these cases

Scheme III[a]



Scheme IV



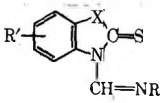
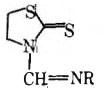
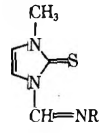
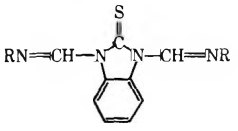
where measurements were made (see Table II), this absorption was located at ca. 145 ppm, upfield only from the thiocarbonyl resonance.

Experimental Section

Representative procedures for the preparation of the materials listed in Tables I and II are as follows:

1,3-Dioxo-*N*-(2,6-xylyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1a). Technical *N*-(isopropylthio)phthalimide[15] (4.4 g, 0.02 mol) was placed in 100 mL of acetonitrile with 2.6 g of 2,6-xylyl isocyanide. The mixture was heated to reflux after an initial IR at room temperature indicated partial reaction (C=N band emerging at 6.2–6.3 μm). After 30 min at reflux, the reaction was substantially complete, although 0.6 g of additional sulfenamide was added, as it became clear that this reagent contained significant amounts of phthalimide. The cooled mixture was filtered to remove phthalimide and solvent evaporated from the filtrate to give a mushy solid that

Table II. α Adducts[a] From Isocyanides and Heterocyclic Thioamides

material[b]	registry no.	R	R′	X	% yield	mp, °C	pertinent spectral data[c-e]
 7							
a	66858-93-3	2,6-$(CH_3)_2C_6H_3$		S	64	150–151	NMR δ 7.1–7.5 (m, 3, ArH), 9.00 (m, 1, 4-BT), 9.29 (s, 1, CH=N); ^{13}CH=N 148.2, ^{13}C=S 193.6
b	66858-94-4	2,6-$(CH_3)_2C_6H_3$	5-Cl	S	67	175–180	IR 6.05 μm (C=N); NMR δ 7.4 (m, 2, ArH), 9.17 (m, 1, 4-BT), 9.27 (s, 1, CH=N); ^{13}CH=N 147.9, ^{13}C=S 193.6
c	36858-95-5	2,6-$(CH_3)_2C_6H_3$	6-NO_2	S	36	>290	NMR δ 8.3 (m, 2, ArH), 9.33 (d, J = 8 Hz, 4-BT), 9.35 (s, 1, CH=N)
d	36858-96-6	2,6-$(CH_3)_2C_6H_3$	6-C_2H_5O	S	69	155–156	NMR δ 1.4 (t, 3, CH_2CH_3), 4.03 (q, 2, CH_2CH_3), 6.8–7.2 (m, 5, ArH), 8.97 (d, J = 8 Hz, 4-BT), 9.30 (s, 1, CH=N)
e	66858-97-7	2,6-$(CH_3)_2C_6H_3$		O	50	167–168	NMR δ 7.2–7.4 (m, 3, ArH), 8.4 (m, 1, 4-BO), 8.96 (s, 1, CH=N); ^{13}CH=N 146.8, ^{13}C=S 181.0
f	66858-98-8	cyclohexyl		S	34	131–132	NMR δ 1.1–2.2 (m, 10, cyclohexyl), 3.40 (m, 1, CHN=C), 7.2–7.5 (m, 3, ArH), 8.83 (m, 1,4-BT), 9.32 (s, 1, CH=N); ^{13}CH=N 145.4, ^{13}C=S 192.6
g	66922-24-5	2,6-$(CH_3)_2C_6H_3$		NH		245–247	NMR (Me_2SO), 7.0–7.4 (m, 6, ArH), 8.58 (m, 1, 7-BI), 9.23 (s, 1, CH=N)
h	66858-99-9	2,6-$(CH_3)_2C_6H_3$	5-CH_3	NH	40	231–234	NMR δ 2.42 (s, 3, 5-CH_3), 7.0 (m, 5, ArH), 8.40 (m, 1, 7-BI), 9.17 (s, 1, CH=N); ^{13}CH=N 147.0, ^{13}C=S 170.6
 8	66859-00-5				47	125	NMR δ 3.42 (t, 2, CH_2S), 4.60 (t, 2, CH_2N), 8.70 (CH=N); ^{13}CH=N 147.0, ^{13}C=S 200.7
 9	66859-01-6				15	113–115	NMR δ 3.62 (d, J = 1 Hz, 3, NCH_3), 6.75 and 7.6 (2 m, J = 1 Hz, NCH=CHN), 8.88 (s, 1, CH=N)
 10	66858-63-7					268–270	IR 6.05 μm (C=N); NMR δ 7.35–7.6 (m, 2, 5, 6-BI), 8.70–9.02 (m, 2, 4, 7-BI), 9.30 (s, 2, CH=N)

[a] Elemental analyses (C, H, N) consistent with structure. [b] In **8**, **9**, **10**, R = 2,6-$(CH_3)_2C_6H_3$. [c] IR ($CHCl_3$), NMR ($CDCl_3$), ^{13}C in ppm from Me_4Si. [d] All materials possessing 2,6-xylyl displayed NMR δ ca. 2.2 (s, $ArCH_3$) and ca. 7.0 (ArH). [e] BT-benzothiazole, BI-benzimidazole, BO-benzoxazole.

crystallized hard after several hours. Recrystallization from hot methylcyclohexane (after filtering off more phthalimide) afforded 2.9 g of **1a** as a first crop, mp 109–111 °C, and 0.8 g additional compound from the mother liquors.

1,3-Dioxo-*N*-(*tert*-butyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1b). *tert*-Butyl isocyanide (1.66 g, 0.02 mol) was dissolved in 50 mL of dry acetonitrile containing 4.86 g (0.022 mol) of *N*-(isopropylthio)phthalimide. After standing 24 h at room temperature, the isocyanide (IR) had vanished to be replaced by a strong C=N band at 6.2 μm. After solvent removal, the residue was dissolved in hot hexane and filtered and product allowed to crystallize on cooling, thereby yielding 3.3 g of white crystals. An analytical sample was obtained by a second recrystallization from hexane.

1,3-Dioxo-*N*-(ethoxycarbonylmethyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1e). Ethyl 2-isocyanoacetate[16] (0.02 mol, 2.26 g) was mixed with 4.5 g (0.02 mol) of technical *N*-(isopropylthio)phthalimide and allowed to stand at room temperature for 2 days. After this time there was still a trace of isocyanide present as determined by IR. The mixture was filtered to remove small amounts of phthalimide and the filtrate treated on a vacuum rotary evaporator to remove solvent. The residual 3.4 g of oil proved to be nearly pure *1e* (NMR and IR). Scratching induced crystallization and the material was recrystallized from methylcyclohexane to give 2.2 g of solid, while a final recrystallization from hexane furnished the analytical sample.

1,3-Dioxo-*N*-(*N*-isopropylcarbaniloylmethyl)-2-isoindolinecarboximidothioic Acid, Isopropyl Ester (1f), and 5-(*N*-Isopropylanilino)-2-(isopropylthio)oxazole (2a). 2-Isocyano-*N*-isopropylacetanilide[17] (0.02 mol, 4.04 g) and an equimolar amount of *N*-(isopropylthio)phthalimide (4.5 g) were dissolved in 100 mL of acetonitrile and the mixture heated at reflux for 2 h, then permitted to stand overnight. At the same time an identical charge was placed in acetonitrile and without heating the solution was allowed to stand overnight at room temperature. Infrared spectra of both solutions after standing were identical. They were both separately worked up in an identical manner as follows to give essentially the same distribution of products **1f** and **2a**: Acetonitrile was removed under vacuum then the residue taken up in ether and washed with 2.5% caustic to

remove phthalimide. During this process 1.1 g of solid, neutral **1f** was filtered off. The ether filtrate after drying over magnesium sulfate was vacuum treated to remove solvent and the residue triturated with ca. 50 mL of pentane. An additional 1.0 g of **1f** was thereby obtained. The clear pentane solution was evaporated to give 2.5 g of oil as crude **2a.** Although a sample of this material did not survive injection into a GLC column at 200 °C, it was purified by elution with pentane through neutral (Wöhme) alumina, to give after filtering through clay 1.4 g of clear, near-colorless oil which exhibited an NMR spectra indicative of high assay **2a.**

The combined solids obtained as described above were dissolved in chloroform and eluted through a silicic acid column with 98% $CHCl_3$/2% EtOH, to give a viscous white oil, which was characterized by only one spot on TLC. The material was triturated with pentane to give 0.3 g of white powdery solid, which by NMR was shown to consist of both syn and anti α adduct **1f.**

Material **2a,** 0.4 g, was shaken at room temperature with ca. 20 mL of 12% HCl. The oil appeared to nearly dissolve in this medium when crystals appeared. After standing 0.5 h, the acidic mixture was diluted with 25 mL of water and filtered. The washed and then dried crystals were recrystallized from isopropyl alcohol to give 0.24 g of 2-(isopropylthiocarbamoyl)-*N*-isopropylacetanilide: mp 138–139 °C; IR 5.95–6.15 μm (C=O); ^{1}H NMR ($CDCl_3$) δ 1.04 and 1.08 (2 d, 12, J = 7 Hz, 2 $(CH_3)_2CH$), 3.54 (heptet, 1, J = 7 Hz, SCH), 3.60 (d, 2, J = 6 Hz, $HNCH_2$), 4.98 (heptet, 1, J = 7 Hz, NCH), 6.48 (m, broad, 1, NH), 7–7.6 (multiplets, 5, ArH); MS revealed parent molecular ion at 294 and fragmentation pattern consistent with structure.

Anal. Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.19; H, 7 53; N, 9.51. Found: C, 61.19; H, 7.55; N, 9.48.

2-Cyclohexylthio-5-(*N*-isopropylanilino)oxazole (2b). Equimolar amounts (0.01 mol) of 2-isocyano-*N*-isopropylacetanilide and 4-cyclohexylthio-2,6-dimethylmorpholine[18] were heated at reflux in acetonitrile until the isocyanide band had essentially vanished. Upon cooling, the solvent was removed and the residual oil was eluted through neutral alumina with pentane to give, on solvent removal, 2.0 g of **2b.**

2,6-Dimethyl-4-morpholine-*N*-(2,6-xylyl)carboximidothioic Acid, Cyclohexyl Ester (3). 2,6-Xylyl isocyanide (0.05 mol) was mixed in 100 mL of acetonitrile with an equimolar amount of 4-cyclohexylthio-2,6-dimethylmorpholine.[18] The mixture was refluxed for several hours, until the isocyanide band (IR) had essentially disappeared. On evaporation of solvent an oil was obtained which was filtered through clay as product.

***N*-(2,6-Xylyl)benzothiazoline-2-thione-3-carbonimidothioic Acid, Cyclohexyl Ester (4).** 2,6-Xylyl isocyanide (0.01 mol, 1.3 g) and 2-cyclohexyldithiobenzothiazole[18] (0.01 mol, 2.8 g) were mixed together in 50 mL of acetonitrile and the temperature was raised to reflux. After 12 h at this temperature, the mixture was cooled and solvent evaporated to give a viscous syrup. Column chromatography through silica gel (elution with cyclohexane/ethyl acetate v/v 4:1) gave the first elutant collected as **4,** recrystallized hexane, mp 136–138 °C, yield 0.4 g.

***N*-(2,6-Xylyl)-*S*-(2-benzothiazolyl)carbonimidodithioic Acid, *S'*-Cyclohexyl Ester (5a).** The second fraction collected from **4** was rechromatographed with cyclohexane/ethyl acetate (LC) to give upon solvent evaporation 0.6 g of solid, recrystallized from pentane.

Isomerization of 4 and 5a. Solutions of pure **4** and **5a** were separately boiled in CD_3CN for ca. 24 h. During this time (after ca. 12 h) it was established by examining the ^{1}H NMR of the solutions that each had established an equilibrium of ca. 42% **4** and 58% **5a.** Upon evaporation of the NMR solvent, both pure **4** and **5a** were isolated from the reaction mixtures by recrystallization from hexane (**4**) and chromatography (**5a**).

***N*-(2,6-Xylyl)-*S*-(5-chloro-2-benzothiazolyl)carbonimidodithioic Acid, *S'*-Cyclohexyl Ester (5b).** 2,6-Xylyl isocyanide (0.015 mol, 1.96 g) and 5-chloro-2-cyclohexyldithiobenzothiazole[18] (0.015 mol) were mixed together in acetonitrile and the temperature raised to reflux. A clear solution was thereby achieved. Reflux was continued overnight, but on cooling an oil layer was observed. IR of the solvent phase showed almost no isocyanide remaining. The lower layer was separated and scratching induced crystallization of the lower oil layer with 5.1 g filtered from the mixture. An analytical sample was recrystallized from isopropyl alcohol. Material **5b** was examined by single crystal X-ray and found to be monoclinic, space group $P2/a$, with a = 11.515 (3) Å, b = 16.585 (5) Å, c = 11.681 (4) Å, β = 95.66 (2)°, with unit cell volume = 2219.9 Å^3 for Z = 4. Preliminary structural refinement has resulted in R_1 = 0.09. Details of the complete structure refinement will be published elsewhere.[19]

Bis[*N,N'*-(2,6-xylyl)]benzimidazole-1,3-dicarboximidothioic Acid, Dicyclohexyl Ester (6a). 2-Cyclohexyldithiobenzimidazole[20] (0.022 mol, 5.8 g) was mixed in 100 mL of dry acetonitrile with 0.02 mol (2.62 g) of 2,6-xylyl isocyanide and the mixture refluxed overnight. After this time, the IR indicated no remaining isocyanide. Small amounts of solid were filtered off the cooled reaction mixture and the solution treated under vacuum to remove acetonitrile. The residue was taken up in ether and washed with 2.5% caustic, then water. After drying over magnesium sulfate, the material was vacuum treated to remove solvent and the residue permitted to stand under hexane for 2 days. Crystals (4.1 g) were deposited, which were once again recrystallized from isopropyl alcohol. An analytical sample was obtained by a further recrystallization from heptane.

5-Chloro-3-[*N*-(2,6-xylyl)formidoyl]benzothiazoline-2-thione (7b). 5-Chlorobenzothiazoline-2-thione (4.0 g, 0.02 mol) was placed in 100 mL of toluene and heated at reflux with an equimolar amount of 2,6-xylyl isocyanide. After 4 h the isocyanide absorption (IR 4.7 μm) had vanished, and on cooling the product separated. The solid material was removed by filtration, taken up in methylene chloride, and washed with 5% sodium hydroxide (to remove starting thiazole). The dried organic phase was then vacuum treated and the residual solid was recrystallized from ethyl alcohol.

3-[*N*-(2,6-Xylyl)formimidoyl]benzoxazoline-2-thione (7e). Equimolar (0.02 mol) charges of benzoxazoline-2-thione and 2,6-xylyl isocyanide were placed in toluene and heated at reflux until only traces of isocyanide remained as monitored by IR. This reflux period was longer than that required for the sulfur analogues (i.e., **6a**). After cooling and separating the solid by filtration, the product was dissolved in methylene chloride and washed with 5% sodium hydroxide. After drying, the material was vacuum treated and the residue recrystallized from isopropyl alcohol.

1-[*N*-(2,6-Xylyl)formimidoyl]benzimidazolinethione (7g) and 1,3-Bis[*N*-(2,6-xylyl)formimidoyl]-2-benzimidazolinethione (10). Benzimidazoline-2-thione (3.8 g, 0.02 mol) was mixed with an equimolar amount of 2,6-xylyl isocyanide in 100 mL of DMF and refluxed for 12 h. Upon cooling overnight **10** crystallized and was separated and purified by recrystallization from pyridine. The DMF filtrate was poured into 500 mL of water and the solid formed was filtered off, dried, and recrystallized from acetonitrile to give a base soluble 1:1 adduct (**7g**).

5-Methyl-1-[*N*-(2,6-xylyl)formimidoyl]-2-benzimidazolinethione (7h). 5-Methylbenzimidazoline-2-thione (4.1 g, 0.025 mol) was mixed with 6.5 g (0.05 mol) of 2,6-xylyl isocyanide in 150 mL of DMF and the material refluxed for 24 h. On cooling, no solid separated, so the clear DMF solution was poured into water to give solid, which after air drying was recrystallized from acetonitrile to give 2.9 g of a 1:1 adduct (**7h**). There was no evidence for the 2:1 adduct.

3-[*N*-(2,6-Xylyl)formidoyl]thiazolidine-2-thione (8). Thiazolidine-2-thione (2.4 g, 0.02 mol) was placed in diglyme with an equimolar amount of 2,6-xylyl isocyanide. The mixture was refluxed for 6 h, solvent removed, and the residue placed on a porous plate. The material was recrystallized from acetonitrile to give 7.4 g.

Acknowledgment. We are indebted to Mr. Ralph Fuhrhop for preparing some of the intermediates and Mrs. Claudette Deatherage for performing and interpreting several of the ^{13}C NMR spectra.

Registry No.—RNC (R = 2,6-$(CH_3)_2C_6H_3$), 2769-71-3; RNC (R = $(CH_3)_3C$), 7188-38-7; RNC (R = $C_6H_5CH(CH_3)$), 17329-20-3; RNC (R = $C_6H_5CH_2CH(C_6H_5)$), 3128-88-9; RNC (R = C_2H_5O + C(O) + CH_2), 2999-46-4; RNC (R = $C_6H_5N(i\text{-}Pr)CO$ + CH_2), 66858-64-8; *N*-(isopropylthio)phthalimide, 17796-72-4; *N*-(propylthio)phthalimide, 17796-71-3; *N*-(phenylthio)phthalimide, 14204-27-4; *N*-(*tert*-butylthio)phthalimide, 17796-75-7; 4-cyclohexyl-2,6-dimethylmorpholine, 1774-04-5; 2-cyclohexyldithiobenzothiazole, 28084-58-4; 5-chloro-2-cyclohexyldithiobenzothiazole, 52367-82-5; 2-cyclohexyldithiobenzimidazole, 40952-49-6; 2-propyldithiobenzimidazole, 66858-65-9; benzothiazoline-2-thione, 149-30-4; 5-chlorobenzothiazoline-2-thione, 5331-91-9; 6-nitrobenzothiazoline-2-thione, 4845-58-3; 6-ethoxybenzothiazoline-2-thione, 120-53-6; benzoxazoline-2-thione, 2382-96-9; benzimidazoline-2-thione, 583-39-1; 5-methylbenzimidazoline-2-thione, 27231-36-3; thiazolidine-2-thione, 96-53-7; 1-methyl-4-imidazoline-2-thione, 60-56-0; *syn*-**1e,** 66922-22-3; *anti*-**1e,** 66922-23-4; *syn*-**1f,** 66858-66-0; *anti*-**1f,** 66858-67-1.

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Sesquiterpene Lactones of *Eupatorium recurvans*[1]

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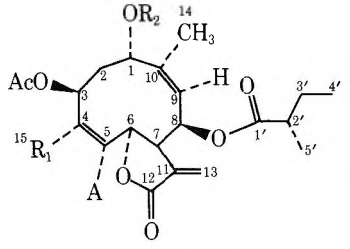
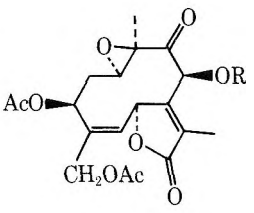
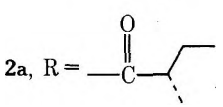
The isolation and structure determinations of three new heliangolides from *Eupatorium recurvans* Small are reported. The major lactone eurecurvin (**1a**) was a *cis*-$\Delta^{4,5}$,*cis*-$\Delta^{9,10}$-germacradienolide, as was a minor lactone constituent **1e**. The third lactone was a trans-$\Delta^{1(10)}$,cis-$\Delta^{4,5}$ isomer, **4a**. Details of the structure and stereochemistry were established by X-ray analysis of **1e** and **4a**.

In the present article we continue our reports[3-5] on constituents of *Eupatorium* species *sensu stricto* which have yielded various cytotoxic and antitumor sesquiterpene lactones and describe the isolation and structure determination of three new heliangolides **1a**, **1e**, and **4a** from *Eupatorium recurvans* Small.[6] *E. capillifolium* (Lam.) Small, *E. compositifolium* Walt., *E. Leptophyllum* DC., and *E. pinnatifidum* Ell. yielded no significant sesquiterpene lactone fractions.[7]



1a, $R_1 = CH_2OH$; $R_2 = H$
b, $R_1 = CH_2OAc$; $R_2 = H$
c, $R_1 = CH_2OAc$; $R_2 = Ac$
d, $R_1 = CHO$; $R_2 = H$
e, $R_1 = CH_3$; $R_2 = H$
f, $R_1 = CH_3$; $R_2 = H$



2a, R = 
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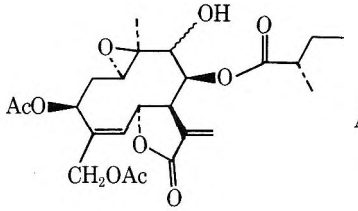

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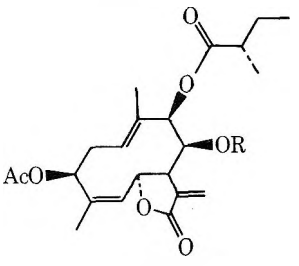
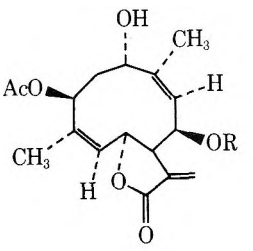
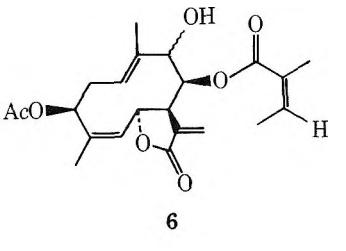


4a, R = H
b, R = Ac





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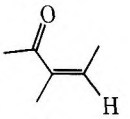
5a, R = 
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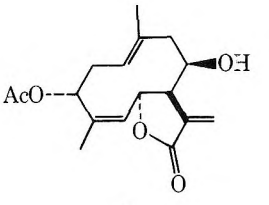

7

The major lactone component of *E. recurvans*, which we have named eurecurvin, $C_{22}H_{30}O_8$, mp 185–186 °C, was an α-methylene γ-lactone as evidenced by the usual criteria [^{1}H NMR spectral data in Table I, narrowly split doublets at 6.45 and 5.72 ppm (H_a and H_b), and appropriate signals of the ^{13}C NMR spectrum in Table II, particularly the triplet at 122.9 ppm]. That it was incorporated in partial structure A was shown by spin decoupling experiments on the lactone and its derivatives in various solvents, which will not be discussed in detail. A vinyl methyl group (broadened signal at 1.83 ppm) was found to be allylically coupled to H_f resonating at 5.44 ppm. Mass and NMR spectral analyses revealed the presence of two ester groups, an acetate and a 2-methylbutyrate.

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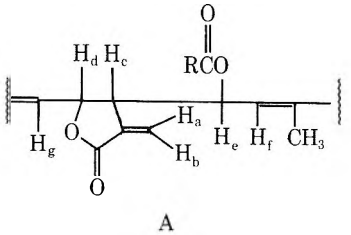
Table I. ^{1}H NMR Spectra of *E. recurvans* Constituents and Derivatives[a]

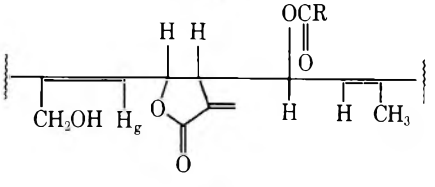
Compd	H-1	H-2	H-3	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15	Side chain & misc.
1a[c]	5.80 dbr (11, 2)	2.45 m (15, 11, 3) 2.64 m (15, 2, 4.5)	5.80 dbr (4.5, 3)	6.03 dbr (11)	6.43 dd (11, 9)	3.32 m (9, 2, 3, 3)	6.29 dbr (6, 2)	5.44 dbr (6)	5.72 d (3) 6.45 d (3)	1.90 br	4.47 br[d]	2.46 m (H-2′), 1.43, 1.72 m (H-3′),0.81 t (H-4),[b] 1.23 (d (H-5′),[b] 2.16 (Ac)[b]
1a[e]	5.40 m	1.97 m 2.29 m	5.34 br	5.60 m	6.00 dd	3.14 m	5.40 m	5.40 m	5.60 d 6.30 d	1.70 br	4.09 t 4.24 t	2.43 m, 1.68, 1.48 m, 1.21 d,[b] 0.89 t,[b] 2.1 (Ac)[b]
1b[c]	5.67 dbr (11, 2)	2.43 m (15, 11, 3) 2.55 m (15, 2, 4.5)	5.79 dbr (4.5, 3)	5.88 br (11)	6.43 dd (11, 9)	3.32 m (9, 2, 3, 3)	6.34 dbr (2, 6)	5.47 dbr (6)	5.74 d (3) 6.47 d (3)	1.90 br	4.69 d (15) 4.90 d (15)	Side chain as in **1a**: 2.06, 2.14 (Ac)[b]
1c[c]	6.71 dbr (11, 2)	2.28 m (15, 11, 3) 2.40 m (15, 2, 4.5)	5.74 dbr (4.5, 3)	5.91 dbr (11)	6.44 dd (11, 9)	3.30 m (9, 2, 3, 3)	6.32 dbr (2, 6)	5.53 dbr (6)	5.74 d (3) 6.48 d (3)	1.82 br	4.67 dbr (15) 4.83 dbr (15)	Side chain as in **1a**: 1.96, 2.06 (Ac)[b]
1d[c]	5.80 dbr (11, 2)	2.48 m	5.74 dbr (4.5, 3)	6.75 dbr (11)	6.45 dd (11, 9)	3.53 m	6.35 dbr (2, 6)	5.41 dbr (6)	5.80 d (3) 6.50 d (3)	1.66 br	9.64	Side chain as in **1a**: 2.13 (Ac)[b]
1e[f]	5.28 dbr[g] (10.5, 3)	2.20 m (16.5, 10.5) 3 2.01 m (16.5, 3, 3)	5.36 ddbr (6, 3)	5.28 dbr[g] (11)	5.96 dd (11, 9)	2.83 m (9, 1.5, 3, 3)	5.89 dbr (6, 1.5)	5.36 d (6)	5.58 d (3) 6.34 d (3)	1.83 br	1.72 br[b]	2.44 m (H-2′), 1.49 m, 1.67 m (H-3′), 0.92 t (H-4′),[b] 1.19 d (H-5′),[b] 2.14 (Ac)[b]
1e[e]	5.34 m	1.92 m 2.27 m	5.25 dd	5.34 m	5.97 dd	3.05 m	5.34 m	5.34 m	5.55 d 6.14 d	1.69 br	1.80 br	Side chain as in **1a**: 2.1 (Ac)[b]
2a[f]	3.85 dd 11, 3)	1.59 m 2.63 m	5.46 dd (6, 2)	5.20 dbr (11)	6.33 dq (11, 1.7)		5.10		1.94 d[b] (1.7)	1.26	4.50 dbr (15) 4.60 dbr (15)	Side chain as in **1a**: 2.07, 2.18 (Ac)[b]
2b[f]	3.92 dd (11, 3)	1.75 m 2.62 m	5.43 dd (6, 2)	5.18 dbr (11)	6.36 dq (11, 1.7)		4.42		2.01 d[b] (1.7)	1.26	4.50 dbr (15) 4.63 dbr (15)	2.07, 2.19 (Ac)[b]
3[f,h]	3.93 m	1.67 m 2.58 m	5.33 m	5.61 dbr (10)	5.69 m	3.07 m	5.69 m	5.33 m	5.90 d (3) 6.43 d (3)	1.32	4.64 br	Side chain same as in **1a**: 2.03, 2.11 (Ac)[b]
4a[f]	5.33 ddbr (10, 4)	2.28 m (16, 6, 4) 2.73 m (16, 10, 3)	5.26 ddbr (6, 3)	5.19 dbr (11, 1.5)	5.82 dd (11, 2)	2.84 m	4.12 br (~4, 2)	5.22 br (~4)	5.73 d (2) 6.40 d (2)	1.85 br	1.79 d (1.5)	Side chain as in **1e**: 2.03 (Ac)[b]
4b[f]	5.36 m (10, 4)	2.33 m (16, 6, 4) 2.74 (16, 10, 3)	5.28 dd (6, 3)	5.18 dbr (11, 1.5)	5.79 dd (11, 2)	2.98 m	5.54 br (~4, 2)	5.36 br (~4)	5.85 d (2) 6.40 d (2)	1.84 br	1.81 d (1.5)	Side chain as in **1e**: 2.03, 2.11 (Ac)[b]

[a] Run at 270 MHz on a Bruker HX-270 instrument with Me_4Si as an internal standard. Values are in ppm: d, doublet; br, broadened singlet; m, multiplet; t, triplet. Unmarked signals are singlets. Values in parentheses are coupling constants in hertz. [b] Intensity of three protons. [c] C_5D_5N solution. [d] Intensity of two protons. [e] $(CD_3)_2CO$ solution. [f] $CDCl_3$ solution. [g] J values obtained by decoupling in C_5D_5N where signals are separated. [h] Run at 90 MHz.

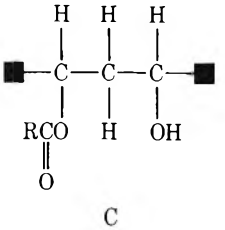
Acetylation (acetic anhydride–pyridine) afforded a mono- and a diacetate, thereby establishing the presence of two hydroxyl groups. One of these was primary, as indicated by the downfield shift and conversion, on acetylation, of a two-proton signal at 4.47 ppm to two doublets (AB system) at 4.69 and 4.90 ppm in the monoacetate and at 4.67 and 4.83 ppm in the diacetate, and allylic, as indicated by MnO_2 oxidation of the parent compound to an α,β-unsaturated aldehyde (downfield shift of H_g from 6.03 to 6.75 ppm). The chemical shift of the aldehyde proton (9.64 ppm) was characteristic of a cis relationship between H_g and the aldehyde group, a conclusion which was confirmed by demonstration of an NOE between H_g and $-CH_2OH$ in the parent compound (15% signal enhancement). Consequently, A could be expanded to B.[8] The other hydroxyl group was secondary, as indicated by the downfield shift of a one-proton signal from 5.80 and 5.67 ppm in the parent compound and monoacetate **1b** to 6.71 ppm in the diacetate **1c**. Spin decoupling experiments with **1a**, **1b**, and **1c** also established the presence of unit C.



A



B



C

Differentiation between the two structural possibilities afforded by the combination of B and C and location of the isobutyrate ester function on C-8 was made possible by oxidation of monoacetate **1b** with Jones reagent. Three major products were isolated which, on the basis of their spectral properties, could be assigned structures **2a**, **2b**, and **3**, generated as the result of an allylic transposition involving the secondary hydroxyl group and the double bond to which H_g is attached. Consequently, the free hydroxyl group of eurecurvin monoacetate is on C-1 and not on C-3.[9] An analogous allylic trans position (without migration of the[11,13] double bond) had previously[12] served to correlate the antileukemic sesquiterpene lactone eupacunin (**5a**) with eupatocunin (**6**).

The fortuitous loss of the isobutyrate residue during the formation of **2b** clearly showed that it was attached to C-8 in the precursors **1b** and **1a** and that the acetate was located at C-3. That the 9,10 double bond was cis was demonstrated by

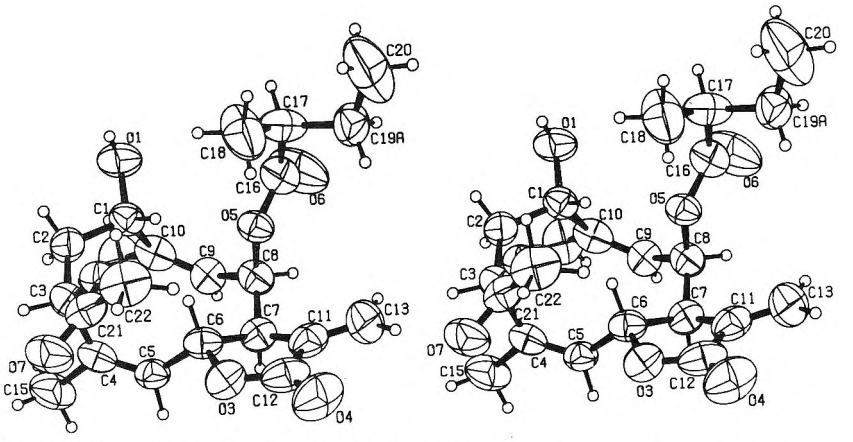


Figure 1. A stereoscopic drawing of a molecule of **1e**. The principal conformation of the isovalerate is shown.

Table II. ^{13}C NMR Spectra of *E. recurvans* Constituents[a]

Carbon atom[b]	1a[c]	1f[d]	4a[d]
1	65.8 d	65.1 d	124.7 d
2	35.4 t	32.4 t	28.7 t
3	72.4 d[e]	73.1 d[e]	74.2 d[e]
4	141.5	143.9	138.5
5	125.9 d	126.0 d	126.9 d
6	75.8 d[e]	74.1 d[e]	76.4 d[e]
7	49.8 d	47.5 d	47.8 d
8	69.1 d	67.0 d	80.9 d[e]
9	124.0 d	123.2 d	78.8 d[e]
10	142.5	139.0	136.2[f]
11	136.3	134.4	135.6[f]
12	170.9	169.2	169.7
13	122.9 t	121.9 t	123.6 t
14	19.9 q	17.6 q	14.2 q
15	65.3 t	23.3 q	23.1 q
1′	175.9	174.8	175.5
2′	42.7 d	41.5 d	41.1 d
3′	27.4 t	26.3 t	26.8 t
4′	10.8 q	11.6 q	11.6 q
5′	17.7 q	16.4 q	16.5 q
1″	170.9	169.2	170.2
2″	21.7 q	21.0 q	21.2 q

[a] Run at 67.9 MHz on a Bruker HX-270 instrument. Values are in ppm. Unmarked signals are singlets. [b] Assignments tentative and not verified by single frequency off-resonance decoupling. [c] CD_3OD solution. [d] $CDCl_3$ solution. [e,f] Assignments may be interchanged.

irradiation at the frequency of the C-10 methyl signal, which resulted in 17% enhancement of the H-9 signal. Analysis of the coupling constants $J_{7,13a}$, $J_{7,13b}$, $J_{6,7}$ and $J_{7,8}$ then showed that the lactone ring of eurecurvin must be trans fused and the C-8 ester side chain β.[13]

We defer discussion of the stereochemistry at C-1 until we have considered a second lactone (**1e**; $C_{22}H_{30}O_7$, mp 113–114 °C), which was isolated in small amount only and seemed to differ from eurecurvin primarily in lacking the primary hydroxyl group (see Tables I and II). Formation of a monoacetyl derivative **1f** from this lactone was accompanied by a downfield shift of a signal in the cluster near 5.3–6.36 ppm, thus identifying the resonance of H-1. Analysis of the ^1H NMR spectra of **1e** and **1f** was facilitated by performing the spin decoupling experiments in $CDCl_3$, C_6D_6, or C_5D_5N to separate relevant signals. This will not be discussed in detail. NOE studies showed that the two double bonds were cis (17% signal enhancement of H-5 on irradiation of H-15, 16% enhancement of H-9 on irradiation of H-14); moreover, the coupling constants indicated that the relative stereochemistry at C-1, C-3,

Table III. Crystal Data for 1e and 4a

	1e	4a
Formula	$C_{20}H_{30}O_7$ (406.48)	$C_{20}H_{30}O_7$ (406.48)
System	Orthorhombic	Trigonal
Space group	$P2_12_12_1$	$P3_1$ or $P3_2$
a	9.812 (7) Å	10.548 (3) Å
b	14.375 (8) Å	
c	15.691 (7) Å	17.418 (5) Å
d_{calcd}	1.219 g cm^{-3}	1.206 g cm^{-3}
Z	4	3

Table IV. Lactone Ring Torsion Angles of 1e and 4a

C(6)–O(3)–C(12)–C(11)	ω_1	−7.8°	6.9°
C(13)–C(11)–C(12)–O(4)	ω_2	−9.9°	4.7°
C(11)–C(7)–C(6)–O(3)	ω_3	−24.6°	13.1°
C(5)–C(6)–C(7)–C(8)	ω_4	89.3°	136.1°

C-6, and C-8 was the same as that of eurecurvin. However, there was no direct evidence for orienting the lactone ring toward C-6 and for attaching the acetate group to C-3 and the isobutyrate to C-8, instead of the reverse. To settle these points and to establish the stereochemistry at C-1,[14] an X-ray analysis of the minor lactone was undertaken.

Crystal data for **1e** are listed in Table III. Figure 1 is a stereoscopic drawing of the molecule which represents the absolute configuration of the molecule (vide infra). The acetate and methyl isobutyrate functions are attached to C-3 and C-8, respectively, as in **1a**, and the configuration of the C-1 hydroxyl is α. The C-4,C-5 and C-9,C-10 bonds are essentially parallel, with the methyl carbons projecting below the plane of the ring. Tables V, VI, and VII, containing bond lengths, bond angles, and torsion angles, and Tables XI and XII, listing final atomic and final anisotropic thermal parameters, are available as supplementary material.

The lactone torsion angles listed in Table IV show that if **1e** possesses the absolute configuration shown in Figure 1, the chirality of the C=CC=O group is negative ($\omega_2 = -9.9°$) and, as usual,[15] paired with the sign of the C(α)–C(β)–C(γ)–O torsion angle (ω_3). The chirality of this chromophore has been related[16] to the Cotton effect of an α,β-unsaturated lactone; since both **1a** and **1e** exhibit negative Cotton effects, the absolute configuration is as shown in the formulas and is the same as in all other sesquiterpene lactones of authenticated stereochemistry.

The close correspondence in the NMR spectra of eurecurvin and lactone **1e**, which if examined in the same solvent differed significantly only in the shifts of protons and carbons in the vininity of the "extra" primary hydroxyl group of **1a** (see Tables I and II), indicated that the configuration of **1b** at C-1

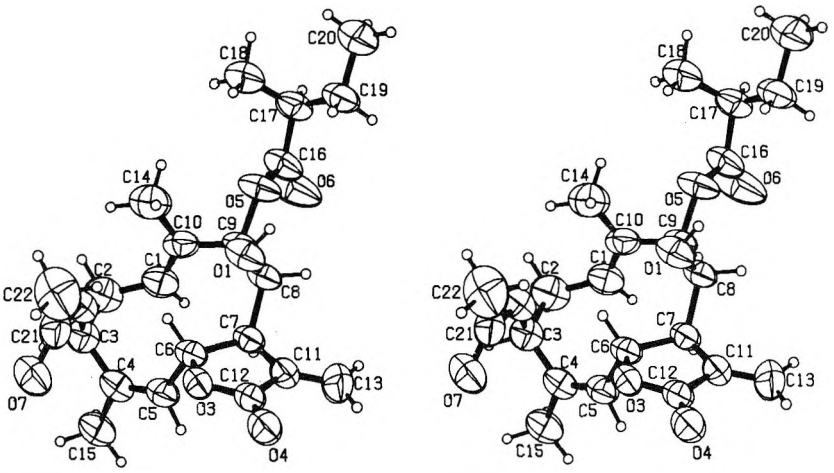


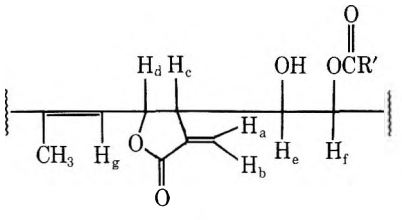
Figure 2. A stereoscopic drawing of a molecule of **4a** showing its conformation in the crystalline state.

was the same as that of **1e.** This was confirmed by application of Horeau's method to **1b,** which was esterified with excess (+)-α-phenylbutyric anhydride. The recovered α-phenylbutyric acid was negative (9.2% optical yield). Hence, the absolute configuration of eurecurvin at C-1 is *S* (OH α).

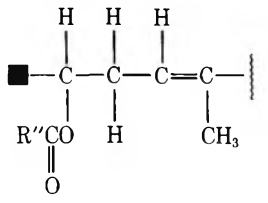
Thus, the conformations and stereochemistries of **1a** and **1e** are the same as those of eupacunin (**5a**) and eupacunoxin (**5b**).[17] It may be assumed that formulas **5a** and **5b** also represent the absolute configurations of these compounds although CD curves of **5a** and **5b** were unfortunately not available.[18]

The epoxides **2a/2b** and **3** must be trans epoxides because Jones oxidation of eupatocunin (**6**) with a trans 1,10 double bond afforded the same substance as the oxidation of eupacunin (**5b**). The stereochemistry at C-1 and C-2 shown in the formulas follows since other work emanating from this laboratory has shown[11] that the oxidative transposition of allylic alcohols, exemplified by conversion of **1a** and **5b** to compounds of this type, is accompanied by retention.

A third lactone, mp 129–131 °C, isomeric with **1e,** was isolated in a small amount only. It incorporated the usual α,β-unsaturated lactone function: two vinyl methyls (broadened singlet and narrowly split doublet at 1.85 and 1.79 ppm), a secondary hydroxyl group (signal at 4.12 ppm which moved to 5.54 ppm on acetylation), an acetate, and a 2-methylbutyrate. Spin decoupling experiments in $CDCl_3$ and C_5D_5N to separate superimposed signals whenever necessary established the presence of partial structure D in which H_d, responsible for a doublet of doublets at 5.82 ppm, was tentatively assigned to the proton under the lactone oxygen and H_e, at 4.12 ppm, to the proton under the hydroxyl. H_e was in turn coupled to a broadened singlet (H_f) at 5.22 ppm, presumably a proton under one of the two ester functions. H_g (doublet at 5.19 ppm), vicinally coupled to H_d, was also allylically coupled to the vinyl methyl resonating at 1.79 ppm; the existence of a strong NOE (18% signal enhancement) showed that the double bond was cis.



D



E

Irradiation of a multiplet at 5.33 ppm simplified multiplets at 2.73 and 2.28 ppm, representing protons which were geminally coupled to each other and vicinally coupled to a third proton resonating at 5.28 ppm. The latter was in turn allylically coupled to the second vinyl methyl responsible for the signal at 1.85 ppm. These results led to partial structure E with a trans double bond because of the absence of an NOE. Combination of D and E then led to the gross structure of formula **4a** which was substantiated by the ^{13}C NMR spectrum and where, because of our failure to obtain homogeneous material from attempts at partial hydrolysis, the distribution of the two ester functions remained uncertain. The lactone ring was trans fused as evidenced by the small values of $J_{6,7}$ and $J_{7,13}$ (2 Hz), typical of H-6β,H-7α heliangolides;[19-21] the small value of $J_{7,8}$ (2 Hz) required that the substituent on C-8 be β orientated. The conclusion that the lactone ring was closed to C-6, a possibility a priori not excluded by the decoupling experiments (vide supra), was supported by the positive Cotton effect, whose sign was in agreement with that of other heliangolides containing a trans-fused lactone ring closed to C-6.[19-24] The values of $J_{2,3}$ corresponded to those of 3-epinobilin;[21] hence, the ester function on C-3 was β oriented.

However, the stereochemistry of the ester function on C-9 could not be derived from the information at hand. If **4a** possesses the same conformation as eupaformonin (**7,** methyls anti),[23] as seems likely, H-8 approximately bisects the angle H_α–C9–H_β and the observed value of $J_{8,9}$ (~4 Hz) is satisfied by either α or β orientation of the ester function on C-9. In a conformation with the two methyl groups syn, the observed value of $J_{8,9}$ requires an ester on C-9 to be α. A similar situation exists in the case of eupatocunin (**6**),[7] for which $J_{8,9}$ was reported as 3 Hz and where the configuration at C-9 remained indeterminate.[25]

To settle the uncertainty about the distribution of the two ester functions between C-3 and C-8 and the stereochemistry at C-9, an X-ray analysis of **4a** was undertaken. Crystal data are listed in Table III; Figure 2 is a stereoscopic drawing of the molecule which, in view of the positive CD, also represents the absolute configuration of the molecule for the reasons adduced earlier in the case of **1e** (see Table IV for lactone ring torsion angles). The 2-methylbutyrate ester function is attached to C-9 and β, as is the acetate on C-3 and the hydroxyl on C-8. As surmised, the conformation resembles that of eupaformonin, with the C-4 methyl projecting below the plane and

the C-10 methyl above the plane of the ten-membered ring. Tables VIII, IX, and X, containing bond lengths, bond angles, and torsion angles, and Tables XIII and XIV, listing final atomic and final anisotropic thermal parameters, are available as supplementary material.

Experimental Section[26]

Extraction of *E. recurvans*. Above the ground parts of *Eupatorium recurvans* Small, collected by Dr. R. K. Godfrey on August 31, 1968, in the pine flatwoods between Cedar Key and Chiefland, Levy Co., Fla. (Godfrey #68143 on deposit in The Florida State University herbarium),[27] wt 20 kg, were extracted with $CHCl_3$ and worked up in the usual fashion[29] to give 180 g of extract. A 100-g amount of the crude extract was chromatographed on 980 g of silicic acid (Mallinckrodt 100 mesh) with solvents of increasing polarity, 500-mL fractions being collected. Elution with benzene and benzene–$CHCl_3$ (fractions 1–58) gave 0.45 g of a crystalline triterpene mixture. Elution of the silicic acid column with $CHCl_3$ (fractions 59–132) gave a gum which was rechromatographed over 150 g of silicic acid ($CHCl_3$) to give a crystalline mixture of **1e** and **4a**, which was separated by LC using an EtOAc–benzene (1:4) solvent system and a Porasil column. Elution of the original silicic acid column with MeOH–$CHCl_3$ (1:24) (fractions 138–144) gave **1a** as the major compound.

Characterization of the Lactones. Lactone **1a**, wt 16 g, mp 185–186 °C, was recrystallized from EtOAc–MeOH: $[\alpha]_D$ +42.3° (*c* 3,01, $CHCl_3$); CD curve $[\theta]_{273}$ −4020; IR bands at 3450, 3430, 1760, 1740, 1650, 1250, 1160, and 1060 cm^{-1}; strong UV end absorption.

Anal. Calcd for $C_{22}H_{30}O_8$: C, 65.55; H, 7.16; O, 30.30; mol wt, 422.1940. Found: C, 65.20; H, 6.93; O, 30.49; mol wt (MS), 422.1927.

Other important mass spectral peaks were at *m/e* 363 ($M^+ - C_2H_3O_2$), 321 ($M^+ - C_5H_6O_2$), 261 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2$), and 243 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2 - H_2O$).

A solution of 0.213 g (6.8×10^{-4} mol) of (±)-α-phenylbutyric anhydride and 0.057 g of **1a** (1.2×10^{-4} mol) in 2 mL of pyridine was allowed to stand at room temperature for 48 h. Excess anhydride was destroyed by adding 2 mL of water and allowing the mixture to stand at room temperature for 12 h. The solution was extracted with ether, and the extract was washed with water, three 10-mL portions of 5% $NaHCO_3$ solution, and again several times with water. The combined aqueous layers were washed with $CHCl_3$, acidified with 1 N H_2SO_4, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and evaporated; this afforded 0.087 g of α-phenylbutyric acid (pure by TLC criteria), $[\alpha]_D$ −0.87°. This corresponded to an optical yield of 9.2%.

Acetylation of 0.4 g of **1a** with acetic anhydride–pyridine furnished **1b** and **1c**, which were separated by preparative TLC (EtOAC–benzene, 1:1). Yield of gummy **1b**, 0.13 g: IR bands at 3490, 1760, 1740, and 1240 cm^{-1}.

Anal. Calcd for $C_{24}H_{32}O_9$: mol wt, 464.2046. Found: mol wt (MS), 464.2047.

1c, yield 0.21 g, was also gummy and had IR bands at 1760, 1740, and 1240 cm^{-1}.

Anal. Calcd for $C_{26}H_{34}O_{10}$: mol wt, 506.2152. Found: mol wt (MS), 506.2150.

Lactone **1e**, yield 160 mg, had mp 113–114 °C after recrystallization from EtOAc–hexane: $[\alpha]_D$ +52.9° (*c* 0.945, $CHCl_3$); CD curve $[\theta]_{267}$ −2440 (MeOH): IR bands at 3500, 1750, 1730, 1650, 1240, 1145, and 1085 cm^{-1}; strong UV end absorption. The mass spectrum did not exhibit the molecular ion; important peaks were found at *m/e* (% composition) 347 ($M^+ - C_2H_3O_2$, 11.9), 305 ($M^+ - C_5H_9O_2$, 83.2), 263 ($M^+ - C_5H_9O_2 - C_2H_2O$, 56), 262 ($M^+ - C_2H_2O - C_5H_{10}O$, 7.7), 245 ($M^+ - C_2H_4O_2 - C_5H_9O_2$, 54.2), 244 ($M^+ - C_2H_4O_2 - C_5H_{10}O_2$, 16.4), 227 (23), 199 (16.4), 167 ($C_9H_{11}O_3$, 17.6) and 163 ($C_{10}H_{11}O_2$, 43.5).

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; O, 27.55. Found: C, 64.86; H, 7.34; O, 27.59.

Acetylation of 20 mg of **1e** with acetic anhydride–pyridine gave **1f** as a gum: IR bands at 1750, 1730, and 1250 cm^{-1}. The low-resolution mass spectrum exhibited diagnostic peaks at *m/e* 448 (M^+), 389 ($M^+ - C_2H_3O_2$), 347 ($M^+ - C_5H_9O_2$), and 227 ($M^+ - 2C_2H_4O_2 - C_5H_9O_2$).

Anal. Calcd for $C_{24}H_{32}O_8$: mol wt, 448.2097. Found: mol wt (MS), 448.2097.

Lactone **4a**, wt 85 mg, had mp 129–131 °C after recrystallization from EtOAc–hexane: $[\alpha]_D$ −82.0° (*c* 1.26, $CHCl_3$); CD curve $[\theta]_{264}$ +1250 (MeOH); IR bands at 3420, 1730, 1650, 1235, 1140, and 1055 cm^{-1}; strong UV end absorption.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44; O, 27.55; mol wt, 406.1990. Found: C, 64.86; H, 7.34; O, 27.40; mol wt (MS), 406.1951.

Other significant peaks in the high-resolution mass spectrum were at *m/e* (% composition) 347 ($M^+ - C_2H_3O_2$, 18.0), 305 ($M^+ - C_5H_9O_2$, 100), 263 ($M^+ - C_2H_2O - C_5H_9O_2$, 11.1), 262 ($M^+ - C_2H_2O - C_5H_{10}O_2$, 14.3), 261 ($M^+ - C_2H_3O - C_5H_{10}O_2$, 3.5), 245 ($M^+ - C_2H_4O_2 - C_5H_9O_2$, 24), 244 ($M^+ - C_2H_4O_2 - C_5H_{10}O_2$, 21), 227 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2 - H_2O$, 18.7), 226 ($M^+ - C_2H_4O_2 - C_5H_{10}O_2 - H_2O$, 11.6), 199 ($C_{14}H_{15}O$, 19.3), and 166 ($C_9H_{10}O_3$, 30.7).

Acetylation of 20 mg of **4a** with acetic anhydride gave **4b** as a gum. The low-resolution mass spectrum exhibited diagnostic peaks at *m/e* 448 (M^+), 389 ($M^+ - C_2H_3O_2$), 347 ($M^+ - C_5H_9O_2$), and 227 ($M^+ - 2C_2H_4O_2 - C_5H_9O_2$).

Oxidation of 1a. A solution of 0.100 g of **1a** in 10 mL of anhydrous ether was stirred at room temperature with 0.100 mg of activated MnO_2, the reaction being followed by TLC. After 4 days, the mixture was filtered and the precipitate washed with ether. The combined filtrate and washings were evaporated, and the residue was purified by preparative TLC (MeOH–$CHCl_3$, 1:19). The major band yielded 80 mg of starting material. A less polar minor band yielded aldehyde **1d** as a gum whose mass spectrum exhibited significant peaks at *m/e* 420 (M^+), 361 ($M^+ - C_3H_2O_2$), 319 ($M^+ - C_5H_9O_2$), 276 ($M^+ - C_5H_9O_2 - C_2H_3O_2$), and 241 ($M^+ - C_2H_3O_2 - C_5H_{10}O_2 - H_2O$).

Oxidation of 1b. To a solution of 0.100 g of **1b** in 10 mL of acetone cooled to 0 °C was added dropwise with stirring Jones reagent until the solution remained red. Stirring was continued for an additional 30 min, at which time excess reagent was destroyed by addition of 2-propanol. After filtration, the filtrate and washings were evaporated; preparative TLC of the residue yielded 15 mg of **2a**, 20 mg of **2b**, and 25 mg of **3** as gums. The IR spectrum of **2a** had bands at 1770 and 1750 cm^{-1}.

Anal. Calcd for $C_{24}H_{30}O_{10}$: mol wt, 478.1839. Found: mol wt (MS), 478.1840.

Other significant peaks in the mass spectrum were at *m/e* 419 ($M^+ - C_2H_3O_2$), 377 ($M^+ - C_5H_9O_2$), 376 ($M^+ - C_5H_{10}O_2$), and 316 ($M^+ - C_5H_{10}O_2 - C_2H_4O_2$).

The IR spectrum of **2b** had bands at 3490, 1760, 1740, and 1730 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_9$: mol wt, 394.1264. Found: mol wt (MS), 394.1267.

Other significant peaks in the mass spectrum were at *m/e* 335 ($M^+ - C_2H_3O_2$), 334 ($M^+ - C_2H_4O_2$), and 274 ($M^+ - 2C_2H_4O_2$).

The IR spectrum of **3** had bands at 3490, 1760, and 1745 cm^{-1}.

Anal. Calcd for $C_{24}H_{32}O_{10}$: mol wt, 480.1995. Found: mol wt (MS), 480.1994.

X-Ray Analysis of 1e. Intensity data were measured on a Hilger-Watts automatic form circle diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The size of the crystal used for data collection was approximately 0.5 × 0.5 × 0.7 mm. There were 1725 independent reflections for $\theta < 57°$, of which 1628 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[30] and was refined by full matrix least squares. In the early stages of refinement it became apparent that C-19 of the isovalerate (see Figure 1, C-4′ in the usual numbering) was disordered. Atom C-19 was replaced by two atoms, C-19A and C-19B, with occupancy factors of 0.75 and 0.25, respectively. With these occupancy factors, the isotropic temperature factors for the two partial atoms were about the same. C-20 serves as the terminal methyl carbon for both C-19A and C-19B. In the final refinement, anisotropic thermal parameters were used for all carbon and oxygen atoms except C-19B and isotropic temperature factors were used for C-19B and the hydrogen atoms. The hydrogen atoms were not refined. The final unweighted and weighted *R* values were 0.057 and 0.079 for the 1628 observed reflections. There were no peaks on the final difference map greater than ±0.2 e/A^{-3}.

X-Ray Analysis of 4a. The size of the crystal used for data collection was approximately 0.15 × 0.20 × 0.9 mm. Of the 1520 independent reflections for $\theta < 57°$, 1306 were considered to be observed. The structure was solved by the multiple solution procedure and was refined by full matrix least squares. Anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were $R = 0.051$ and $R_w = 0.057$ for the 1306 observed reflections. There were no peaks greater than ±0.2 e/A^{-3} on the final difference map.

Extraction of Other *Eupatorium* Species. Chloroform extracts of a previously studied[31] collection of *E. leptophyllum* DC. did not furnish a significant quantity of sesquiterpene lactone fraction; neither did two collections of *E. compositifolium* Walt. (Godfrey #61643 and 67964) nor additional collections of previously studied[32,33] *E. capillifolium* (Lam.) Small and *E. pinnatifidum* Ell.[34]

Registry No.—**1a**, 66922-25-6; **1b**, 66922-26-7; **1c**, 66922-27-8; **1d**, 66922-28-9; **1e**, 66922-29-0; **1f**, 66922-35-8; **2a**, 66922-30-3; **2b**, 66922-31-4; **3**, 66922-32-5; **4a**, 66922-33-6; **4b**, 66922-34-7; (±)-α-phenylbutyric anhydride, 66922-36-9; (−)-α-phenylbutyric acid, 938-79-4.

Supplementary Material Available: Tables V–XIV listing bond lengths, bond angles, torsion angles, final atomic parameters, and final anisotropic thermal parameters of compounds **1e** and **4a** (12 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Work at The Florida State University was supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

(2) Recipient of a grant from the Belgian Commission for Educational Exchange with the U.S.A. and a Fulbright-Hayes Travel Award.

(3) W. Herz and R. P. Sharma, *J. Org. Chem.*, **41**, 1015, 1021 (1976). These papers also contain references to earlier work on *Eupatorium* species.

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(6) For other recent reports on sesquiterpene lactones from *Eupatorium* species, see (a) K. H. Lee, T. Kimura, M. Okamoto, C. M. Cowherd, A. T. McPhail, and K. D. Onan, *Tetrahedron Lett.*, 1051 (1976) (the lactone named eupahyssopin by these workers is the same substance as eupasoppin); (b) K. H. Lee, T. Kimura, M. Haruna, A. T. McPhail, and K. D. Onan, *Phytochemistry*, **16**, 1068 (1977); (c) F. Bohlmann, P. K. Mahanta, A. Suwita, A. A. Natu, C. Zdero, W. Dorner, D. Ehlers. and M. Grenz, *ibid.*, **16**, 1973 (1977).

(7) Our negative results on *E. compositifolium* are in agreement with ref 6c.

(8) Identification of the lactone ring terminus with H_d and the proton under one of the ester side chains with H_e was based on chemical and solvent shifts in a number of related compounds.

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(13) The generalization[19] that $J_{7,13}$ in heliangolides < 3 Hz does not hold for heliangolides possessing a 9,10 double bond.

(14) The values of $J_{1,2a}$ and $J_{1,2b}$ listed in Table I for **1a–e** do not unambiguously distinguish between α and β orientation of the hydroxyl group on C-1.

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(17) This is evident from a drawing[12a] showing the conformation of eupacunin *o*-bromobenzoate as well as from diagrams of the crystal structures of this substance and eupacunoxin *m*-bromobenzoate kindly furnished by Professor G. A. Sim. The planar representations of these compounds and of their congener eupacunolin by Kupchan and co-workers are somewhat confusing as they show a β-orientated hydroxyl group on C-1, although the hydroxyl group is actually α with respect to the plane of the ten-membered ring. The confusion results from depicting C-1 as a reentrant carbon atom, which our planar formulas **1** and **5** avoid. For comments on the problem of representing germacranolides and suitable conventions, see D. Rogers, G. P. Moss, and S. Neidle, *J. Chem. Soc., Chem. Commun.* 142 (1972).

(18) Small samples of eupacunin (**5a**), eupacunoxin (**5b**), and eupatocunin (**6**) were supplied by the Developmental Therapeutics Program, Chemotherapy, National Cancer Institute. Unfortunately, they were not sufficiently pure enough (due to polymerization) to permit the measurement of their CD's for the purpose of establishing their absolute configurations by comparison with the CD's of **1a** and **1e** (for eupacunin and eupacunoxin) and **4a** (for eupatocunin). The chemical shifts and coupling constants exhibited by **5a** and **5b** were essentially identical with those of **1e** in the same solvent (except for the protons of the ester side chain).

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(25) The NMR spectrum of crude eupatocunin (see ref 18) at 270 MHz was not sufficiently well resolved to permit analysis. However, it seems very likely that its stereochemistry at C-9 is identical with that of **4a**.

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(33) Plants grouped under the name *E. pinnatifidum* are temporary diploid hybrids or hybrid segregates of strikingly distinct morphology with *E. perfoliatum* as one parent and *E. capillifolium* or perhaps *E. compositifolium* as the other.[35] The plant material duplicates that of the collection previously[28,32] referred to as *E. capillifolium* x *perfoliatum*.

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Adjacent Lone Pair (ALP) Effects in Heteroaromatic Systems. 1. Isotope Exchange of Ring Hydrogens in Alkylimidazoles

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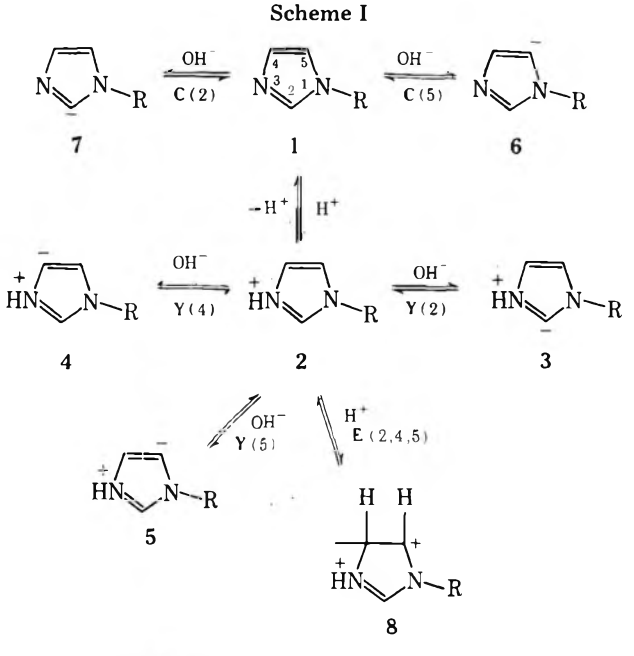
Solvent deuterium isotope exchange (D_2O, 50 °C) is readily observed above pD 5 at C-2 in imidazole and its *C*- or *N*-alkyl derivatives. The intermediate is an ylide, formed by base-catalyzed abstraction of H-2 from the imidazolium ion [path Y(2)]. A similar, but much slower, exchange can be observed at C-4 [Y(4)] or at C-5 [Y(5)] at 100 °C. In strongly alkaline media, NH–imidazoles exchange more rapidly at C-4 or C-5 by a carbanion pathway (C), involving C-proton abstraction from the neutral molecule; in *N*-alkylimidazoles, however, *only* H-5 exchanges by the C pathway [C(5)]. The resistance to carbanion formation at C-4 is ascribed to the *adjacent lone pair* (ALP) effect—a significant electrostatic repulsion between lone pairs in the coplanar, sp^2 orbitals at N-3 and C-4. The partial contributions of the Y and C pathways are evaluated from kinetic data at pD 10–11 and in 1 N NaOD, respectively. For 1-methylimidazole (1 N NaOD, 100 °C), C(5) exchange occurs 15 times faster than Y(5), and Y(5) exchange is three times faster than Y(4). NMR signals for H-4 and H-5 are assigned on the basis of (1) spin-decoupling experiments, (2) nuclear Overhauser enhancements, (3) chemical transformations of 1-methylimidazole-d_2, and (4) $\Delta\delta$ values. It is shown that ring protons adjacent to *N*-methyl can be differentiated from other ring protons by a characteristic shift in δ with variation of solvent ($\Delta\delta$); furthermore, H-5 appears at higher field than H-4 in nonpolar solvents, and this order is reversed for polar solvents.

A number of ring-fluorinated imidazoles have recently become available through a photochemical synthesis developed in this laboratory.[2] In preparation for various biochemical and pharmacological studies with these and related compounds,[3] we explored the possibilities for isotopic labeling of the ring by means of direct exchange with D_2O and T_2O. The initial results were sufficiently at variance with our expectations (based on literature data for imidazole itself)[4] that a more detailed study seemed desirable both for theoretical and practical ends. The study involved an examination of both alkyl- and electronegatively-substituted imidazoles, and led to the formulation of some general concepts regarding C–H acidity in these heteroaromatic systems. In this first paper of the series,[5] we summarize known pathways for exchange in imidazoles, present new data on the exchange of ring hydrogens in both *N*-methyl- and *C*-methylimidazoles, and offer interpretations which may have more general applicability.

Earlier studies on isotope exchange have dealt with imidazole,[4] *N*-methylimidazole,[4] and 4(or 5)-substituted imidazoles such as histidine, histamine, and their derivatives.[6] Information on the effects of an electronegative substituent on rates and sites of exchange has been limited to one report on nitroimidazoles.[7] Detailed kinetic studies with imidazole[4e,f] and with *N*-methylimidazole[4e,f] have demonstrated the existence of three basic pathways for exchange, which we shall designate the ylide (Y), carbanion (C), and electrophilic (E) pathways (Scheme I). Symbols, such as Y(2) and C(5), designate the specific ring positions under discussion. Each pathway prevails in a different pH region, and the pathways show large differences in $\Delta F^{\ddagger}$.

Scheme I



a, R = H; b, R = alkyl

The most facile exchange, which occurs at C-2, has been studied at 25–80 °C and follows the rate expressions

$$\text{rate} = k_Y[\text{ImH}^+][\text{OH}^-]$$

$$k_{obsd} = k_Y K_w/(K_1 + [\text{H}^+]) \quad (1)$$

in which K_1 is the dissociation constant for the imidazolium ion ($\text{ImH}^+ \rightarrow \text{Im}$) and K_w is the ion product for water. This rate law is consistent with the log k_{obsd}/pH profile,[8] and is supported by the demonstration of an even more facile exchange in 1,3-dimethylimidazolium ion (in which the positive charge cannot be lost by dissociation).[4f] For *N*-alkylimidazoles (**1b**), the constancy of k_{obsd} in the alkaline region (Figure 1, curve B) results from the fact that an increase in $[\text{OH}^-]$ is directly offset by a decrease in $[\text{ImH}^+]$ (**2b**). For imidazole itself, however (Figure 1, curve A), k_{obsd} decreases again at high pH due to the formation of the (presumably unreactive) Im^- species. In both compounds, at moderate temperatures and at pH values between 7 and 11, total exchange at C-2 can be achieved conveniently without measurable exchange at C-4 or C-5 (Table I).

Exchange at C-4 or C-5 is very much slower than at C-2 (Table I), earlier experimental data having been obtained at 160–190 °C;[4e,f] yet, the log k_{obsd}/pH profiles suggest exchange mechanisms, Y(4) and Y(5), analogous to Y(2). At 50 °C and neutral or mildly alkaline pH, exchange at C-2 (in 1-methylimidazole) occurs 10^4–10^5 as rapidly as at C-4 or C-5. This relatively high kinetic acidity of H-2 ($t_{1/2}$ = 42 min), and its strikingly greater reactivity than that of H-4 or H-5, may be the combined result of several phenomena: (1) the inductive influence of two nitrogen atoms on C-2 vs. one on C-4 or C-5; (2) the effect of a full positive charge on C-2 vs. a partial charge on C-4 or C-5; (3) the possibility of slightly greater s character

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Table I. Solvent Deuterium Exchange of Ring Protons in Alkylimidazoles[a]

imidazole	registry no.	Y(2),[b] 10^2k_{obsd}	C(5),[c] 10^3k_{obsd}	Y(4), 10^5k_{obsd}	Y(5),[d] 10^5k_{obsd}
1-methyl	616-47-7	1.65	1.67	4.13[c,d]	11.3
1,2-dimethyl	1739-84-0		0.42	4.13[c,d]	4.13
1,4-dimethyl	6338-45-0	0.92	0.36		1.49
1,5-dimethyl	10447-93-5	1.43		3.72[c,d]	
imidazole	288-32-4	0.58	6.47	3.85[d]	3.85
2-methyl	693-98-1		1.07	3.85[d]	3.85
4-methyl	822-36-6	0.50	23.1		3.50

[a] All rates are min^{-1}. [b] At 50 °C, pD 10–11; under these conditions, no exchange is observed at H-4 or H-5 for any compound in 720 h. [c] At 100 °C, 1 N NaOD. [d] At 100 °C, pD 10–11.

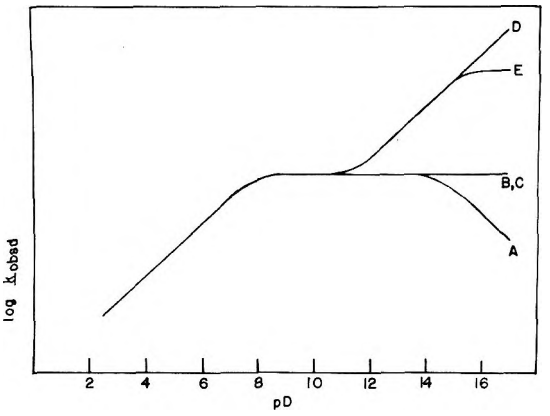
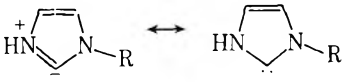


Figure 1. Theoretical curves illustrating the several pathways for exchange of imidazole ring protons, and the effect of pD and change in the state of ionization: A, path Y(2) for imidazole; B, path Y(2) for 1-methylimidazole; C, path Y(4) for 1-methylimidazole; D, exchange of H-5 in 1-methylimidazole [Y(5) below and C(5) above, pD 11]; E, exchange of H-4 and H-5 in imidazole [Y(4,5) below and C(4,5) above, pD 11]. No numerical relationships are implied by the coincidence of the curves.

in the C(2)–H bond; and (4) enhanced stabilization of the ylide intermediate (3) through resonance with a neutral carbene form (9), which resonance stabilization is not available to 4 or 5.



3 9

The protons at C-4 and C-5 of 1-methylimidazole show relatively little difference in rate of exchange by the Y pathway up to pH ~12 (Table I and ref 4f); curiously, however, one of these hydrogens exchanges much more rapidly than the other at higher pH (Figure 1, curves C and D), with a linear dependence of k_{obsd} on base concentration.

$$\text{rate} = k_C[\text{Im}][OH^-]$$

$$k_{obsd} = k_C[OH^-] \quad (2)$$

The data are consistent with path C, involving the slow formation of an sp^2 carbanion (6) from the neutral imidazole species. Presumably, H-2 in 1-methylimidazole could also undergo exchange by a carbanion (7) pathway [C(2)], if the much more facile Y(2) pathway did not exist.[5] For imidazole itself, k_{obsd} for the C(5) pathway approaches a constant value at high pH (Figure 1, curve E), because the increase in $[OH^-]$ is offset by a decrease in [Im]. In the present study, we demonstrate that the more acidic proton in 1-methylimidazole is H-5, and not H-4 as previously assigned.[4f]

A third pathway for exchange (E) is found in strongly acidic media.[4f] At all three ring-carbon positions, log k_{obsd} increases directly with H_0, suggesting proton attack on 2

Table II. NMR Signal Assignments for *N*-Methylimidazole Ring Protons

ref	solvent	δ, ppm H-2	H-4	H-5
10a	$CDCl_3$	7.41	6.86	7.05
4c		7.41	6.86	7.05
10b		7.47	7.08	6.88
10c,f		7.43	7.05	6.90
a		7.41	7.03	6.87
10d	C_6D_{12}	7.41	7.05	6.88
4f	D_2O	7.63	7.13	7.03
10e		7.60	7.08	7.00
a		7.57	7.00	7.07

[a] Present investigation.

$$\text{rate} = k_E[\text{ImH}^+][H_0]$$

$$k_{obsd} = k_E[H_0] \quad (3)$$

and the intermediacy of species such as 8. In this case, H-2 is ~100-fold less reactive to exchange than H-4 or H-5, presumably because amidine resonance must be lost in the course of proton attack at C-2.

Since the carbanion pathway (C) has been observed only in very strongly alkaline media and at high temperature, it has received relatively little attention.[4f] As the basicity of the imidazole ring is reduced, and the acidities of the ring hydrogens are enhanced, by the introduction of electronegative groups, exchange by path C becomes significant at lower pH and lower temperature and may, in fact, replace path Y in importance.[5] Accordingly, we found it necessary to explore the chemistry of path C more fully and, in particular, to account for the differences in reactivity at C-4 and C-5.

Results and Discussion

NMR Assignments. In *N*-alkylimidazoles, H-4 and H-5 generally have different δ values. Since the kinetics of solvent deuterium isotope exchange are most conveniently followed by NMR changes, there must be an unequivocal correlation of the two protons with their NMR signals. In Table II are summarized the δ assignments given to the ring protons of *N*-methylimidazole in previous studies;[10] in general, these assignments were based on a qualitative evaluation of electronic effects and are inconsistent with respect to H-4 and H-5. The signal at lowest field is unquestionably that for H-2.[11] On the basis of three experimental criteria, we have concluded that the ring proton signal at highest field (in nonpolar solvents) corresponds to H-5, and that H-5 is much more acidic than H-4. The order of the H-4 and H-5 signals is reversed in shifting from solvent $CDCl_3$ to D_2O. In earlier work,[4f] path C has been ascribed to exchange at C-4; as a result of our demonstration of this solvent reversal, however, the explanation offered by Wong and Keck for the order of acidities of H-4 and H-5 becomes invalid. The same NMR criteria were

Table III. NMR Solvent Shifts ($\Delta\delta$) for *N*-Methylimidazoles

imidazole	position	δ, ppm			Δδ, ppm	
		$CDCl_3$	Me_2SO-d_6	D_2O[a]	Δ_1[b]	Δ_2[c]
1-methyl	H-2	7.41	7.55	7.57	−0.14	−0.16
	H-4	7.03	6.88	6.99	+0.15	+0.04
	H-5	6.87	7.08	7.07	−0.21	−0.20
1,2-dimethyl	H-4	6.87	6.68	6.84	+0.19	+0.04
	H-5	6.77	6.97	6.97	−0.20	−0.20
1,4-dimethyl	H-2	7.25	7.37	7.45	−0.12	−0.20
	H-5	6.55	6.75	6.82	−0.20	−0.27
1,5-dimethyl	H-2	7.35	7.45	7.48	−0.10	−0.13
	H-4	6.74	6.59	6.73	+0.15	+0.01

[a] Adjusted to pD 10 to exclude partial ring protonation. [b] $\Delta_1 = \delta_{CDCl_3} - \delta_{Me_2SO\text{-}d_6}$. [c] $\Delta_2 = \delta_{CDCl_3} - \delta_{D_2O}$.

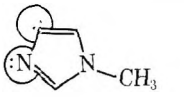
applied to several other *N*-methylimidazoles, both to confirm the validity of the methods and to extend their applicability.

1. Spin-Decoupling and NOE Experiments. While the NMR signals for H-4 and H-5 are primarily triplets (in *N*-methylimidazole),[12] the signal which occurs at higher field in $CDCl_3$ shows significant fine structure, which we attribute to four-bond coupling ($J < 0.3$ Hz) with the protons of the *N*-methyl group. Irradiation at the *N*-methyl frequency results in sharpening of the triplet at δ 6.87 and loss of fine structure; no change is seen in the signal at δ 7.03. Assignment of the higher field signal to H-5 receives further support from nuclear Overhauser enhancement (NOE) experiments: saturation of the *N*-methyl protons by double resonance produced a 13% increase in peak intensity for the signal at δ 6.87 and a 3% increase for that at δ 7.03. The validity of these criteria was confirmed by examination of 1,4- and 1,5-dimethylimidazole, whose structures had been established by chemical degradation[13b] and by unequivocal synthesis.[13c,d]

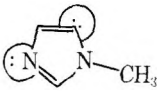
2. Solvent Effects on δ Values. In a variety of azole systems, δ values for ring protons adjacent to *N*-alkyl groups have been found to have a solvent dependence which distinguishes them from other ring protons. In the original study,[10c] *N*-methylimidazole was the only imidazole system subjected to this analysis; we have extended the method to a variety of substituted *N*-methylimidazoles and, on the basis of 20 compounds examined to date, have found no exceptions[14] to the following rule: for protons adjacent to the *N*-methyl group, $\delta_{CDCl_3} - \delta_{Me_2SO\text{-}d_6}$ (= Δ_1) or $\delta_{CDCl_3} - \delta_{D_2O}$ (= Δ_2) have significant negative values (−0.1 to −0.6); for any remaining ring protons, these Δ values are either close to zero or are positive (Table III). The Δδ test provides the same proton assignments for *N*-methylimidazole as were obtained by spin-decoupling and NOE techniques. The reliability of this analytical tool is strengthened by the consistency of the results for the known 1,4- and 1,5-dimethylimidazoles (Table III).

3. Chemical Transformation. *N*-Methylimidazole was subjected to exchange in 1 N NaOD at 100 °C; after 16 h, H-2 and one of the remaining protons had exchanged completely, while the third proton (at δ 6.99 in D_2O and 7.03 in $CDCl_3$) had exchanged only to a negligible extent. This product, *N*-methylimidazole-d_2, was nitrated[13a] to give a mixture containing 90% 1-methyl-4-nitroimidazole-d_2 and 10% 1-methyl-5-nitroimidazole-d_1. Since the structures of the isomeric nitro derivatives had been established by chemical degradation[13a] and since all proton signals for the two isomers show uniquely different δ values,[10b] it was relatively simple to use NMR not only to determine the ratio of the isomers following nitration, but also to demonstrate that the proton surviving exchange in *N*-methylimidazole is H-4 (δ 7.03 in $CDCl_3$). Furthermore, spin decoupling has no effect on the single ring proton signal of *N*-methylimidazole-d_2. On the basis of the NMR assignments and the nitration results, we conclude that H-5 had exchanged in preference to H-4.

Basis for Selective Exchange in *N*-Methylimidazoles. The carbanion intermediates necessary for exchange at C-4 or C-5 by path C are **10** and **11**, respectively. It is evident that **10** contains lone pairs in *adjacent*, coplanar, sp^2 orbitals, while the same lone pairs in **11** are *nonadjacent*. Thus, electrostatic



10



11

repulsion alone may be sufficient to render **10** energetically less favorable than **11**. The energy difference between these two carbanions must be significant since, at 100 °C, H-5 can be exchanged completely by path C without measurable C exchange at H-4 over 90–100 h; even at 163 °C, there is no evidence for the formation of **10**.[15] This selectivity in carbanion formation, which we find to be general for *N*-alkylimidazoles, we have named the *adjacent lone pair* (ALP) effect.[16]

Unusual exchange properties of pyridine and diazine rings have been interpreted on the basis of such electrostatic interaction.[17] In *N*-alkylpyridinium ions and in pyridine *N*-oxide, the order of base-promoted hydrogen exchange is H-2 > H-3 > H-4;[18] this order is consistent with labilization of the ring hydrogens via a combination of σ-, π-, and field-inductive transmission from the positively-charged ring nitrogen atom, and with damping of the effect with increasing distance. In pyridine itself, however, H-2 is the least acidic proton;[18] it is reasonable that the sp^2 lone pair on nitrogen would resist strongly the creation of an sp^2 carbanion at the most proximate ring carbon atom. The ALP effect is eliminated as soon as the lone pair on nitrogen is utilized in covalent bonding, even by protonation.[19]

For an N-alkylimidazole, the rate of exchange by path Y(4) or Y(5) is independent of pD at any value at least 1.5 units higher than its p*K* (Figure 1, curve C). Accordingly, paths Y and C can be differentiated by comparison of exchange rates at pD 10–11, in which range the base-dependent path C makes a negligible contribution, and in 1 N NaOD, in which medium exchange by path C greatly overwhelms that by path Y. For 1-methylimidazole in 1 N NaOD at 100 °C, C(5) is 15 times as fast as Y(5) and 40 times as fast as Y(4) (Table I). A very slow C(4) pathway is ruled out by the fact that exchange at this position is no faster than 1 N NaOD than at pD 10–11.

Exchange in *C,N*-Dimethylimidazoles. The ALP effect was subjected to further validation by study of the isomeric *C,N*-dimethylimidazoles. In the case of 1,2-dimethylimidazole, δ values for H-4 and H-5 were assigned on the basis of spin-decoupling experiments and Δδ values (Table III). In 1 N NaOD at 100 °C, C(5) exchange occurs ca. tenfold as fast as Y(5) or Y(4), the latter exchanges showing essentially the same rate (Table I). As in the case of 1-methylimidazole, no C(4) exchange can be detected (cf. 12) after 5 days at 100 °C. The 2-methyl group, by virtue of its electron-releasing ability,

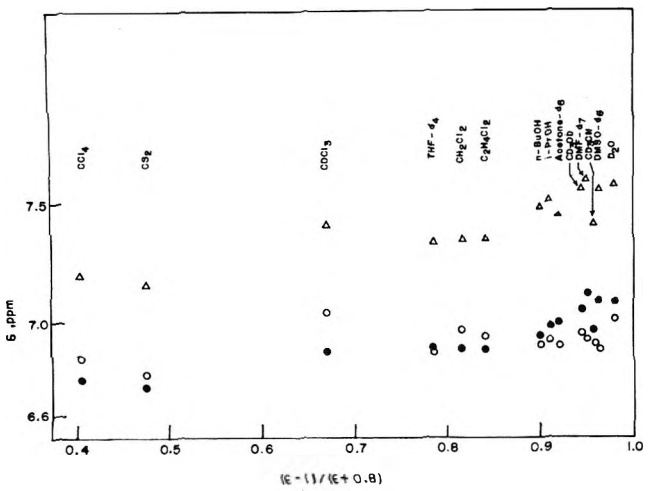
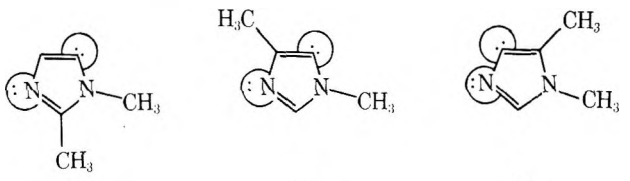


Figure 2. Plot of NMR δ values for ring protons of *N*-methylimidazole vs. a function of ε, the solvent dielectric constant: △, H-2; ○, H-4; ●, H-5. For each solvent, assignments of H-4 and H-5 were made on the basis of spin-decoupling experiments.

exerts a three- to fourfold decrease in the rate of C(5) or Y(5) exchange relative to 1-methylimidazole, but has practically no effect on Y(4).



12 13 14

The ALP effect is seen again in a comparison of 1,4- and 1,5-dimethylimidazoles (Table I) and their respective carbanions (**13** and **14**). In 1 N NaOD at 100 °C, C(5) exchange in 1,4-dimethylimidazole occurs 24 times as fast as Y(5) exchange, and 10 times as fast as Y(4) exchange in 1,5-dimethylimidazole.[20] In the latter compound, the rate of C-4 exchange is the same at pD 11 as in 1 N NaOD; thus, exchange at this position occurs only by path Y. The energetically unfavorable carbanion (**14**) may be capable of generation in the presence of a strong, nonaqueous base; this possibility is under investigation.

Exchange in NH–Imidazoles. As already indicated, the rate of Y(2) exchange in imidazole falls off in strong base (Figure 1, curve A) due to the formation of the Im^- species. A similar decrease in rate is to be expected for Y(4) and Y(5) exchange and, thus, k_Y for NH–imidazoles is best evaluated only at the lower pD (10–11). In fact, however, exchange at C-4 or C-5 in imidazole is considerably *faster* in 1 N NaOD than at lower $[OD^-]$. Based on an estimated $pK_2(D_2O) = 15.2$,[21] imidazole should be only partially in the Im^- form in this medium,[22] and the C–H bonds in imidazole may be sufficiently acidic to permit the transient existence of carbanion **15**; this species, as in the cases of **11**, **12**, or **13**, would not be

15

subject to the ALP effect at C-5. Since path C(5) is 170 times as fast as path Y(5) for imidazole (Table I), the effect of a high concentration of base in decreasing the rate of the Y(5) pathway is easily overwhelmed by its favorable effect on the C(5) pathway. A plot of log $k_{C(obsd)}$ vs. pD should follow the pK_2 titration curve (analogously to curve E of Figure 1), leveling off at base concentrations which are experimentally unattainable in D_2O. In accordance with the ALP effect, carbanion **15** has been formulated in the lower energy form; because of tautomerism, however, C-4 and C-5 are experimentally indistinguishable.

For 2-methylimidazole, pK_2 is ~0.6 unit higher than for imidazole;[23] accordingly, C(5) exchange should be favored by the greater concentration of neutral species present in 1 N NaOD, but retarded by the electron-releasing ability of the methyl group. As shown in Table I, 2-methylimidazole exchanges at C-5 ca. sixfold more slowly than does imidazole, suggesting the latter factor to be the more significant.

In 4-methylimidazole, C(5) exchange is much faster than for any other compound examined in this study. The result is surprising, since pK_2 for the compound is probably comparable to that for 2-methylimidazole and since the 4-methyl group should be somewhat more effective than 2-methyl in retarding carbanion formation at C-5 (cf. k_{obsd} values for 1,2- and 1,4-dimethylimidazole). At the present time, we cannot offer a reasonable explanation for this phenomenon.[5] Both 2- and 4-methylimidazole undergo C(5) exchange faster than their 1-methyl derivatives. Although deactivation by the 1-methyl group may be due simply to electron release, it is possible that this substituent offers significant steric hindrance to the formation of a solvated carbanion at the adjacent C-5 position.

In principle, the ALP effect should also exist between C-2 and N-3. Its occurrence or nonoccurrence cannot be determined with the present series of compounds, however, since Y(2) exchange may be 500–1000 times as fast as C(2) exchange (based on C(5) data). As demonstrated in the following paper,[5] studies with electronegatively-substituted imidazoles show that the ALP effect at C-2 is either much weaker than at C-4 or is absent entirely.

Buffer Catalysis. In principle, a proton exchange dependent on hydroxide ion should also be subject to catalysis by weaker general bases, although the magnitude of the catalysis may be immeasurably small. Since the ylide pathway for exchange requires proton abstraction from an already protonated species, this pathway should show particular sensitivity to buffer catalysis over a wide pH range. Relatively few attempts to demonstrate buffer catalysis of exchange in heteroaromatic systems have been recorded, with inconclusive results;[4g] in particular, Wong and Keck[4f] found no measurable phosphate buffer catalysis in Y(2) exchange in imidazole or *N*-methylimidazole. Preliminary to a more extensive investigation of this question, we have found that exchange of H-2 in *N*-methylimidazole at pD 4.9 *is* enhanced 4.3-fold in the presence of 1 M acetate buffer (0.2 M substrate, 50 °C). General base catalysis of the carbanion pathway should also be demonstrable and is described in the following paper.[5]

Solvent Effects (Δδ Values). We have shown that comparison of δ values for the C-4 and C-5 protons of 1-methyl- and 1,2-dimethylimidazole in several solvents offers a convenient and reliable means for assignment of the proton signals. The data of Table III demonstrate the need for caution, inasmuch as the order of these signals in $CDCl_3$ is reversed in D_2O for both compounds. As an extension of these observations, we have obtained δ values for *N*-methylimidazole protons in 14 solvents (Figure 2). The δ values do not provide a statistically acceptable correlation when plotted against solvent parameters such as E_T[24] or various functions of the dielectric constant (ε).[25] These δ values were obtained at a single concentration of *N*-methylimidazole; a more complete analysis would require extrapolation to zero concentration, although the effect of concentration may be too small[10e] to account for the several serious deviations in Figure 2. The basis for the overall effect of solvent polarity, as well as the differential effects at the several ring positions (Δδ values), are not

clear and are still under investigation. In any case, it is obvious from Figure 2 that the order of δ values for H-4 and H-5 in *N*-methylimidazoles is reversed in shifting from a nonpolar to a polar solvent, and that signal assignments cannot be made on the basis of electron density considerations alone.

Experimental Section[26]

Materials. 1-Methylimidazole, 2-methylimidazole, and 1,2-dimethylimidazole were obtained from commercial sources; NMR spectra showed these compounds to be of acceptable purity. Commercial samples of 4(5)-methylimidazole could not be freed of unidentified contaminants. This compound was prepared from acetol acetate, formaldehyde, and ammonia,[27] and purified by distillation: bp 90–92 °C (0.35 mm); NMR ($CDCl_3$), δ 2.25 (3 H, d, CH_3), 6.76 (1 H, m, H-4(5)), 7.55 (1 H, d, H-2).

1,4- and 1,5-Dimethylimidazoles. A solution of 4(5)-methylimidazole (2.46 g, 0.03 mol) in 3 mL of benzene was stirred at 5 °C while a solution of methyl iodide (4.68 g, 0.033 mol) in 2 mL of benzene was added over 10 min; the mixture was then heated at reflux for 30 min. Evaporation of the solvent gave a yellow oil which was dissolved in 20 mL of water. The solution was adjusted to pH 9.5 and was extracted with five 30-mL portions of chloroform. The combined extracts were washed with saturated brine and dried (Na_2SO_4). Evaporation of solvent gave 2.41 g of yellow oil which, according to its NMR spectrum, was composed mainly of ca. equal parts of the desired isomers. Separation was effected by chromatography on 320 g of neutral alumina and elution with chloroform–1% methanol, the 1,4 isomer emerging first in 32% yield; slower fractions provided the 1,5 isomer in 27% yield. Both compounds were obtained as oils, and were identified by mass spectra and by comparison of their NMR spectra with those of materials prepared by unequivocal synthesis.[13d]

Nitration of *N*-Methylimidazole-d_2. A solution of 1.0 g of *N*-methylimidazole in 10 mL of 1 N NaOD was heated at 100 °C for 16 h. The solution, after cooling, was extracted with five 15-mL portions of ethyl acetate. The combined extracts were washed with a small amount of saturated brine and dried (Na_2SO_4). Evaporation of the solvent gave a colorless oil (0.83 g); its NMR spectrum in both D_2O and $CDCl_3$ showed only one proton peak in the aromatic region, whose area was slightly less than one-third that of the *N*-methyl peak.

A solution of 0.50 g of this material in 1 mL of concentrated nitric acid was stirred at 0 °C while 2 mL of concentrated sulfuric acid was added in portions over 30 min. The mixture was boiled gently for 2 h, poured into 5 mL of cold water, and brought to pH 5 with 10% sodium hydroxide. A precipitate was collected (0.36 g), which was characterized by NMR and mass spectra as 2,5-dideuterio-1-methyl-4-nitroimidazole. Extraction of the filtrate provided an additional 0.16 g of nitrated material which, according to its NMR spectrum, was composed of the above compound and 2-deuterio-1-methyl-5-nitroimidazole in a 2:1 ratio. NMR spectral analysis was based on comparison with the spectra of the nondeuterated isomers,[7,10b] prepared by published procedures[13a] and separated by chromatography. 1-Methyl-4-nitroimidazole: NMR ($CDCl_3$) δ 3.76 (3 H, s, N-CH_3), 7.44 (1 H, br, H-2), 7.78 (1 H, d, J = 1.5 Hz, H-5). 1-Methyl-5-nitroimidazole: NMR ($CDCl_3$) δ 3.98 (3 H, s, N-CH_3), 7.59 (1 H, br, H-2), 8.05 (1 H, d, J = 1.2 Hz, H-4).

NMR Spectra. Values of δ and J were measured on a Varian HA-100 spectrometer relative to internal (or external) tetramethylsilane or to sodium 3-(trimethylsilyl)propionate-d_4 for D_2O solutions. Room temperature was maintained at 25 °C while the probe temperature was measured at 30 °C. Spin-decoupling and NOE experiments were performed in the usual manner.[28] A Varian A-60 spectrometer was used for kinetic measurements.

Kinetic Measurements. Sodium deuterioxide (40%) was obtained from BioRad Laboratories and D_2O from Aldrich Chemical Co. Solutions of the imidazoles in D_2O (0.2 M) were brought to the desired pD at a Corning pH meter (Model 101). Measured pD values were adjusted by addition of the correction factor 0.40.[29] NMR sample tubes containing the imidazole solutions were maintained at the desired temperature ±0.5 °C in a thermostatically controlled bath or by immersion in a steam cone. At various intervals, the tubes were plunged into an ice bath to quench the exchange reaction and then brought back to 25 °C for NMR measurement. Each signal was integrated four to six times and the results were averaged; deviations never exceeded 5%. Nonexchanging *C*- or *N*-methyl groups were used as internal integration standards. In the case of imidazole itself, the signal for sodium 3-(trimethylsilyl)propionate-d_4 was used as an integration standard; in parallel runs, internal sodium trimethylacetate was used with essentially the same results. No decomposition was observed for any of the compounds. Pseudo-first-order rate constants were determined graphically over two or more half-lives for Y(2) and C(5) exchanges, and over 1–2 half-lives for Y(4,5) exchanges. The values of k_{obsd} in Table I are averages of two to three runs, with deviations of 5–10%.

Registry No.—2,5-Dideuterio-1-methyl-4-nitroimidazole, 66769-96-8; 2-deuterio-1-methyl-5-nitroimidazole, 66769-97-9; 1-methyl-4-nitroimidazole, 3034-41-1; 1-methyl-5-nitroimidazole, 3034-42-2.

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(23) On the basis of the data then available, T. C. Bruice and G. L. Schmir [*J. Am. Chem. Soc.*, **80**, 148 (1958)] were able to demonstrate an approximately linear correlation between pK_1 and pK_2 values for imidazoles. We have verified the linear relationship with additional pK data (to be published)

and, based on pK_1 for 2-methylimidazole as 7.85 (H_2O), estimate pK_2 = 15.1 (H_2O) or 15.8 (D_2O).
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Adjacent Lone Pair (ALP) Effects in Heteroaromatic Systems. 2. Isotope Exchange of Ring Hydrogens in Nitro- and Fluoroimidazoles

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The ring protons of nitro- and fluoroimidazoles (and their *N*-methyl derivatives) undergo base-catalyzed exchange in D_2O by a combination of carbanion (C) and ylide (Y) pathways. In the C pathway, a proton is abstracted from the neutral imidazole species, and in the Y pathway, from the imidazolium ion. In 4-X-imidazoles, C exchange occurs more readily at C-5 than at C-2, log k_C correlating with σ_o^0 for the NH- and with σ_p^0 for the *N*-methyl series. For 1-methyl-4-nitroimidazole, $t_{1/2}$ = 2 min at C-5 (50 °C, 0.2 N NaOD). In 1-methyl-5-X-imidazoles, exchange at C-4 occurs only by the Y pathway, carbanion formation in the neutral species being retarded by the *adjacent lone pair* (ALP) effect at N-3. The same effect is seen in the lack of C exchange at C-4 in 1-methyl-2-X-imidazoles. The ALP effect is considerably weaker or nonexistent at C-2. Most exchanges *across* the ring show correlations of log *k* with σ_m^0. 4-Alkylimidazoles (but not 1,4-dialkylimidazoles) show enhanced C exchange at C-5, which may result from the existence of a trace concentration of the ketimine tautomer. Enhanced exchange at C-5 in 2-fluorohistidine is ascribed to a combination of the ketimine effect, C exchange involving catalysis by hydroxide ion *and* intramolecular general base catalysis by the side-chain primary amine function. The use of buffer catalysis for the tritium labeling of poorly reactive imidazoles is described.

In the first paper of this series,[2] we summarized present knowledge on pathways for isotopic exchange of ring hydrogens in imidazole, *N*-methylimidazole, and their *C*-methyl derivatives (Scheme I of preceding paper):[2] base-catalyzed exchange occurs by a carbanion (C) pathway, in which a proton is abstracted from the *neutral* imidazole species in the rate-limiting step, and/or an ylide (Y) pathway, involving base attack on the imidazolium *ion*. In addition, we established unequivocal assignments for the NMR signals of these hydrogens, presented new data on the rates of solvent–deuterium exchange, and demonstrated that considerable differences in proton acidity are observed at C-4 and C-5, positions which should be fairly equivalent in electron density. These differences were interpreted on the basis of the *adjacent lone pair* (ALP) effect: a ring-nitrogen atom bearing an sp^2 lone pair provides a sizable electrostatic obstacle to the generation of an sp^2 carbanion at an adjacent ring-carbon atom. While operation of the ALP effect is readily demonstrable at C-4 (adjacent to the lone pair at N-3), the magnitude of the effect at C-2 could not be evaluated because ylide exchange (Y) at the latter position may be 500–1000-fold faster than carbanion (C) exchange. Ylide exchange is not subject to the ALP effect because the lone pair at N-3 is utilized in formation of the imidazolium ion. We had hoped, therefore, that electronegative substituents at C-4 or C-5 might retard the Y pathway at C-2 and permit an evaluation of C exchange at the latter position. Further, it was conceivable that an electronegative group at C-5 might reduce or negate the ALP effect at C-4.

For various biological studies, we also needed practical routes to tritium-labeled fluoroimidazoles, as well as data on tritium loss from the labeled materials.[3] Initial studies had already indicated that the apparent acidities[4] of the ring hydrogens in these compounds are inconsistent with expectations based on nonfluorinated imidazoles. Thus, at pD 11 and 50 °C, $t_{1/2}$ = 7 h for exchange of H-2 in histidine,[5] while H-2 in 4(5)-fluorohistidine fails to exchange over a wide range in temperature or pD.[6] In contrast, H-5 in 2-fluorohistidine exchanges with $t_{1/2}$ = 20 h under the stated conditions, while H-5 in histidine is totally inert to exchange (except at very high temperatures). In our attempt to rationalize the behavior of the fluoroimidazoles, we were also led to examine imidazoles containing nitro[7] and several other substituents. Since alkylation of the imidazole NH eliminates complications due to ionization in basic media, 1-methyl-X-imidazoles (series 1–3) were examined first. The principal compounds investigated are summarized in Chart I.

Chart I

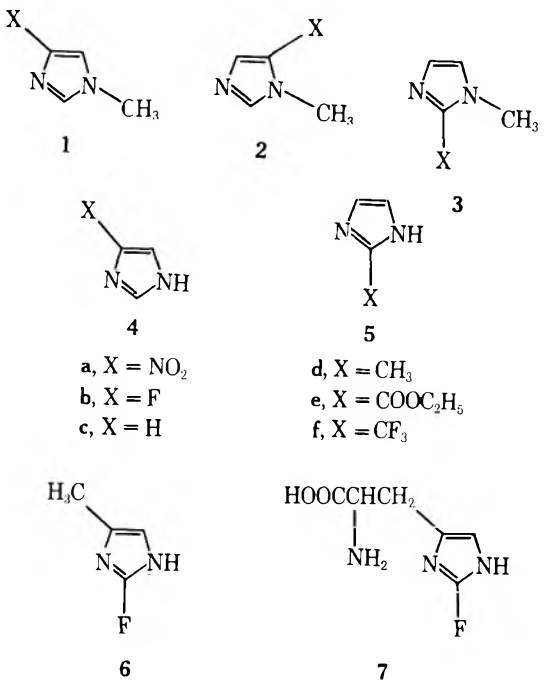

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Table I. NMR Solvent Shifts ($\Delta\delta$) for *N*-Methylimidazoles[a]

Compd	Registry no.	position	δ, ppm			Δδ, ppm[b]	
			$CDCl_3$	Me_2SO-d_6	D_2O	Δ_1	Δ_2
1a	3034-41-1	H-2	7.44	7.82	7.74	−0.38	−0.03
		H-5	7.78	8.37	8.19	−0.59	−0.41
2a	3034-42-2	H-2	7.59	8.02	7.92	−0.43	−0.33
		H-4	8.05	8.02	8.11	+0.03	−0.06
3a	1671-82-5	H-4	7.17	7.19	7.20	−0.02	−0.03
		H-5	7.20	7.67	7.45	−0.47	−0.25
1b	66787-67-5	H-2	7.04	7.32	7.36	−0.28	−0.32
		H-5	6.43	6.85	6.81	−0.42	−0.38
2b	66787-68-6	H-2	7.42	7.58	7.50	−0.16	−0.08
		H-4	6.57	6.72	6.68	−0.15	−0.11
3b	66787-69-7	H-4	6.67	6.61	6.67	+0.06	0
		H-5	6.67	6.95	6.82	−0.28	−0.15
1e	41507-56-6	H-2	7.56	7.77	*c*	−0.21	
		H-5	7.66	8.02	*c*	−0.36	
2e	66787-70-0	H-2	7.63	7.97	*c*	−0.34	
		H-4	7.79	7.70	*c*	+0.09	
3e	30148-21-1	H-4	7.09	7.12	*c*	−0.03	
		H-5	7.17	7.50	*c*	−0.33	

[a] Parallel data for *N,C*-dimethylimidazoles are given in ref 2. [b] $\Delta_1 = \delta_{CDCl_3} - \delta_{Me_2SO\text{-}d_6}$; $\Delta_2 = \delta_{CDCl_3} - \delta_{D_2O}$. [c] Insufficiently soluble in D_2O to provide reliable δ values.

Results

General Methods. NMR Assignments. Identification of ring-proton NMR signals cannot be made unequivocally by application of electron density considerations,[8] and we relied on the techniques previously used[2] for the simpler *N*-methylimidazoles: (1) spin decoupling; (2) nuclear Overhauser enhancement; (3) solvent-dependent $\Delta\delta$ values; and (4) chemical transformation. The first two methods depend on the fact that four-bond coupling between the protons of the *N*-methyl group and any adjacent ring hydrogen is readily observed, while coupling to the distal hydrogen is not discernible. Thus, irradiation at the *N*-methyl frequency results in loss of fine structure and increase in peak height for adjacent protons, but is without effect on the signal for a distal proton. The third method is based on an empirical generalization: for protons adjacent to the *N*-methyl group, $\Delta\delta_1$ ($=\delta_{CDCl_3} - \delta_{Me_2SO\text{-}d_6}$) and $\Delta\delta_2$ [$=\delta_{CDCl_3} - \delta_{D_2O}$] have significant negative values (−0.10 to −0.60); for the remaining ring proton, these Δ values are usually less than ±0.10 (Table I).[2,9] To date, 1-alkyl-5-fluoroimidazoles (e.g., **2b**) are the only compounds which have given equivocal results in the solvent shift analysis. Identification of NMR signals in all fluoroimidazoles is confirmed, however, by spin decoupling and by examination of coupling constants: $J_{4(H)5(F} \simeq J_{4(F)5(H)} \simeq 7$–$8$ Hz; $J_{2(H)4(F)} \simeq J_{2(F)4(H)} \simeq 1$–$2$ Hz; $J_{2(H)5(F)} \simeq J_{2(F)5(H)} \simeq 0$ Hz.[10] While electronegativity considerations suggest that the imidazole proton closer to the nitro group should appear at lower field in **1a** and **2a**, such an argument is inapplicable to **3a**, making the $\Delta\delta$ criterion especially valuable in the latter case. For **1a**, additional verification was obtained by its transformation to **1b** following isotope exchange (see below).

Kinetic Analysis. Rates of exchange of imidazole-ring protons in D_2O (over a wide pD range) were obtained by integration of NMR peak areas at various time intervals and at reaction temperatures which provided conveniently measurable rates. For *N*-methylimidazole and its *C*-alkyl derivatives, exchange at C-2 occurs, overwhelmingly, via the imidazolium ion and the Y pathway [Y(2)].[2] At any pD more than 1.5 units above the p*K* of the compound, an increase in $[OD^-]$ is directly offset by a decrease in $[ImD^+]$, and further increase in the basicity of the exchange medium will have no effect on $k_{Y(obsd)}$ (ref 2, Figure 1B). By virtue of its inductive effect, an electronegative substituent at C-4 or C-5 should enhance the acidity of H-2; at the same time, however, $k_{Y(obsd)}$ may be reduced because of the reduction in p*K*. Thus, at a pD low enough to provide significant $[ImD^+]$, $[OD^-]$ may be vanishingly small. A priori, one cannot predict the net effect of these opposing factors on Y exchange. Values of k_{obsd} were obtained at pD 9.5–10, generally at 50 °C. In this pD range, $k_{Y(obsd)}$ has attained its maximum value and the contribution of $k_{C(obsd)}$ is negligible for most compounds. For the weakly basic fluoro- and nitroimidazoles, values of k_{obsd} at pD 5 or 7 showed little variation from those at the higer pD (as expected). For very reactive or poorly reactive compounds, extrapolation to 50 °C was calculated from data at other temperatures, using an average value of $E_a = 21$ kcal/mol. Temperature-dependence studies with three compounds provided E_a values in the range 20–22 kcal/mol. Specific rate constants (k_Y) were calculated from the equation

$$k_{Y(obsd)} = k_Y K_W/(K_1 + [D^+]) \quad (1)$$

in which K_W is the ion product of D_2O and K_1 is the dissociation constant for ImD^+, both constants estimated for the reaction temperature (see Experimental Section). Since $k_1 \gg [D^+]$ at pD 9.5–10, the contribution of $[D^+]$ in eq 1 can usually be ignored. Exchange at C-4 or C-5 in *N*-methylimidazole also occurs by an ylide (Y) mechanism, but at a rate 10^4 to 10^5 slower than at C-2.[2] The same considerations regarding electronegative substituents should be applicable, although the inductive effect of the group should be felt more strongly at the adjacent ring position than at C-2. Values of $k_{Y(4)}$ and $k_{Y(5)}$ were obtained similarly to $k_{Y(2)}$ by use of eq 1 and $E_a = 21$ kcal/mol.

In *N*-methylimidazole, exchange at C-5 also occurs by a carbanion [C(5)] mechanism in strongly basic media; this pathway involves the neutral imidazole species, and k_{obsd} is directly proportional to $[OD^-]$. For this compound (in 1 N NaOD at 100 °C), C(5) exchange is ~15-fold faster than Y(5) exchange, ~40-fold faster than Y(4) exchange, but 800-fold slower than Y(2) exchange. Under these conditions, $t_{1/2} = 7$ h for C(5), while C(4) exchange could not be detected over 200 h. Values of total k_{obsd} were determined in alkaline media (0.05–1 N NaOD), both the temperature and pD range sometimes being limited by the stability of the compound to ring degradation or solvolysis of the substituent. Values of $k_{C(obsd)}$ were obtained by subtraction of $k_{Y(obsd)}$ (measured at pD 9.5–10) from total k_{obsd}. Plots of $k_{C(obsd)}$ vs. $[OD^-]$ provided reasonably linear slopes with values = k_C. Even in

Table II. Values of k_{obsd}[a] and k[b] for Deuterium Isotope Exchange (50 °C) in Imidazoles

Series	Ring Site	Path	NO_2 10^5k_{obsd}	NO_2 k	F 10^5k_{obsd}	F k	H 10^6k_{obsd}	H k	CH_3 10^6k_{obsd}	CH_3 k	σ^0	ρ	log k_0	Figure
1	2	C[c]		4.33×10^{-2}		2.33×10^{-5}	d		d			e		
		Y	0.68	6.46×10^{9}	1.25	2.63×10^{7}	16500	1.62×10^{5}	9170	7.59×10^{4}	m	6.72	5.22	3A
	5	C		2.24		2.41×10^{-4}		2.06×10^{-5}		4.44×10^{-6}	p	6.00	-4.66	1A
		Y	10.7	7.76×10^{10}	1.46	3.02×10^{7}	1.41	13.8	0.19	1.55	o	7.10	1.17	2A
2	2	C		0.15		2.80×10^{-2}	d		d			e		
		Y	82.5	1.00×10^{9}	49.5	1.05×10^{7}	16500	1.62×10^{5}	14300	3.72×10^{4}	m	5.64	5.18	3B
	4	C	f		f		f		f					
		Y	0.37	4.47×10^{6}	0.17	3.63×10^{4}	0.52	5.13	0.46	1.18	o	4.28	0.72	2B
3	4	C	f		f		f		f					
		Y	g		g		0.52	5.13	0.52	0.68		e		
	5	C		1.16×10^{-2}		5.07×10^{-5}		2.09×10^{-5}		5.26×10^{-6}	p	3.42	-4.81	1B
		Y	g		g,h		1.41	13.8	0.52	0.68		e		
4[i]	2	C	g		g		d		d					
		Y[j]	0.20[k]	5.01×10^{8}	0.96	5.07×10^{6}	5630	7.59×10^{4}	4950	1.76×10^{4}	m	5.54	4.83	3C
	5[l]	C		1.40		3.96×10^{-2}		8.24×10^{-5}		2.90×10^{-4}	o	3.27	-4.08	2C
		Y	g,k		g		0.49	2.88[m]	0.44	1.38		e		
5[i]	5[n]	C		60.8		0.05		8.24×10^{-5}		1.38×10^{-5}	m	8.70	-4.17	3D
	4,5[o]	Y	g,k		g		0.49	2.88[m]	0.48	0.40[m]		e		
6[i]	5	C				3.06								
7[i,p]	5	C				2.83								
		C'[q]				1.37×10^{-3}								

[a] Min^{-1}. [b] $M^{-1}min^{-1}$. [c] For path C, k_{obsd} is a linear function of $[OD^-]$. [d] Masked by the much faster Y exchange. [e] Only two experimental points available. [f] No measurable exchange because of the ALP effect. [g] No measurable exchange in 30 d at 50° and/or 8 d at 100°. [h] Too unstable in D_2O to evaluate k_{obsd}. [i] Values of k_{obsd} and k include adjustment for f_{ImN^-}. [j] For X = CF_3, $k_{obsd} = 3.89 \times 10^{-5}$ min^{-1} and $k = 3.31 \times 10^{7}$ $M^{-1}min^{-1}$. [k] Insoluble in D_2O alone; kinetics run in D_2O containing 20% DMSO-d_6, adjusted to pD 7 with CD_3COOD. [l] The 1,4-tautomer is considered the kinetically active species. [m] Since the kinetically active species is symmetrical, a statistical correction has been applied to k. [n] Although H-4 and H-5 are experimentally indistinguishable, the 1,4-tautomer is considered the active species. [o] H-4 and H-5 are experimentally indistinguishable. [p] Based on loss of tritium in H_2O. [q] Specific rate constant due to intramolecular general base catalysis by the side-chain primary amine function, in min^{-1}.

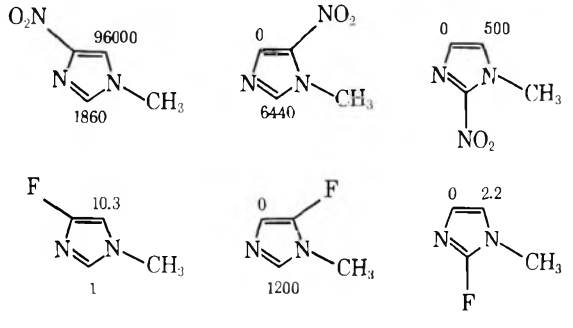


Figure 1. Relative rate constants (k_C) for carbanion exchange in nitro- and fluoro-1-methylimidazoles.

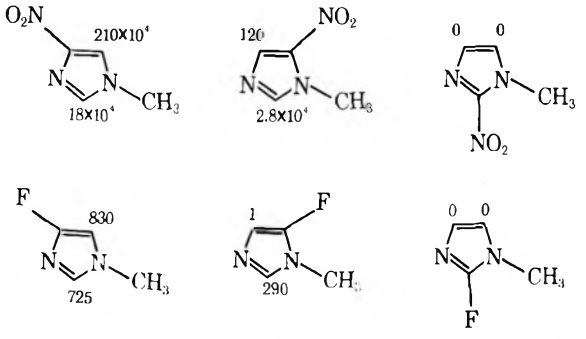


Figure 2. Relative rate constants (k_Y) for ylide exchange in nitro- and fluoro-1-methylimidazoles.

the most rapid exchanges, the contribution of the C pathway at pD 9.5–10 could be neglected. Values of k_C and k_Y are summarized in Table II, and relative rate constants for the two pathways are shown in Figures 1 and 2, respectively. The pK (H_2O, 25 °C) values used for Y pathway calculations are given in Table III, and methods for their conversion to pK (D_2O, 50 °C) are given in the Experimental Section. For the ylide pathways, values of k_{obsd} are also given in Table II to emphasize their lack of correlation with substituent parameters. Wherever "no detectable exchange" is indicated in Table II, runs were continued for 30–60 days at 50 °C and/or 8 days at 100 °C, stability permitting. The values of ρ in Table II are derived from the Hammett correlations of Figures 3–5, the latter being based on the set of σ^0 values proposed by Cohen and Takahashi (Table IV).[11]

1-Methyl-4-X-imidazoles (Series 1). Exchange at C-5 occurs by a combination of C and Y pathways, the former being far more significant in basic media. Thus, for X = NO_2, 0.02% of the total k_{obsd} is due to Y exchange in 0.2 N NaOD, while the fraction rises to 23% for X = F. In fact, H-5 in **1a** is remarkably acidic for a nonquaternized heterocycle with $t_{1/2} \simeq 2$ min at 50 °C in this medium. Introduction of a 4-nitro group into 1-methylimidazole increases total k_{obsd} at C-5

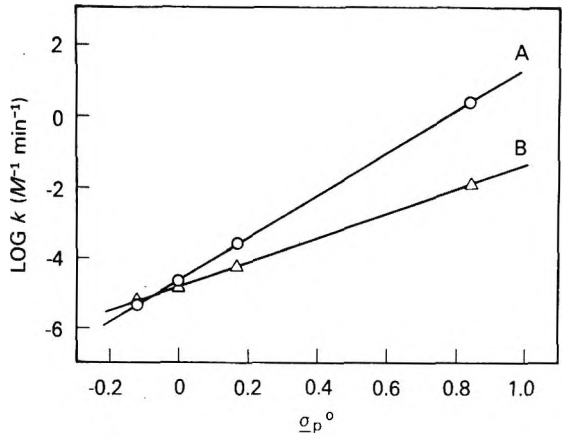


Figure 3. Hammett correlations of σ_p^0 for X vs. log k: A, series 1, log $k_{C(5)}$; B, series 3, log $k_{C(5)}$.

Table III. pK Values (25 °C) Used in Calculations

	X =				
series	NO_2	F	H	CH_3	CF_3
1	−0.60[a]	1.90[b]	7.13[b]	7.20[b]	
2	2.13[c]	3.85[b]	7.13[b]	7.70[b]	
3	−0.44[a]	2.30[b]	7.13[b]	8.00[b]	
4 (pK_1)	−0.15[a]	2.44[d]	7.00[e]	7.56[b]	2.28[e]
4 (pK_2)	9.20[a]	11.92[b]	14.52[f]	15.10[e]	10.6[e]
5 (pK_1)	−0.20[g]	2.40[d]	7.00[e]	7.85[b]	
5 (pK_2)	7.15[a]	10.45[d]	14.52[f]	15.10[e]	
6 (pK_1)		3.06[d]			
6 (pK_2)		10.70[d]			
7 (pK_1)		1.22[d]			
7 (pK_2)		10.55[d]			

[a] Average of values given in ref 31. [b] Present investigation. [c] Reference 12. [d] H. J. C. Yeh, K. L. Kirk, L. A. Cohen, and J. S. Cohen, *J. Chem. Soc., Perkin Trans. 2*, 928 (1975). [e] L. A. Cohen and P. A. Cohen, manuscript in preparation. [f] D. J. Brown, *J. Chem. Soc.*, 1974 (1958). [g] E. Laviron, *Bull. Soc. Chem. Fr.*, 2840 (1963).

Table IV. σ^0 Values Used in Hammett Correlations[a]

σ^0	NO_2	F	CH_3	CF_3
σ_o^0	1.38[b]	0.88[b]	−0.16	0.91
σ_m^0	0.68	0.33	−0.07	0.48
σ_p^0	0.84[b]	0.17[b]	−0.12	0.54

[a] Reference 11. [b] Value for aqueous media.

86 000-fold in 0.2 N NaOD, but only 75-fold at pD 9.5; further, the nitro group is 7100-fold as effective as fluorine in promoting exchange at C-5 in 0.2 N NaOD, but only seven times as effective at pD 9.5. On the basis of the four substituents (including H) for which kinetic data has thus far been obtained, values of log $k_{C(5)}$ provide an acceptable Hammett correlation with aromatic σ_p^0 (Figure 3A); values of log $k_{Y(5)}$, on the other hand, correlate best with σ_o^0 (Figure 4A). In the latter scale, the contribution of σ^I is doubled[11] and, presumably, the change to the σ_o^0 scale is related to the presence of positive charge in the kinetically active species for ylide exchange. The correlation with full σ^0 ($\sigma^I + \sigma^R$) for both pathways shows that the kinetic acidity of the proton is determined by the *net* electron density at C-5. The magnitudes of the ρ values (Table II) show a high degree of sensitivity to electronic effects, paralleling those generally observed at an sp^2 carbon of the benzene ring.

In **1c** and **1d**, exchange at C-2 occurs overwhelmingly by the Y pathway; in fact, any contribution due to C exchange is indiscernible even in 1 N base. Introduction of electronegative

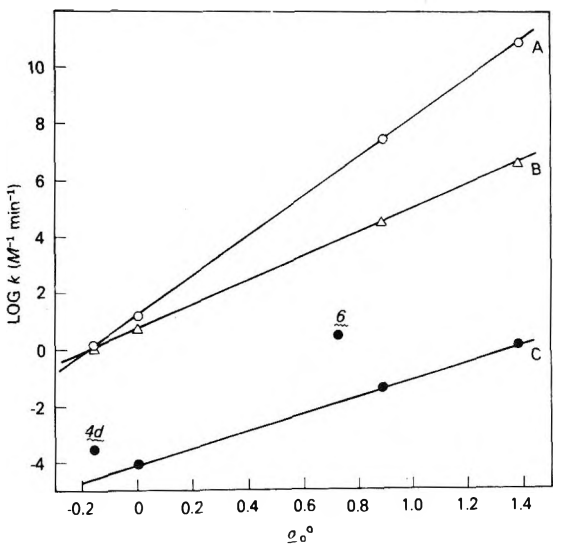


Figure 4. Hammett correlations of σ_o^0 for X vs. log k: A, series 1, log $k_{Y(5)}$; B, series 2, log $k_{Y(4)}$; C, series 4, log $k_{C(5)}$.

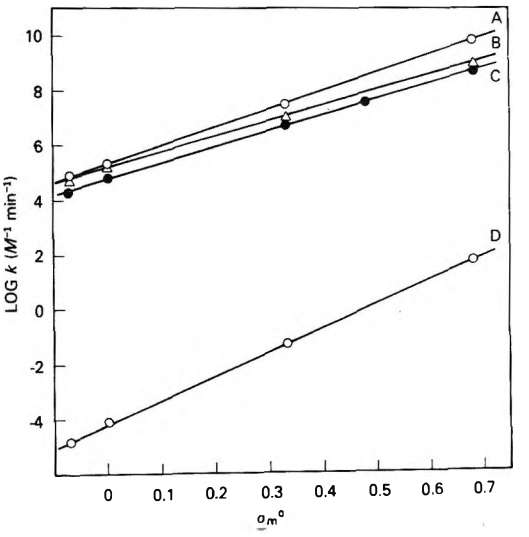


Figure 5. Hammett correlations of σ_m^0 for X vs. log k: A, series 1, log $k_{Y(2)}$; B, series 2, log $k_{Y(2)}$; C, series 4, log $k_{Y(2)}$; D, series 5, log $k_{C(5)}$.

substituents at C-4, however, markedly depresses $k_{Y(2)obsd}$; evidently, the reduction in pK_1 is more critical than inductive activation of H-2 by the group at C-4. Although $k_{Y(2)obsd}$ *decreases* with increasing electron withdrawal (Table II), $k_{Y(2)}$ (which takes account of the variations in K_1 and, thus, in [ImD$^+$]) shows an order consistent with electron withdrawal. Values of log $k_{Y(2)}$ correlate with σ_m^0 (Figure 5A). We were initially puzzled by the fact that values of $k_{Y(obsd)}$ for the two ring protons in series 1 show opposing trends; this phenomenon, however, is simply a consequence of the greater electron-withdrawing effect of 4-X at C-5 than at C-2. Electron withdrawal by the nitro and fluoro groups results in measurable C(2) exchange; log $k_{C(2)}$ may follow the σ_m^0 scale, as does log $k_{Y(2)}$, although only two experimental points are currently available. On the basis of these two points, $k_{C(2)obsd}$ for 1-methylimidazole (in 1 N NaOD at 50 °C) should be almost 10^6 slower than $k_{Y(2)obsd}$. For X = NO_2, H-5 is 52-fold as reactive as H-2 in the C pathway and 12-fold as reactive in the Y pathway. The lower reactivity at C-2 relative to C-5 is due to the greater distance between X and the proton undergoing exchange and, perhaps, to a partial ALP inhibition of carbanion formation at C-2.

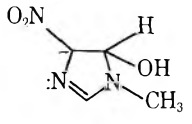
1-Methyl-5-X-imidazoles (Series 2). The magnitude of

the ALP effect at C-4 is strikingly evident in this series, since a C(4) pathway is not observed, *even* with a nitro group at C-5. Slow exchange via the Y(4) pathway is observed, however, and the substituent effect correlates with σ_o^0 (Figure 4B), as in series **1**. Interestingly, the ρ value is 2.8 units less than for series **1**, a factor which may result from the different sites of N-protonation relative to the substituent.

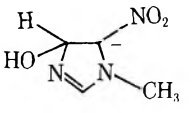
As in series **1**, the C(2) pathway can be observed only for X = NO_2 or F. The 5-nitro group is 3.5-fold as effective as 4-nitro in enhancing the acidity of H-2, possibly due to "para" resonance withdrawal in the former case; to our surprise, however, the 5-fluoro group is 1200-fold as effective as 4-fluoro. Hopefully, rate data for additional members of both series will help explain this unusual order of enhancements, which suggests that the magnitudes (or pathways) of electronic transmission from C-4 and C-5 to C-2 are significantly different; the nonequivalence in $J_{4(F)2(H)}$ and $J_{5(F)2(H)}$ has been noted earlier.[10] For series **2**, $k_{Y(2)}$ is consistently lower than for series **1**, while both series provide acceptable correlations of log $k_{Y(2)}$ with σ_m^0 (Figures 5B and 5A, respectively). The effect of higher pK_1 values in series **2** over series **1**[12] is seen in the values of $k_{Y(2)obsd}$, which are 94-fold greater for X = NO_2 and 40-fold for X = F.

1-Methyl-2-X-imidazoles (Series 3). C(5) exchange in **3a** is 13-fold slower than C(2) exchange in **2a** and 550-fold slower in **3b** than in **2b**. Presumably, the enhanced acidity at C-2 results from the extra inductive effect of N-3 and/or other factors (see Discussion); in addition, electronic transmission from X-5 to C-2 may be stronger than from X-2 to C-5, for reasons not yet obvious. In any case, it is clear that, if *any* ALP effect exists at C-2, it is considerably weaker than at C-4. Compound **3b** (X = F) is only 2.4-fold as reactive as **3c** (X = H) in C(5) exchange, and a Hammett correlation for this series can be achieved only with σ_p^0 (Figure 3B). It is noteworthy that σ_p^0 provides the best correlation for the two cases in which carbanion formation is required at C-5. This σ^0 scale does not hold for Y(5) exchange in series **1** or for C(5) exchange in the corresponding NH–imidazoles (see below); presumably, the *N*-methyl group serves to reduce electron density at C-5. Y(5) exchange cannot be detected in **3a** or **3b**, due to the combined effect of low pK and the distance of the substituent from the reaction site. For the same reasons, Y(4) exchange is not seen for either compound, while C(4) exchange is not detected for any member of the series because of the ALP effect. Based on the data for **3c** and **3d**, we estimate $t_{1/2} \simeq 1$ year (50 °C) for Y(5) exchange in **3a**, and even longer at C-4. Similar estimates suggest that Y(5) exchange should be reasonably observable for **3b**. Although the compound is sufficiently stable in 1 N NaOD (100 °C) to exhibit C(5) exchange, it decomposes too rapidly at pD 7–11 (50 °C) to provide rate data for Y(5) exchange. The instability of **3b** in the lower pD range arises from the fact that displacement of the 2-fluoro group occurs only when the ring is protonated.[13]

Instability of *N*-Alkylnitroimidazoles. Compounds **1a**, **2a**, and **3a** decompose in alkaline media, the rates of breakdown rising sharply with base concentration and with temperature. Under comparable conditions, **1a** and **3a** are 50–150-fold, respectively, more stable than **2a**. We consider the first step in breakdown of **1a** and **2a** to involve β addition of hydroxide ion to the 4,5-double bond, leading to the adducts **1a′** and **2a′**, respectively. The greater stability of **1a** may lie, therefore, in the fact that **1a′** cannot form as readily, being subject to an ALP effect not present in **2a′**. The onset of breakdown is readily detected by the appearance of new NMR signals; the multiplicity of the signals and their transience, however, prevented any speculation on the structures of intermediates. Ultimately, the *N*-methyl signal is lost completely, apparently by evaporation of methylamine. The breakdown of **3a** in base may involve an addition–elimination mechanism at C-2 but, in contrast with the behavior of **3b**, the nitro compound is stable at neutral pD. Apparently, the nitro group is sufficiently electron withdrawing to induce base attack on the neutral molecule, while ring protonation of the 2-fluoroimidazole is necessary to achieve adequate electron deficiency at C-2. A detailed study of these dual pathways is in progress.



1a′

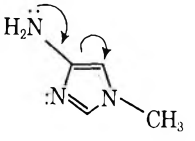


2a′

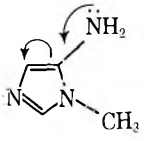
We have ignored consideration of isotope exchange via addition–elimination mechanisms, in which OD^- adds to the carbon atom carrying the electronegative group. Since nitro and fluoro are far better leaving groups than hydroxyl, it seems highly unlikely that the addition intermediates would revert to the starting compounds. Furthermore, such pathways cannot be considered for X = H or CH_3, and a duality of pathways is inconsistent with the linearity of the Hammett correlations.

Chemical Transformation. Although we had little reason to question the identity of the protons undergoing fast and slow exchange in **1a** and **2a**, chemical transformation provided a means for additional verification. Compound **1a** was converted to **1a**-d_2 by exhaustive exchange in 0.1 N NaOD (100 °C); the more labile deuterium atom was then back-exchanged in 0.1 N NaOH, and the resulting **1a**-*d* was converted into **1b**-*d* by zinc reduction, diazotization, and irradiation in fluoroboric acid. Since the product showed J_{HF} = 8.0 Hz, the hydrogen atom in **1b**-*d* must be adjacent to fluorine and, therefore, H-5 must be the more acidic proton.

Under the same exchange conditions, **2a** gave only a monodeuterated product, but the conversion of **2a** to **2b** has defied repeated efforts. Even when the intermediate 5-amino-1-methylimidazole (**9**) was generated from its stable *tert*-butoxycarbonyl derivative in fluoroboric acid, it failed to provide **2b** after diazotization and irradiation. Ultraviolet spectral analysis showed only traces of a diazonium chromophore after addition of nitrite, indicating **9** to be extremely unstable. The ALP effect may be operating to retard vinylamine resonance in **9**, but should have no effect in **8** and may even enhance resonance overlap in the latter case.[14,15]



8



9

4-X-Imidazoles (Series 4). Kinetic analyses of isotopic exchanges in the NH–imidazoles must take account of ionization to their anions in alkaline media. Since the latter species appear to be resistant to exchange in the temperature range investigated, values of total k_{obsd} were adjusted for the fraction of NH species present in each medium, based on the pK_2 values given in Table III; specific rate constants were then calculated as for the *N*-methylimidazoles. It is assumed that the ALP effect is operative throughout the series and, therefore, that the 4-X tautomer is the only (or more) reactive species. Arguments have been advanced[16] that the 4-X tautomer is thermodynamically preferred for most substituents. Exchange at C-5 occurs predominantly by the C pathway, values of log $k_{C(5)}$ correlating with σ_o^0 (Figure 4C); this result stands in contrast with the σ_p^0 correlation required for the corresponding exchange in series **1**. Electronegative substitution has a stronger enhancement effect in this series than in series **1**, a factor which may again be due to the absence of

the *N*-methyl group. Figure 4C shows 4-methylimidazole to have an anomalously high rate of C(5) exchange, a phenomenon also observed with 2-fluoro-4-alkylimidazoles (see below). Y(5) exchange is apparently too slow to be measured for **4a** or **4b**; on the basis of the data obtained for **4c** and **4d** (Table II), we estimate the half-time for exchange of H-5 in **4a** (D_2O, 100 °C) at 5 years![17]

Carbanion exchange at C-2 could not be detected for any member of this series, while Y(2) exchange does occur and can be correlated with σ_m^0 (Figure 5C).[17] Values of $k_{Y(2)}$ are fairly similar to those for series **1** and the ρ values differ by 1.2 units.

2-X-Imidazoles (Series 5). Carbanion exchange at C-5 was observed for all members of the series, and log $k_{C(5)}$ values correlate with σ_m^0 (Figure 5D). Values of k_{obsd} for 2-X-imidazoles are lower than those for the 4-X series; after adjustment for NH ionization, however, values of $k_{C(5)}$ for the former series are impressive, that for **5a** being 43-fold that for **4a** and ~5000 times as great as for **3a**. This puzzling result is also observed with X = F, since **5b** is 1000-fold as reactive as **3b**. As in the case of series **4**, Y(5) exchange was not observed for **5a** or **5b**.

4-Alkylimidazoles. This series of studies had been undertaken originally in an attempt to account for the surprisingly facile tritium exchange at C-5 in 2-fluorohistidine (**7**); e.g., at pH 9 (50 °C) this compound exchanges 800-fold faster than does 2-fluoroimidazole. The complex pH dependence for exchange (Figure 6) is inconsistent with simple C or Y pathways, and suggests a role for an additional ionizing group. Indeed, the results are wholly in accord with C exchange involving a combination of hydroxide ion catalysis and intramolecular general base catalysis by the side-chain primary amine function.

$$k_{obsd} = \{k_C[OH^-] + k'_C[f_{RNH_2}]\}f_{Im} \quad (2)$$

In this rate expression, f_{RNH_2} = fraction of α-amino group in the unprotonated form (pK 8.85) and f_{Im} = fraction of neutral imidazole species (pK_2 10.55); k'_C is the specific rate constant for intramolecular general base catalysis of carbanion formation. An approximate value for k'_C was obtained by assuming the contribution of $k_C[OH^-]$ to k_{obsd} to be very small at the lower pH values. Curve-fitting was then performed by approximation, providing the values of $k'_C = 1.58 \times 10^{-4}$ min^{-1} (30 °C) and $k_C = 0.33$ M^{-1} min^{-1} (30 °C). For comparison with the data for other compounds, these values were adjusted to 50 °C (Table II), taking E_a = 21 kcal/mol. These comparisons have limited validity, since H/D and H/T isotope effects have not been evaluated. The rate of tritium exchange is enhanced in the presence of carbonate buffer; e.g., at pH 9.2 (0.1 M buffer), k_{obsd} is increased almost threefold.

After taking account of the contribution of an intramolecular pathway,[20] we find that k_C for H-5 in 2-fluorohistidine is still 50-fold greater than that for 2-fluoroimidazole. We were led, therefore, to examine the simpler analogue, 2-fluoro-4-methylimidazole (**6**); this compound also showed an unusually high value for $k_{C(5)}$, the latter being 60 times that for 2-fluoroimidazole and 250 times the predicted value (Figure 2C) based on $\Sigma\sigma^0$.

We have noted that k_{obsd} for C(5) exchange in 4-methylimidazole (**4d**) is also anomalously high, being *ca.* fourfold greater than the same exchange in imidazole and 21-fold greater than in 2-methylimidazole. For this compound, $k_{C(5)}$ is 10 times as great as the value predicted from Figure 4C. These three examples (**4d**, **6**, and **7**) demonstrate that an alkyl group at C-4 provides a significant enhancement effect on C(5) exchange. There seems no obvious way for an alkyl group to stabilize an adjacent carbanion; therefore, we tentatively suggest an alternative pathway for exchange, via the still undetected tautomer, **10**.[19] It is noteworthy that rate enhancement is not seen with 1,4-dimethylimidazole, in which compound such tautomerism cannot occur.

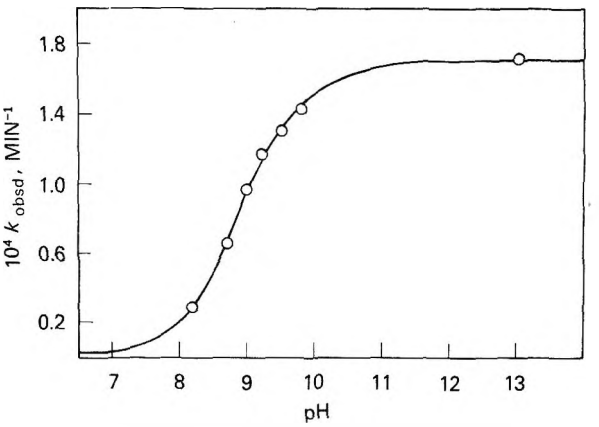
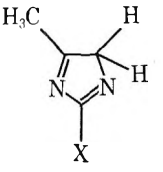


Figure 6. Dependence of total k_{obsd} on pH for loss of tritium from 2-fluorohistidine-5-^3H in H_2O at 30 °C: ○, experimental values; —, curve calculated from eq 2 and specific rate constants cited in text.



10

Buffer Catalysis. Since the Y mechanism for exchange involves the attack of a base on the imidazolium ion, it is ideally suited for catalysis by buffer species. We have already reported that exchange of H-2 in *N*-methylimidazole is catalyzed by acetate buffer.[2] Tritium incorporation at H-2 of histidine is also promoted by phosphate and Tris buffers, these findings having been applied for preparative purposes.[20] Labeling at C-2 in 4-fluoroimidazole occurs at pD 3–10 by the Y pathway, with $t_{1/2}$ = 1200 h at 50 °C or 15 h at 100 °C; the exchange is even slower in more acidic or more alkaline media. Since pK_1 for **4b** is 2.44, chloroacetic acid (pK 2.88) was chosen for possible catalysis of Y exchange; in 1 M buffer (pD 2.44, 50 °C), a 32-fold enhancement was obtained. The same buffer system was then used to achieve tritium labeling at C-2 in 4-fluorohistidine under very mild and practical conditions.

In the chloroacetate buffer medium, exchange of H-5 in fluoroimidazole is also accelerated ($t_{1/2}$ = 13 h at 50 °C). In the absence of buffer, Y(5) exchange could not be observed at any pD; if the buffer species were catalyzing the Y pathway, extrapolation from the values of $k_{Y(5)}$ for **4c** and **4d** suggests a buffer enhancement factor for **4b** of 40 000! Since this factor seems unreasonably large, it may be the C(5) pathway which is being catalyzed by chloroacetate ion, providing a tenfold enhancement at pD 2.44 over k_{obsd} in 0.1 N NaOD; pending the acquisition of additional kinetic data, however, the role of the buffer catalyst at C-5 remains uncertain. Data were presented above for the intramolecular general base catalysis of C exchange in 2-fluorohistidine and, thus, it appears that both the C and Y pathways are sensitive to buffer catalysis.

Other Substituted Imidazoles. Studies with **4f** at pD 10 provided a value for Y(2) exchange (Table II and Figure 3C); however, the compound decomposes too rapidly in more alkaline media to provide data for C(2) exchange. The carbethoxyimidazoles (**1e**, **2e**, and **3e**) failed to show Y exchange at 50 °C (pD 7–10); at 100 °C, ester hydrolysis occurred too rapidly to provide usable data.

Discussion

Certain of the k_Y values in Table II are close to the range for diffusion-controlled reactions.[21] Thus, $k_{Y(5)}$ for **1a** = 7.76

Table V. Half-Times for Exchange in 1-Methylimidazoles at 50 °C

	0.1 N NaOD			pD 9–10		
	H-2	H-4	H-5	H-2	H-4	H-5
none	42 min	2.5 yr	138 days	42 min	2.5 yr	1 yr
4-nitro	2.7 h		3 min	55 days		4.5 days
5-nitro	44 min	>2 yr		14 h	132 days	
2-nitro		>2 yr	10 h		>2 yr	>2 yr
4-fluoro	33 days		12 days	38 days		33 days
5-fluoro	3.5 h	>2 yr		23 h	285 days	
2-fluoro		>2 yr	97 days		>2 yr	>2 yr

$\times 10^{10}$ M^{-1} min^{-1} at 50 °C or 8.33×10^7 M^{-1} s^{-1} at 25 °C. This rate constant for base-catalyzed formation of the vinyl carbanion is ca. $1/50$ of the k_{OH} value for proton loss from HCN.[22] Considering that C-5 in **1a** is subjected to the combined electron demands of the 4-nitro group, two ring nitrogen atoms, *and* a positive charge in the ring, a total electronegativity approaching that of the triply-bonded nitrogen in HCN is not unreasonable. Furthermore, in their review on base-catalyzed proton exchange in heterocycles,[23] Elvidge et al. have argued that, because vinyl carbanions are usually not resonance stabilized, their kinetic acidities should be compared with those of oxygen acids rather than those of the common carbon acids.

The kinetic results with nitro- and fluoroimidazoles (Table II, Figure 1) have clearly shown the existence of significant carbanion-mediated exchange at C-2. In view of the powerful ALP effect of N-3 in preventing carbanion formation at C-4, it is somewhat surprising that a C(2) pathway can be observed at all. We might argue that electron withdrawal by *two* ring nitrogen atoms can partially counteract the ALP effect at C-2; yet, it seems unreasonable that the magnitude of such withdrawal could so greatly exceed the combined electronegativities of N-3 and a 5-nitro group operating on C-4. Very strong bases (e.g., butyllithium in tetrahydrofuran) abstract H-2 from *N*-alkylimidazoles with essentially total specificity.[24] This fact appears to support the absence of a significant ALP effect at C-2; yet, we cannot rule out the possibility that proton abstraction is preceded by coordination of the lithium atom with the lone pair at N-3 and, thus, occurs by a Y rather than C pathway. It is also noteworthy that, in the presence of methoxide ion, C-2 in pyrimidine is the *least* acidic position in the ring;[25] this carbon atom is also flanked by two nitrogen atoms, but the corresponding carbanion would be subject to two ALP interactions.

It is also conceivable that the sp^2 carbanion at C-2 is electronically different from that at C-4 or that the imidazole ring becomes partially deformed from planarity when H-2 is lost, thus reducing lone-pair repulsion. Alternatively, we may invoke greater s character (hence, greater acidity) in the C(2)–H bond than in that at C-4;[25] this explanation is supported both by crystal structure data for imidazole[26] and by ^{13}C–^1H coupling constants.[27] At best, however, orbital interactions through bonds or space are not yet well understood,[28] and the imidazole case clearly demands further study.

These studies have demonstrated that both ylide and carbanion exchange in substituted imidazoles follow reasonably logical, but complex, patterns. Although we fully recognize that the Hammett correlations (based on four points) have only limited reliability, they have proved useful in predicting the conditions necessary to observe exchange with other substituted imidazoles. Further studies are in progress and, hopefully, the use of all three σ^0 scales will be supported with additional kinetic data. In addition to the large difference in ALP effect between C-2 and C-4, several phenomena have emerged which merit further exploration: (1) the enhancement effect of 4-alkyl substituents; (2) intramolecular general base catalysis in 2-fluorohistidine; and (3) buffer catalysis of both the C and Y pathways. Other surprising results have been obtained in studies of acid-catalyzed exchange; these results will be reported separately.

A wide variety of ring-substituted histamines and histidines have been prepared for biological studies (in progress). On the basis of the results herein reported, random or site-specific tritium labeling of the imidazole ring in these compounds has become attainable in practice. The very large spread in half-times for exchange (see examples in Table V) permits highly specific labeling in many cases. For poorly exchangeable protons, exchange is also attainable by the use of elevated temperatures or buffer catalysis; the optimum pH for such catalysis can be predicted from the pK value of the compound and the appropriate Hammett plot (Figures 3–5).

Experimental Section[29]

Materials. The following compounds were synthesized by known methods: **1a**,[30] **1d**,[2] **2a**,[30] **2d**,[2] **3a**,[31] **3e**,[22] **4b**,[33] **4d**,[2] **4e**,[34] **4f**,[35] **5a**,[36] **5b**,[33] and **7**.[13] Imidazole, 1-methylimidazole, 2-methylimidazole, 1,2-dimethylimidazole, and 4-nitroimidazole were obtained from commercial sources.

4-Fluoro-1-methylimidazole (1b). A solution of 5.08 g (0.04 mol) of **1a** in 120 mL of 48% aqueous fluoroboric acid was chilled to −10 to −15 °C with dry ice–acetone and 9.15 g (0.14 atom) of zinc powder was added over 30 min with stirring. At this point, the UV spectrum of the reaction mixture (measured on a small aliquot diluted with water) showed total loss of the nitro chromophore. The mixture was filtered through glass wool, and a solution of 3.2 g (0.048 mol) of sodium nitrite in 20 mL of water was added with stirring over 20 min at −10 °C. The solution was purged with nitrogen and was irradiated for 5 h by the procedure described previously.[33] The fluoroboric acid solution was then neutralized to pH 8 with concentrated sodium hydroxide (cold) and was subjected to continuous extraction with ethyl acetate for 48 h. The extract was evaporated to give a semisolid residue, which was chromatographed on 150 g of silica gel. Elution with ethyl acetate–ether (1:1) gave 1.0 g (25%) of **1b** as a pale yellow semisolid; NMR ($CDCl_3$) δ 3.66 (3 H, d, CH_3), 6.43 (1 H, q, H-5), 7.04 (1 H, m, H-2); $J_{4,5}$ = 8.0, $J_{2,4}$ = 1.8, and $J_{2,5} \simeq 1$ Hz.

The same compound was obtained by direct methylation of 4-fluoroimidazole with methyl iodide or dimethyl sulfate, using standard procedures.

4-Fluoro-1-methylimidazole-*d* (1b-*d*). 1-Methyl-4-nitroimidazole (0.5 g) was added to 50 mL of 0.1 N NaOD and the mixture was stirred at ambient temperature. When solution was complete (~15 min), NMR showed one proton to have exchanged completely. The solution was then heated at 100 °C for 1.5 h, at which point the remaining proton had exchanged completely. This product was isolated by extraction with ethyl acetate and the more labile deuterium atom washed out by exposure to 0.1 N NaOH for 15 min. The monodeuterio compound was converted to 4-fluoro-1-methylimidazole-*d* by the procedure described above. Since this product showed $J_{H,F}$ = 8.0 Hz, the deuterium atom must be at C-2, and the very labile hydrogen atom in **1a** must be that at C-5.

5-Fluoro-1-methylimidazole (2b). Direct methylation of 4-fluoroimidazole with methyl iodide or dimethyl sulfate, under neutral or basic conditions, and in polar or nonpolar media, gave **1b** exclusively. Repeated efforts to prepare **2b** from **2a**, following the reduction–irradiation procedure used for the conversion of **1a** to **2a**, failed completely. Presumably, the intermediate 5-amino-1-methylimidazole is very short-lived, even at the low temperature of reduction. Alternatively, 5-amino-1-methylimidazole (**9**) was generated in fluoroboric acid solution from its *tert*-butoxycarbonyl derivative (see below), but again failed to produce **2b**. The only successful approach,

which follows, depends on a S_N1 rather than the common S_N2 pathway for nitrogen alkylation.

To a solution of 0.129 g (1.5 mmol) of 4-fluoroimidazole (**4b**) in 15 mL of dry acetonitrile was added a solution of 0.125 mL (2 mmol) of methyl iodide in 2 mL of acetonitrile, followed by portionwise addition of 0.414 g (2 mmol) of silver perchlorate. The mixture was stirred 1 h, another 0.125 mL of methyl iodide was added, and stirring was continued another hour at 40 °C. Two more portions of methyl iodide were added, with stirring for 1 h at 40 °C after each addition. The mixture was filtered and the filtrate was concentrated to a semisolid. This material was dissolved in 30 mL of ethyl acetate, the solution was washed with two 10-mL portions of saturated sodium bicarbonate, dried (Na_2SO_4), and evaporated to a colorless semisolid, 0.103 g (69%) of **2b**. Crystallization of the product from chloroform gave needles: mp 87–88 °C; NMR ($CDCl_3$) δ 3.62 (3 H, s, CH_3), 6.57 (1 H, d, H-4), and 7.42 (1 H, br, H-2); $J_{4,5}$ = 7.5, $J_{2,4}$ = 1.0, and $J_{2,5} \simeq 0$ Hz.

2-Fluoro-1-methylimidazole (3b). A. To a solution of 2-amino-1-methylimidazole (bisulfate)[37] (3.65 g, 0.025 mol) in 150 mL of 48% fluoroboric acid was added a solution of 1.90 g (0.0275 mol) of sodium nitrite in 5 mL of water, over 10 min with stirring and ice cooling. The mixture was irradiated for 3 h, at which point the diazonium chromophore at 306 nm had disappeared. The reaction mixture was neutralized with concentrated NaOH to pH [] (dry ice cooling); the solution was then extracted with five 60-mL portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated to a semisolid residue. Chromatography on 150 g of silica gel and elution with chloroform (2% ethanol) gave **3b** as a pale yellow liquid: 0.87 g (35%); NMR ($CDCl_3$) δ 3.56 (3 H, s, CH_3), 6.67 (1 H, s, H-4), 6.67 (1 H, s, H-5); $J_{4,5}$ = 1.6, $J_{2,4}$ = 1.6, and $J_{2,5} \simeq 0$ Hz.

B. Direct methylation of 2-fluoroimidazole with dimethyl sulfate gave only the 1,3-dimethylimidazolium species, which underwent rapid loss of fluorine by solvolysis. The product was identified as 1,3-dimethyl-2-imidazolone.

N-Methylation of Ethyl Imidazole-4-carboxylate. To a solution of 4.20 g (0.03 mol) of **4e**[34] in 25 mL of methanol was added a solution of 8.52 g (0.06 mol) of methyl iodide in 10 mL of methanol, and the mixture was heated at reflux for 8 h. Evaporation of solvent gave a brown oil which was chromatographed on 120 g of silicic acid. Elution with chloroform (1.5% methanol) gave 1.82 g (40%) of **2e** as a pale yellow oil; NMR ($CDCl_3$) δ 1.38 (3 H, t, $CH_2\mathbf{CH_3}$), 3.96 (3 H, s, N-CH_3), 4.36 (2 H, q, $\mathbf{CH_2}CH_3$), 7.63 (1 H, m, H-2), 7.79 (1 H, d, H-4). Continued elution with the same solvent gave 0.22 g (5%) of **1e** as a pale yellow oil; NMR ($CDCl_3$) δ 1.37 (3 H, t, $CH_2\mathbf{CH_3}$), 3.81 (3 H, s, N-CH_3), 4.38 (2 H, q, $\mathbf{CH_2}CH_3$), 7.56 (1 H, m, H-2), 7.66 (1 H, d, H-5).

1-Methylimidazole-5-carbohydrazide. A solution of 2.31 g (0.015 mol) of **2e** in 5 mL of hydrazine hydrate was heated at 100 °C for 1 h. The solution was concentrated to ~2 mL under reduced pressure and chilled, giving 1.71 g (81%) of colorless prisms, mp 187–187.5 °C. Further concentration of the filtrate gave an additional 0.32 g (15%) of a less pure material.

***tert*-Butyl 1-Methylimidazole-5-carbamate.** To a solution of 1.40 g (0.01 mol) of 1-methylimidazole-5-carbohydrazide in 6 mL of water and 2 mL of concentrated hydrochloric acid was added dropwise over 10 min, with stirring at 0 °C, a solution of 1.04 g (0.015 mol) of sodium nitrite in 2 mL of water. The mixture was stirred 20 min at 0°, neutralized to pH 7 with 10% sodium hydroxide, and extracted with five 10-mL portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated to a pale brown semisolid, 1.41 g (93%). The acyl azide is unstable and was used immediately for the next step.

The total yield of crude azide was added to 20 mL of dry *tert*-butyl alcohol and the solution was heated at reflux for 2.5 h.[33] Evaporation of solvent gave a yellow solid which was crystallized twice from ethyl acetate and once from methanol to give 1.49 g (81%) of colorless leaflets, mp 173 °C.

Anal. Calcd for $C_9H_{15}N_3O_2$: C, 54.80; H, 7.67; N, 21.30. Found: C, 54.25; H, 7.28; N, 21.73.

This product was used to generate 5-amino-1-methylimidazole in fluoroboric acid solution. The aminoimidazole, however, failed to give **2b** when processed in a manner similar to that for the synthesis of **4b**.

2-Fluoro-4-methylimidazole (6). This compound was prepared from crude 2-amino-4-methylimidazole,[37] using the procedure and the scale described above for the preparation of **3b**. Total disappearance of the diazonium chromophore at 320 nm required irradiation for 1.5 h. The fluoroboric acid solution was neutralized to pH 7 (cold) and was extracted with five 100-mL portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated to a semisolid; chromatography on 59 g of silica gel and elution with ether gave a colorless powder, which was sublimed and recrystallized from ligroin–ether (4:1): mp 81–81.5 °C (10% yield based on aminoacetone hydrochloride hydrate, the precursor of 2-amino-4-methylimidazole); NMR ($CDCl_3$) δ 2.20 (3 H, t, CH_3), 6.40 (1 H, m, H-4 or H-5); $J_{2,4(5)}$ = 1.3 Hz.

Anal. Calcd for $C_4H_5N_2F$: C, 47.99; H, 5.03; N, 27.99; F, 18.98. Found: C, 47.87; H, 5.12; N, 28.77; F, 18.68.

2-Fluoro-L-histidine-*5*-^3H. To a solution of 75 mg of 2-fluoro-L-histidine (**7**) in 1 mL of tritiated water (5.0 Ci) was added 100 μL of triethylamine. The solution was stirred at ambient temperature for 4.5 days and was lyophilized. Normal water was added and the lyophilization repeated. The residue was treated with methanol and the solvent evaporated. Finally, the material was triturated with a small volume of cold methanol and filtered to give 32.5 mg of crystalline material with a specific activity of 40 mCi/mmol.

Tritium Loss From 2-Fluoro-L-histidine-*5*-^3H. A stock solution of 4.9 mg/mL of water of the labeled compound was prepared with specific acitvity of 3.9 μCi/μol. A 50-μL aliquot was added to 5.0 mL of 0.1 KCl. The pH was adjusted to the desired level with 0.05 N NaOH and was maintained at that level throughout the run by use of a Radiometer autoburette (Model ABU 12). The temperature was maintained at 30 °C by circulation of water from a Haake water bath through the jacketed reaction vessel. A slurry of one part Dowex 50 H^+x 8 (200–400 mesh) and three parts water was prepared; 1-mL aliquots of the slurry were added to Pasteur pipettes which had been loosely plugged with glass wool, and the columns were washed with water until the effluent was neutral. At various time intervals, 100-μL aliquots of the reaction mixture were transferred to the Dowex columns, the columns were washed with 5 × 0.5 mL of water, and the total effluent from each column was counted with a Perkin-Elmer liquid scintillation counter (Model 3375). Initial rates (up to ~10% exchange) were used to determine rate constants; initial and subsequent radioactivity counts were taken as measures of concentration of unreacted substrate.

p*K* Measurements. p*K* values were obtained for the new compounds and for others for which data were unavailable or literature values were in doubt. p*K* values were calculated from pH measurements in water at 25 °C (Corning pH meter, Model 101). Samples of 20–40 mg were used, and seven to ten aliquots of acid or base added. p*K* values were calculated for each addition and averaged to give the values in Table III; deviations were usually <0.10 unit. The effect of temperature on p*K* was determined (up to 70 °C) for several compounds by following the change in pH of a half-neutralized solution. The averaged results were considered applicable to all compounds in the study: for pK_1, $pK(50\ °C) = pK(25\ °C) - 0.50$ and $pK(100\ °C) = pK(25\ °C) - 0.30$.[38] Values of $pK(D_2O, 25\ °C)$ were calculated from the relationship $pK(D_2O) = 1.018\ pK(H_2O) + 0.43$ (Table III, footnote *d*). Temperature effects on $pK(D_2O)$ were assumed comparable to those in H_2O. For $pK_w(D_2O, 50\ °C)$, 14.18 was used;[39] for 100 °C, pK_w = 13.13 was estimated by extrapolation.

Kinetic Measurements. The techniques used to follow rates of exchange by NMR spectroscopy are described in the previous paper.[2] For series **4** and **5**, δ values are shifted in alkaline media, and may even become inverted in order. Upon completion of an exchange run, the solution was neutralized and the NMR spectrum compared with that of the original compound; since **4a** and **5a** are insoluble in water, the neutralized mixtures were saturated with NaCl and the compounds were extracted into Me_2SO-d_6 prior to spectral comparison. For C exchange, rate constants were obtained at three or four concentrations of NaOD, and k_C determined as the slope of a plot of $k_{C(obsd)}$ vs. [OD^-]. Ylide exchange was measured in D_2O solutions which were brought to pD 9.5–10 (25 °C) with 0.1 N NaOD. Specific rate constants for Y exchange were calculated according to eq 1.

Acknowledgment. We are grateful to Dr. H. J. C. Yeh (of this laboratory) for providing the 100-MHz NMR spectra, and for performing the spin-decoupling and nuclear Overhauser enhancement experiments.

Registry No.—**1b** deuterium derivative, 23968-98-1; **1c**, 616-47-7; **1d**, 6338-45-0; **2d**, 10447-93-5; **3d**, 1739-84-0; **4b**, 30086-17-0; **4d**, 822-36-6; **4e**, 23785-21-9; **5d**, 693-98-1; **6**, 57212-35-8; **7**, 50444-78-5; **7** tritium derivative, 66787-71-1; 2-amino-1-methylimidazole (bisulfate), 66787-72-2; 1-methylimidazole-5-carbohydrazide, 23585-00-4; *tert*-butyl 1-methylimidazole-5-carbamate, 66787-73-3; 1-methylimidazole-5-methylazide, 66787-74-4; 5-amino-1-methylimidazole, 66787-75-5; 2-amino-4-methylimidazole, 6653-42-5.

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Spiro Meisenheimer Complexes from 7-(2-Hydroxyethoxy)-4-nitrobenzofurazan and 7-(2-Hydroxyethoxy)-4-nitrobenzofuroxan. A Kinetic Study in Aqueous Solution

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Cyclization of 7-(2-hydroxyethoxy)-4-nitrobenzofurazan (**3**) and 7-(2-hydroxyethoxy)-4-nitrobenzofurazan (**6**) occurs in aqueous solution containing base to give the spiro Meisenheimer-type complexes **5** and **8**, which have a high thermodynamic stability. A similar reaction occurs in Me_2SO where the structures of **5** and **8** could be fully characterized by ^1H NMR spectroscopy. The kinetics of formation and decomposition of **5** and **8** have been studied by the stopped-flow method between pH 1 and 12 in aqueous solution. It is found that **5** is only 2.5-fold more stable than **8** ($pK_a^5 = 6.86$; $pK_a^8 = 7.26$), but it forms and decomposes much faster than its furoxanic analogue. These differences in rates are attributed to the *N*-oxide group, which probably exerts a very unfavorable influence on the C–O bond-forming and bond-breaking processes associated with formation and decomposition of the furoxanic adduct **8**. The ring opening of **5** and **8** is subject to general acid catalysis in aqueous solution with a Brønsted coefficient α of 0.44. The results are discussed by comparison with those obtained for benzenic analogues.

The proposal[2-4] that the antileukemic activity of some benzofurazan and benzofuroxan derivatives may be due to their ability to easily form Meisenheimer-type complexes with essential cellular SH and/or amino groups has increased interest in the adducts obtained from covalent addition of nucleophiles to these compounds. There is now convincing structural evidence, mainly from NMR studies, that such adducts are formed in the reaction of a variety of mono- and dinitrobenzofurazans and -benzofuroxans with hydroxide and methoxide ions.[5-10] The thermodynamic and kinetic data for

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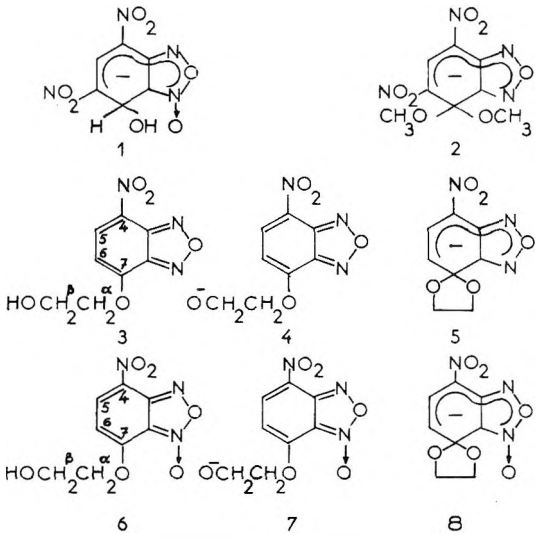
the formation and decomposition of this class of adducts have been reported mainly for the dinitro complexes **1** and **2**.[2a,9,11] This is because formation of the mononitro adducts is frequently complicated by the occurrence of a number of other reactions, some of which are irreversible.[8b,10] In order to avoid these complications and to carry out a comprehensive quantitative analysis of the formation and decomposition of mononitro adducts, we became interested in furazanic and furoxanic substrates leading to the formation of spiro complexes. Such systems have been successfully used in benzenic series.[12–14] In the present work, we report data obtained for the formation and decomposition of spiro complexes **5** and **8** derived from the cyclization of 7-(2-hydroxethoxy)-4-nitrobenzofurazan (**3**) and 7-(2-hydroxyethoxy)-4-nitrobenzofuroxan (**6**), respectively, in aqueous solution.

Results

When base is added to an aqueous solution of the yellow-colored parent ethers **3** and **6**, there is an immediate appearance of colorless species with absorption spectra showing maxima at 330 and 339 nm, respectively. Similar spectra are obtained in Me_2SO solution, showing that the same species form in both solvents. Since ^1H NMR measurements in water were precluded by low solubility of the substrates, confirmation that these species are the spiro complexes **5** and **8** was



obtained from ^1H NMR spectroscopy in Me_2SO solution. Thus, addition of base to a solution of **3** or **6** in Me_2SO-d_6 results in an immediate reduction in the intensity of the signals characteristic of the ring and methylenic protons of **3** (δ, internal reference Me_4Si, 8.48 (H-5, d, J = 10 Hz), 8.02 (H-6, d, J = 10 Hz), 4.64 (α-CH_2, t), 3.84 (β-CH_2, t)) and **6** (δ 8.58 (H-5, d, J = 9 Hz), 6.83 (H-6, d, J = 9 Hz), 4.33 (α-CH_2, t), 3.83 (β-CH_2, t)) and the development of new sets of signals consistent with the postulated structures of **5** and **8**. In particular, as expected on formation of anionic complexes, the ring protons H-5, H-6 now absorb at higher field and give two doublets which are seen at δ 6.84 and 6.25 (J = 10 Hz) in the case of **5** and δ 7.12 and 4.95 (J = 9 Hz) in the case of **8**. Also, in conformity with results reported for benzenic unsymmetrical spiro adducts,[14] the nonequivalent dioxolane methylene protons of **5** and **8** give rise to a complex multiplet centered at 4.16 ppm in both cases. The resolution of these multiplets was not sufficient to allow an AA′ BB′ analysis. After the addition of 1 equiv of base was completed, the stable spectra consisted only of the signals associated with **5** and **8**. They were also similar to the spectra of solutions in Me_2SO-d_6 of the complexes **5** and **8** isolated as crystalline potassium salts (see Experimental Section).

The formation of **5** and **8** is essentially complete at pH 10.

Scheme I

$$3\ (\text{or } 6)\ (\text{GOH}) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 5\ (\text{or } 8)\ \text{spiro complex} + H^+ \quad (1)$$

$$3\ (\text{or } 6)\ (\text{GOH}) + OH^- \overset{K}{\rightleftharpoons} 4\ (\text{or } 7)\ (GO^-) \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 5\ (\text{or } 8)\ \text{spiro complex} \quad (2)$$

To carry out a comprehensive thermodynamic and kinetic study of the formation and decomposition of these spiro adducts, we have investigated the reactions in the pH range of 1–12, using dilute hydrochloric acid solutions, various buffer solutions, and dilute potassium hydroxide solutions. The ionic strength was always kept constant at 0.2 M by adding KCl as needed. All pH values have been measured relative to the standard state in pure water, allowing the calculation of the hydrogen ion concentration $[H^+]$ of the solutions from the hydrogen ion activity a_{H^+} by means of the relation $[H^+] = a_{H^+}/\gamma_\pm$, where $\gamma_\pm$ is the trace activity coefficient in 0.2 M KCl ($\gamma_\pm = 0.75$[15]).

Equilibrium Measurements. In the large pH range studied, the possible pathways for interconversion of the glycol ethers **3** and **6** (GOH) and corresponding adducts **5** and **8** are shown in Scheme I. Whereas the first pathway involves direct internal cyclization of GOH, the second pathway, which is evidently much more favored in alkaline media, involves a rapid proton transfer from the glycol side chain to base followed by a slower internal cyclization of the formed glycolate anions (GO^-) **4** and **7**.

As previously pointed out by different workers,[12c,d13] the values of the equilibrium constant K governing the ionization of the OH group of the parent glycols are unlikely to be much higher than 0.1 M^{-1} in water. Hence, at the pH used in the present work, the product $K[OH^-]$ will be $\ll 1$, and the anion concentration $[GO^-]$ can be neglected compared to the glycol concentration [GOH]. Accordingly, the stoichiometric equilibrium constant K_c (eq 3) usually associated to the conversion of GOH to spiro adducts through eq 2 may be reduced to the simplified eq 4 from which eq 5 can be deduced. In eq 5 K_2 is the equilibrium constant governing the internal cyclization of GO^-. Furthermore, relation 7 holds between K_c and the equilibrium constant K_a (eq 6) associated with the formation of adducts through eq 1 at μ = 0.2 M (K_w is the autoprotolysis constant of water; pK_w = 14.17 at 20 °C).

$$K_c = \frac{[\text{complex}]}{([\text{GOH}] + [\text{GO}^-])[\text{OH}^-]} \quad (3)$$

$$K_c = \frac{[\text{complex}]}{[\text{GOH}][\text{OH}^-]} \quad (4)$$

$$K_c = KK_2 \quad (5)$$

$$K_a = \frac{[\text{complex}][\text{H}^+]}{[\text{GOH}]} \quad (6)$$

$$K_a = K_c \times \frac{K_w}{\gamma_\pm^2} \quad (7)$$

Measurements of the equilibrium optical densities at the absorption maxima of the adducts were made at 20 °C in buffered solutions in the pH ranges 6.5–8 and 6.8–8.5 for **5** and **8**, respectively. As expected, a plot, not shown, of log $(OD - OD_0)/(OD_c - OD)$ vs. pH according to the equation

$$\log \frac{OD - OD_0}{OD_c - OD} = \log Ka + pH + \log \gamma_\pm \quad (8)$$

where OD is the equilibrium optical density at a given pH, OD_c the optical density in a basic solution where complex formation is quantitative and OD_0 the optical density of the parent

Table I. Experimental and Calculated Pseudo-First-Order Rate Constants, k_{obsd}, k_f, and k_d, for the Formation and Decomposition of the Furazanic Adduct 5 in Water[a]

pH	k_{obsd}, s^{-1}	k_f, s^{-1}	k_d, s^{-1}	pH	k_{obsd}, s^{-1}	k_f, s^{-1}	k_d, s^{-1}
1.30[b]	147	3.1×10^{-4}	147	5.29[c]	0.24	4.80×10^{-3}	0.235
1.46[b]	118	3.56×10^{-4}	118	5.98[d]	0.23	2.08×10^{-2}	0.208
1.72[b]	63.4	3.49×10^{-4}	63.4	6.30[d]	0.275	4.7×10^{-2}	0.227
1.98[b]	36	3.6×10^{-4}	36	6.72[d]	0.386	0.137	0.249
2.04[b]	30.5	3.5×10^{-4}	30.5	7.05[d]	0.605	0.327	0.278
2.12[b]	24.3	3.28×10^{-4}	24.3	7.38[d]	0.915	0.656	0.26
2.20[b]	18.8	3.12×10^{-4}	18.8	7.52[e]	1.34	1.045	0.294
2.35[b]	14.23	3.33×10^{-4}	14.23	7.89[e]	2.87	2.56	0.308
2.46[b]	11.36	3.43×10^{-4}	11.36	7.94[g]	2.65	2.3	0.252
4.04[c]	0.54	6×10^{-4}	0.54	8.30[f]	6	5.72	0.274
4.34[c]	0.375	8.77×10^{-4}	0.374	8.62[g]	11.28	11.03	0.253
4.64[c]	0.278	1.29×10^{-3}	0.277	8.91[g]	22.4	22.14	0.254
4.96[c]	0.26	2.46×10^{-3}	0.26	9.10[g]	32.4	32.2	0.244

[a] At zero buffer concentration; $\mu = 0.20$ M; $t = 20$ °C. [b] HCl solutions (4.5×10^{-3}–6.5×10^{-2} M). [c] Acetate buffer. [d] Phosphate buffer. [e] *p*-Cyanophenoxide buffer. [f] Bicarbonate buffer. [g] Borate buffer.

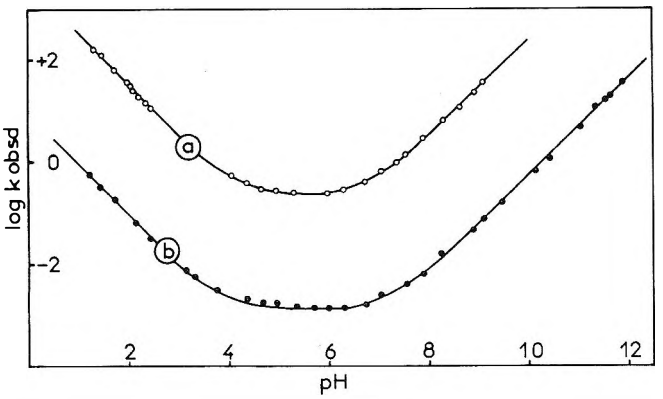


Figure 1. pH dependence of k_{obsd} (s^{-1}) for the formation and decomposition of adducts 5 (plot a) and 8 (plot b) in water: 20 °C, μ = 0.20 M.

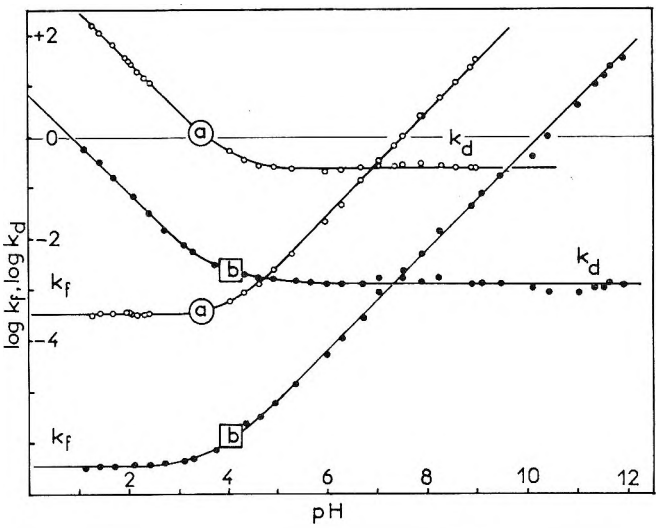


Figure 2. pH dependence of k_f (s^{-1}) and k_d (s^{-1}) for the formation and decomposition of adducts 5 (plots a) and 8 (plots b) in water: 20 °C, μ = 0.20 M.

glycol, gives a straight line of slope +1 in both cases and affords

$$K_a(5) = 1.38 \times 10^{-7}\ M^{+1}; \qquad K_a(8) = 5.5 \times 10^{-8}\ M^{+1}$$

Using eq 7, we also obtain values of K_c

$$K_c(5) = 1.17 \times 10^{7}\ M^{-1}; \qquad K_c(8) = 4.68 \times 10^{6}\ M^{-1}$$

Kinetic Measurements. The kinetics of the interconversion of **3**, **6** and adducts **5**, **8** were studied spectrophotometrically at 330 and 339 nm, respectively, by using stopped-flow as well as conventional methods. In all runs, the concentrations of acid, base, or buffer components were in large excess over substrate concentration, assuring pseudo-first-order kinetics throughout. The logarithmic values of the observed first-order rate constant k_{obsd} for the combined formation and decomposition of **5** and **8** at 20 °C are plotted in Figure 1 as a function of pH. Since buffer catalysis of the decomposition of **5** and **8** has been observed in the more acidic buffers (chloracetate, formate, and acetate buffers) the k_{obsd} values used at pH <5 in these pH profiles are those extrapolated to zero buffer concentration. In contrast, no buffer catalysis has been detected in the more basic buffers. As can be seen smooth pH–rate profiles were obtained despite the fact that buffers of varying chemical types were used.

The rate constant k_{obsd} reflects the rate of approach to equilibrium between the parent ethers and the adducts and can be expressed as the sum of the individual pseudo-first-order rate constants k_f and k_d, respectively, for the formation and decomposition of **5** and **8**. Using a treatment similar to one previously described[9,16] k_f and k_d may be calculated from eq 9 and 10 where $pH_{1/2}$ is the experimental pH value corresponding to the half-formation of **5** ($pH_{1/2}$ 6.98) and **8** ($pH_{1/2}$ 7.38).

$$k_f = \frac{k_{obsd}}{1 + (10^{-pH}/10^{-pH_{1/2}})} \tag{9}$$

$$k_d = \frac{k_{obsd}}{1 + (10^{-pH_{1/2}}/10^{-pH})} \tag{10}$$

Tables I and II present the values of k_f and k_d calculated in this way at 20 °C together with the experimental values of k_{obsd}.

Complete data are graphically represented in Figure 2 which shows the pH dependence of k_f and k_d. These pH profiles are consistent with equations of the form

$$k_f = k_1 + k_2K[OH^-] = k_1 + \frac{k_2KK_w}{a_{H^+}\gamma_\pm} \tag{11}$$

$$k_d = k_{-2} + k_{-1}[H^+] = k_{-2} + \frac{k_{-1}a_{H^+}}{\gamma_\pm} \tag{12}$$

Scheme I shows the reactions to which the various rate constants refer, viz., k_2 and k_1 refer to internal cyclization of the anions and the parent glycols, respectively, while k_{-2} and k_{-1} refer to the noncatalyzed and H^+-catalyzed ring opening of the adducts, respectively. The various rate coefficients could easily be determined from the two linear portions of the k_f and k_d pH rate profiles (high and low pH regions of each) respectively. We thus obtain: $Kk_2 = 3.1 \times 10^6\ M^{-1}\ s^{-1}$, k_{-2} =

Table II. Experimental and Calculated Pseudo-First-Order Rate Constants, k_{obsd}, k_f, and k_d, for the Formation and Decomposition of the Furoxanic Adduct 8 in Water[a]

pH	k_{obsd}, s^{-1}	k_f, s^{-1}	k_d, s^{-1}	pH	k_{obsd}, s^{-1}	k_f, s^{-1}	k_d, s^{-1}
1.12[b]	0.568	3.12×10^{-7}	0.567	6.72[g]	1.59×10^{-3}	2.85×10^{-4}	1.3×10^{-3}
1.42[b]	0.305	3.34×10^{-7}	0.304	7.05[g]	2.64×10^{-3}	8.41×10^{-4}	1.79×10^{-3}
1.72[b]	0.155	3.39×10^{-7}	0.154	7.52[h]	4.29×10^{-3}	2.48×10^{-3}	1.80×10^{-3}
2.12[b]	6.62×10^{-2}	3.64×10^{-7}	6.61×10^{-2}	7.89[h]	6.34×10^{-3}	4.84×10^{-3}	1.51×10^{-3}
2.42[b]	3.1×10^{-2}	3.40×10^{-7}	3.09×10^{-2}	8.23[h]	1.59×10^{-2}	1.39×10^{-2}	1.96×10^{-3}
2.72[b]	1.6×10^{-2}	3.69×10^{-7}	1.59×10^{-2}	8.91[i]	4.38×10^{-2}	4.25×10^{-2}	1.25×10^{-3}
3.12[b]	7.8×10^{-3}	4.29×10^{-7}	7.79×10^{-3}	9.11[i]	7.48×10^{-2}	7.34×10^{-2}	1.36×10^{-3}
3.30[c]	5.65×10^{-3}	4.70×10^{-7}	5.64×10^{-3}	9.47[i]	0.164	0.162	1.32×10^{-3}
3.74[d]	3.11×10^{-3}	7.12×10^{-7}	3.11×10^{-3}	10.16[i]	0.8	0.8	1.33×10^{-3}
4.34[e]	2.15×10^{-3}	1.96×10^{-6}	2.14×10^{-3}	10.42[i]	1.45	1.45	1.32×10^{-3}
4.64[e]	1.75×10^{-3}	3.17×10^{-6}	1.74×10^{-3}	11.05[j]	6.4	6.4	1.36×10^{-3}
4.94[e]	1.75×10^{-3}	6.33×10^{-6}	1.74×10^{-3}	11.35[j]	10.68	10.67	1.14×10^{-3}
5.36[f]	1.48×10^{-3}	1.40×10^{-5}	1.46×10^{-3}	11.53[j]	19.5	19.5	1.38×10^{-3}
5.68[f]	1.42×10^{-3}	2.77×10^{-5}	1.39×10^{-3}	11.65[j]	26.81	26.80	1.44×10^{-3}
5.98[g]	1.36×10^{-3}	5.20×10^{-5}	1.30×10^{-3}	11.89[j]	35.33	35.32	1.09×10^{-3}
6.30[g]	1.39×10^{-3}	1.06×10^{-4}	1.28×10^{-3}				

[a] At zero buffer concentration; $\mu = 0.20$ M; $t = 20$ °C. [b] HCl solutions (10^{-3}–0.1 M). [c] Citrate buffer. [d] Formate buffer. [e] Acetate buffer. [f] Succinate buffer. [g] Phosphate buffer. [h] *p*-Cyanophenoxide buffer. [i] Borate buffer. [j] NaOH solutions (10^{-3}–7×10^{-3} M).

Table III. Kinetic and Equilibrium Data for Spiro Complex Formation in Water and Deuterium Oxide

		5[a]	8[a]	10	12
H_2O	KK_2, M^{-1}	1.17×10^{7}[b]	4.68×10^{6}[b]	1.8×10^{7}[e]	3×10^{4}[b,h]
		1.24×10^{7}[c]	4.10×10^{6}[c]	2.1×10^{7}[c,f]	3.9×10^{4}[c,h]
				1.6×10^{7}[c,g]	
	Kk_2, M^{-1} s^{-1}	3.1×10^{6}	5.5×10^{3}	6.3×10^{5}[f]	9×10^{4}[h]
	k_{-2}, s^{-1}	0.25	1.34×10^{-3}	0.03[f]	2.3[h]
	k_1, s^{-1}	3.4×10^{-4}	3.3×10^{-7}		
		4.1×10^{-4}[d]	2.95×10^{-7}[d]		
	k_{-1}, M^{-1} s^{-1}	2.7×10^{3}	5.9	2.2×10^{3}[h]	1.8×10^{4}[h]
D_2O	KK_2, M^{-1}	2.17×10^{7}[c]	6.8×10^{6}[c]		
	Kk_2, M^{-1} s^{-1}	4.35×10^{6}	7.5×10^{3}		
	k_{-2}, s^{-1}	0.20	1.1×10^{-3}		1.7[h]
	k_1, s^{-1}	1.43×10^{-4}[d]	1.1×10^{-7}[d]		
	k_{-1}, M^{-1} s^{-1}	4.13×10^{3}	9.3	3.3×10^{3}[h]	
	KK_2 (H_2O)/KK_2 (D_2O)	0.57	0.60		
	Kk_2 (H_2O)/Kk_2 (D_2O)	0.71	0.73		
	k_{-2}(H_2O)/k_{-2} (D_2O)	1.25	1.22		1.35[h]
	k_1 (H_2O)/k_1 (D_2O)	2.86[i]	2.70[i]		
	k_{-1} (H_2O)/k_{-1} (D_2O)	0.65	0.63	0.66[h]	

[a] This work, $t = 20$ °C, $\mu = 0.2$ M. [b] KK_2 determined spectrophotometrically. [c] KK_2 calculated from the ratio Kk_2/k_{-2}. [d] k_1 calculated from $k_{-1} \times KK_2 \times K_w$ (D_2O)/$\gamma_\pm^2$ with pK_w (D_2O) = 15.05 at 20 °C. [e] Reference 18 at 25 °C. [f] Calculated at 20 °C from ref 17. [g] Reference 17 at 25 °C. [h] Reference 13b at 25 °C. [i] Calculated from the values of k_1 estimated according to footnote *d*.

0.25 s^{-1}, $k_1 = 3.4 \times 10^{-4}$ s^{-1}, and $k_{-1} = 2.7 \times 10^{3}$ M^{-1} s^{-1} for **5** and $Kk_2 = 5.5 \times 10^{3}$ M^{-1} s^{-1}, $k_{-2} = 1.34 \times 10^{-3}$ s^{-1}, $k_1 = 3.3 \times 10^{-7}$ s^{-1}, and $k_1 = 5.9$ M^{-1} s^{-1} for **8**. In both cases, the KK_2 values calculated from the ratio Kk_2/k_{-2} are in fairly good agreement with the KK_2 values determined spectrophotometrically (see Table III).

Inserting the values obtained for these parameters into the expression given by eq 13 for k_{obsd}, we see that at low pH (pH <4), only the reverse reaction of **5** (or **8**) + H^+ → **3** (or **6**) is important while, above pH 8, only the reaction of **3** (or **6**) + OH^- ⇌ **4** (or **7**) → **5** (or **8**) is important. This is in agreement with our experimental results.

$$k_{obsd} = \frac{k_{-1}a_{H^+}}{\gamma_\pm} + k_{-2} + k_1 + \frac{k_2 K K_w}{a_{H^+}\gamma_\pm} \qquad (13)$$

In the intermediate pH range, values of k_{obsd} are identical to those of k_{-2}, showing that the plateaus observed in the experimental pH profiles of Figure 1 correspond to the uncatalyzed ring opening of **5** and **8** and that adduct formation from internal cyclization of the glycols is negligible under our experimental conditions. Therefore, the intersections in Figure 1 between the k_{-2} plateaus and the straight lines of slope +1 yield the $pH_{1/2}$ values corresponding to the half-formation of **5** and **8**. We thus obtain $pH_{1/2}$ 6.93 and 7.36 for **5** and **8**, respectively, in excellent agreement with values determined thermodynamically.

As previously noted, buffer catalysis was observed in solutions of the most acidic buffers and was investigated in some detail with the chloracetate–chloracetic acid, formate–formic acid, and acetate–acetic acid systems. As is apparent from Figure 3 which presents the data for complex **8** in the acetate–acetic acid buffer, plots of the observed rate constant k_{obsd} vs. the undissociated acid concentration [AH] are linear with pH dependent intercepts but pH independent slopes. Thus, k_{obsd} can be expressed by eq 14 where k_{AH} is the second-order rate constant for catalysis of the ring opening of **5** and **8** by the buffer species AH:

$$k_{obsd} = k_{-2} + k_{-1}[H^+] + k_{AH}[AH] \qquad (14)$$

Table IV summarizes the k_{AH} values determined from the slopes for the three buffer systems. Also, as expected and shown in Figure 4, a plot of the intercepts vs. the hydrogen ion concentration affords in both cases a straight line with an intercept equal to k_{-2} and a slope equal to k_{-1}. We thus ob-

Table IV. Rate Constants k_{AH} for Acid Catalysis of the Ring Opening of Spiro Complexes in Water

buffer acidic species	pK_a[a]	k_{AH}, M^{-1} s^{-1} 5[b]	8[b]	10[c]	12[c]
H_3O^+	−1.74	2700	5.9	2200	18000
chloracetic acid	2.84	41	0.11	12	300
formic acid	3.74	11.7	0.024	2.3	60
acetic acid	4.64	4.75	0.011	0.9	25
water	15.66	7.2×10^{-5}	2.35×10^{-7}	2.14×10^{-6}	2.5×10^{-4}

[a] pK_a at $\mu = 0.20$ M. [b] This work at $t = 20$ °C, $\mu = 0.20$ M. [c] Reference 13b at $t = 25$ °C, $\mu = 0.30$ M.

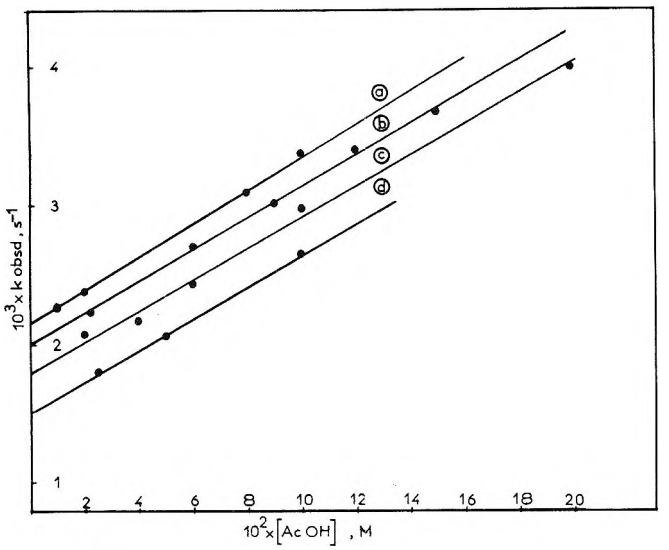


Figure 3. Effect of acetic acid concentration and pH on k_{obsd} for the decomposition of 8 in water: 20 °C, $\mu = 0.20$ M; (a) pH 4.04; (b) pH 4.17; (c) pH 4.34; (d) pH 4.64.

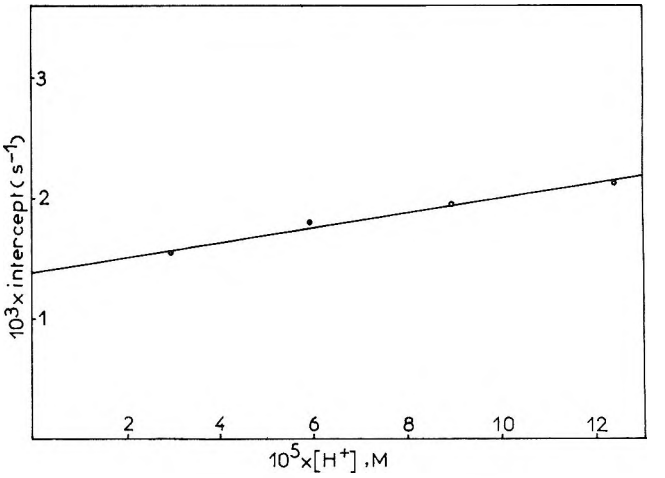


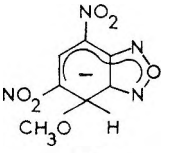
Figure 4. Plots of the intercepts of lines in Figure 3 against the hydrogen ion concentration: 20 °C; $\mu = 0.20$ M.

tain: $k_{-2} = 1.38 \times 10^{-3}$ s^{-1}, $k_{-1} = 6.2$ M^{-1} s^{-1} for the benzofuroxan adduct 8 and $k_{-2} = 0.22$ s^{-1}, $k_{-1} = 2.5 \times 10^3$ M^{-1} s^{-1} for the benzofurazan adduct 5. Within experimental error, these values agree well with the one previously determined from the pH profiles of Figure 2.

The rates of formation and decomposition of 5 and 8 have also been determined in deuterium oxide at 20 °C. The observed solvent isotope effects on KK_2, Kk_2, k_{-2}, and k_{-1} are given in Table III.

Discussion

Effect of the Annelated Furazan and Furoxan Rings on Spiro Complex Formation. The values of equilibrium and rate constants for the formation and decomposition in water of spiro complexes 5 and 8 are collected in Table III which also includes some literature data on previously studied benzenic spirocomplexes 10 and 12 derived from 1-(2-hydroxyethoxy)-2,4,6-trinitrobenzene (9)[13b,17,18] and 1-(2-hydroxyethoxy)-2,4-dinitrophtalene (11).[13b] As can be seen from a comparison of the KK_2 values, the stability of the adducts 5 and 8 relative to the parent ethers is of the same order of magnitude as that of the trinitro adduct 10 (the ratios KK_2(10)/KK_2(5) and KK_2(10)/KK_2(8) are equal to 1.7 and 4.6, respectively) but much greater than that of the naphtalenic adduct 12 (the ratios KK_2(5)/KK_2(12) and KK_2(8)/KK_2(12) are equal to about 300 and 115, respectively). These results clearly demonstrate the very strong stabilizing influence exerted by the annelated furazan and furoxan rings on Meisenheimer-type adducts. That KK_2 is about 2.7-fold greater for 5 than for 8 indicates that the furazan moiety is somewhat more efficient than the furoxan one in stabilizing the adducts. Interestingly, this stability difference between 5 and 8 is similar to the one we have found between the adducts 13 and 14 formed from methanol and methoxide ion



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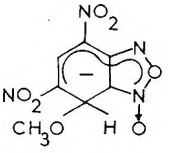

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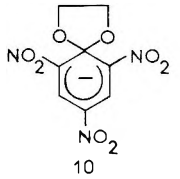
attack on 4,6-dinitrobenzofurazan and 4,6-dinitrobenzofuroxan in methanolic solution: pK_a(13) = 6.15;[19] pK_a(14) = 6.46.[20] These results are consistent with the notion that the electron-donating effect of the oxygen atom of the *N*-oxide group may partially reduce the overall electron-withdrawing effect of the furoxan ring compared with that of the furazan analogue.[21]

Despite their similar stability, 5 and 8 have drastically different rates of formation and decomposition. For the adduct formation, Kk_2 is about 560-fold greater for 5 than for 8, whereas the ratio k_1(5)/k_1(8) for direct internal cyclization of the parent ethers is found to be equal to about 1600. For adduct decomposition, the ratios k_{-2}(5)/k_{-2}(8) and k_{-1}(5)/k_{-1}(8) of the rate constants for the noncatalyzed and H^+-catalyzed ring opening are equal to about 200 and 700, respectively. One possible reason for differences in the rates of formation might be a stronger stabilization of the parent glycol 6 due to an intramolecular hydrogen bonding to the *N*-oxide group. This would decrease the equilibrium constant *K* governing the ionization of the side chain of 6, and hence Kk_2 for the formation of 8, as well as the k_1 value for direct internal cyclization of 6. However, this does not appear to be



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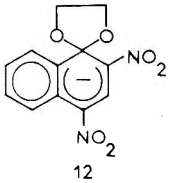

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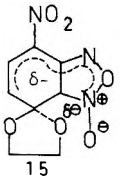
an attractive explanation since such hydrogen bonding would require the formation of a nine-membered ring, a process which is not expected to be very favorable. There is evidence that it probably does not take place. If hydrogen bonding was present in **6**, one would expect different isotope effects on KK_2, Kk_2, and k_1 for **8** than on the similar terms for **5**. As can be seen in Table III, this is not borne out by the experimental data; in fact, the ratios $KK_2(H_2O)/KK_2(D_2O)$, $Kk_2(H_2O)/Kk_2(D_2O)$, and $k_1(H_2O)/k_1(D_2O)$ are about the same in the two systems. Also, we note that the values for the $KK_2(H_2O)/KK_2(D_2O)$ and $Kk_2(H_2O)/Kk_2(D_2O)$ ratios are identical to those recently reported by Bernasconi[17] for the formation of the spiro complex derived from 1-(3-hydroxypropoxy)-2,4,6-trinitrobenzene ($KK_2(H_2O)/KK_2(D_2O)$ = 0.585; $Kk_2(H_2O)/Kk_2(D_2O)$ = 0.74). Furthermore, there seems to be no compelling reason why a stronger stabilization of **6** should also affect the rate of decomposition of the adduct **8** relative to that of its analogue **5**. In fact, and in accord with previous discussions of similar situations,[22,23] any reasonable explanation of the slower rates of formation and decomposition of **8** must invoke an effect on the transition states which is not present (or present to a smaller extent) in either the reactants (**6** or **7**) or in the adduct **8**. We believe that this effect is connected with the presence of the *N*-oxide group and may be explained in terms of electrostatic considerations. Thus, we note that the negative glycolate oxygen can be removed from the N–O oxygen in the glycolate anion **7**, minimizing the repulsion, whereas in the adduct **8**, no negative charge is left on the glycolate oxygen. In contrast, important electrostatic repulsion between the two oxygens may be expected in the transition state **15**, which would result in an increase in its energy and in a concomitant decrease in the Kk_2 and k_{-2} values. When considering the k_1, k_{-1} pathway, similar electrostatic destabilization of the transition state **16** might arise



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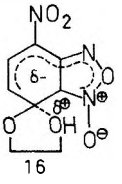
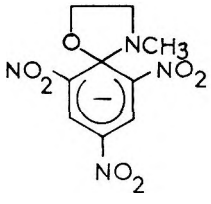


16

from repulsion between the partially positive glycolate oxygen and the positive aza nitrogen, causing a decrease in the k_1, k_{-1} values. Since similar effects cannot operate in furazan series, this would explain the higher rates of formation and decomposition for **5** than for **8**.

Buffer Catalysis. The present work shows the absence of buffer catalysis of the formation of the adducts **5** and **8**, indicating that, in the corresponding experimental conditions (pH >6), the parent ethers GOH and anions GO^- are in rapid equilibrium and the internal cyclization of these latter is rate determining. In contrast, under certain experimental conditions (pH <5), general acid catalysis of the decomposition of the adducts can be observed. As can be seen in Figure 5, plots of log k_{AH} values vs. the pK_a values for the catalyzing acids are linear with slopes giving values of 0.44 and 0.43, respectively, for the Brönsted coefficient α. These results are, indeed, quite similar to those reported by Crampton[13b] and Bernasconi[24] for the acid-catalyzed decomposition of benzenic spiro adducts **10**, **12**, **17**, and **18**. Also, as proposed by these authors,



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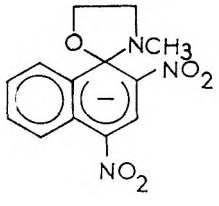

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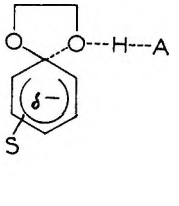

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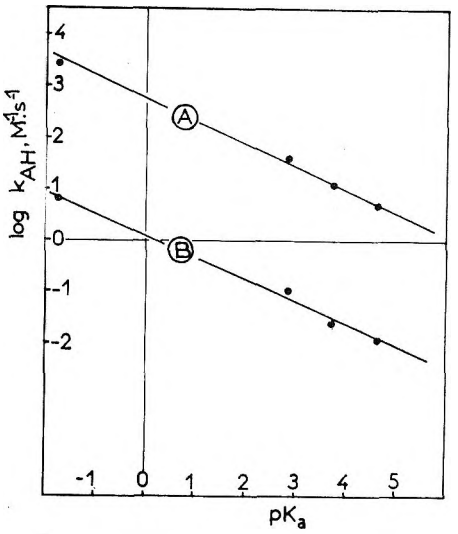

Figure 5. Brönsted plots for the acid catalyzed decomposition of adducts **5** (plot A) and **8** (plot B).

the most probable mechanism for the reaction is a concerted process, with a transition state such as **19**. The microscopic reverse of this step, i.e., general base-catalyzed cyclization of the ethers **3** and **6**, cannot be observed under conditions where buffer catalysis is effective because the equilibrium favors the ether over the complex, in agreement with the low values calculated for k_1.

An estimation, using the Brönsted plots of Figure 5, of the k_{AH} values for the less acidic general acids present in the buffer solutions ($H_2PO_4^-$, HCO_3^-, boric acid) confirms that the catalytic effects of these species are undetectable in our experimental conditions. Of special interest are the k'_{AH} values ($k_{AH} \times 55.55$) of 4×10^{-3} and 1.30×10^{-5} s^{-1} calculated for catalysis of the decomposition of **5** and **8**, respectively, assuming that water is acting as a general acid. Comparing the values with the experimental values of 0.25 and 1.21×10^{-3} s^{-1} measured for k_{-2} reveals, in agreement with the weak isotope effect found for this step ($k_{-2}(H_2O)/k_{-2}(D_2O)$ is of about 0.65 in both cases), that the noncatalyzed decomposition of the adducts does not occur via a biomolecular reaction involving the transition state **19** (A = OH) but is certainly a unimolecular reaction. Thus, the formation and decomposition of **5** and **8** are exclusively described by eq 2 at pH >5. At pH 5, the acid catalyzed ring opening of the adducts begins to compete with the noncatalyzed one and becomes the predominant pathway at pH <4.

Experimental Section

Materials. 7-(2-Hydroxyethoxy)-4-nitrobenzofurazan (**3**) and -benzofuroxan (**6**) were prepared at room temperature by adding 5 mL (5 *m*M) of 1 M sodium glycolate in ethylene glycol dropwise to a suspension of 1 g (≃5 mM) of 7-chloro-4-nitrobenzofurazan or -benzofuroxan in 40 mL of ethylene glycol. The solutions were allowed to stand for 1 h and then acidified by concentrated hydrochloric acid, diluted with water, and extracted with chloroform or ethyl acetate. After repeated washing with dilute hydrochloric acid solutions, the $CHCl_3$ or ethyl acetate solutions were dried over $MgSO_4$ and evaporated to yield brown crystals of **3** or **6** which were recrystallized from ethanol or a $CHCl_3$–acetone mixture: **3**, mp 115 °C; **6**, mp 124 °C.

The spiro adducts **5** and **8** were prepared as potassium salts by addition of nearly 1 equiv of 1 M methanolic potassium methoxide to a solution of the parent molecules **3** and **6** in acetonitrile. After the reaction, the solvent was evaporated off and the solid residues were washed repeatedly with anhydrous ether and then dried in vacuo. The adducts so obtained showed UV–visible and ^1H NMR spectra identical to those obtained when they were generated in situ from base addition to aqueous or Me_2SO solutions of the parent ethers. Acidification resulted in quantitative regeneration of the starting materials.

HCl and KOH solutions were prepared from Titrisol. Buffer solsolutions[9] were made up from the best available commercial grades of reagents.

Rate and pH Measurements. Stopped-flow determinations were performed on a Durrum stopped-flow spectrophotometer, the cell compartment of which was maintained at 20 ± 0.5 °C. Other kinetic measurements were made using a Beckman Acta-3 spectrophotometer. All kinetics runs were carried out under pseudo-first-order conditions with a substrate concentration of about 4×10^{-5} M. Rate constants are accurate to ±3%.

The pH was measured on a Radiometer Model pH meter according to standard methods. The pH values are relative to the standard state in pure water. The pD values were obtained by adding 0.40 to the pH meter reading.[25]

Acknowledgments. We are very thankful to Professor Claude F. Bernasconi (University of California—Santa Cruz) for helpful suggestions and assistance in the preparation of the manuscript.

Registry No.—**3**, 66770-00-1; **5** potassium salt, 66770-01-2; **6**, 66770-02-3; 8 potassium salt, 66787-92-6; 7-chloro-4-nitrobenzofurazan, 10199-89-0; 7-chloro-4-nitrobenzofuroxan, 18378-13-7.

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Reversed Micellar Catalysis. Catalysis of Dodecylammonium Propionate Reversed Micelles in the Hydrolysis of Alkyl *p*-Nitrophenyl Carbonates

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The hydrolysis rates of methyl and dodecyl *p*-nitrophenyl carbonates in nonpolar organic solvents such as benzene and hexane were greatly enhanced by dodecylammonium propionate, DAP. The rate of hydrolysis was proportional to the square of the detergent concentration. At higher concentration of water than about 1×10^{-1} M the rate decreased with the increase in water concentration, while at lower concentration than 1×10^{-1} M the rate was almost irrespective of the water content. The rate varied greatly among five nonpolar solvents adopted, which was interpreted in terms of the substrate partitioning into the micellar core. Thermodynamic parameters of activation suggest that the mobility of the activation complex is highly restricted at the transition state ($\Delta S^{\ddagger} = -30$ to -53 eu), nevertheless the large rate enhancement is brought about by the term of enthalpy of activation ($\Delta H^{\ddagger} = 2$–11 kcal mol^{-1}), which overwhelms the unfavorable enthropy term. Hexadecyltrimethylammonium propionate was about fourfold less effective to the reaction than DAP, while benzyldimethylhexadecylammonium chloride showed no catalytic effect at all under the same reaction conditions.

Reversed micellar catalysis is roughly classified into two categories: (1) the catalysis by detergent itself in the reversed micelles provided with the functional detergents and (2) the assistance of the restricted (rigid) field produced in the interior core of reversed micelles. The former is exemplified in studies such as the mutarotation of glucose,[3] the decomposition of Meisenheimer complex,[4] and the hydrolyses of sucrose,[5] ATP,[6] and 2,4-dinitrophenyl sulfate,[7] where the general acid–base catalysis with detergents is concerned. The latter cases are seen in the ATP hydrolysis as catalyzed with the Mg^{2+} ion[6] and the aquation of tris(oxalato)chromate(III).[8]

In this work, through the kinetic investigation for the hydrolytic decomposition of alkyl *p*-nitrophenyl carbonates in the DAP reversed micelles, which belongs to the category (1), we would like to extend the scope of reversed micellar catalysis.

Experimental Section

Materials. Dodecylammonium propionate (DAP) was prepared according to the method described earlier.[9] Hexadecyltrimethylammonium propionate (CTAP) was prepared by the replacement of the counteranion of hexadecyltrimethylammonium hydroxide with propionic acid by the aid of the anion exchange column chromatography (Amberlite IRA-400) technique. The surfactant, CTAP, was very hygroscopic and difficult to submit to the elemental analysis. CTAP was stored over phosphorus pentaoxide in a vacuum desiccator and the purity was established by TLC, IR, and NMR spectra. Benzyldimethylhexadecylammonium chloride (CBDACl) was commercially obtained. Syntheses of methyl- (**1a**) and dodecyl-*p*-nitrophenyl carbonates (**1b**) are described elsewhere.[10] Distilled water using a glass distillator was used throughout all the kinetic runs. All the organic

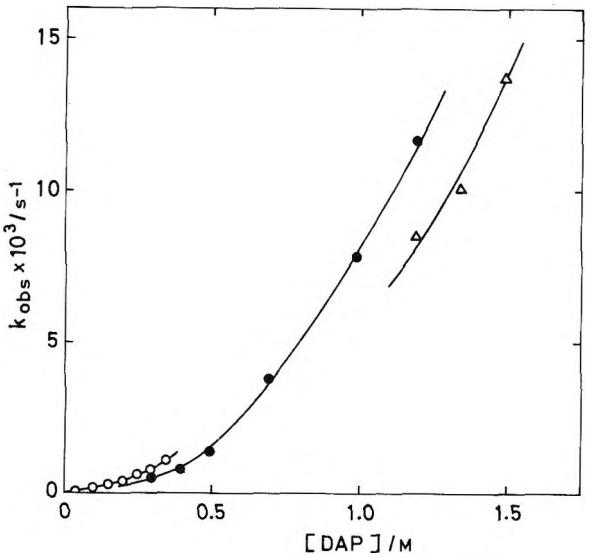


Figure 1. Correlations between the observed first-order rate constants and DAP concentration in the hydrolysis of **1b** (1.97×10^{-5} M) with different concentrations of water: (○) 2.78×10^{-4} M, (●) 0.495 M, and (△) 0.99 M in benzene at 25.0 °C.

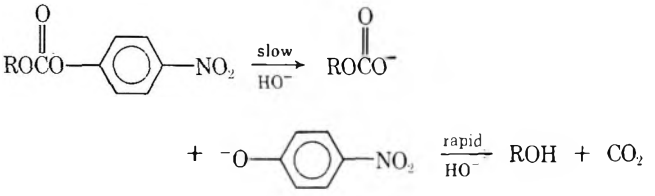
solvents used was purified, dried, and stored over molecular sieve Linde type 4A. Since surfactants used in this work excepting CTAP were water free, the contamination of water in these systems was usually caused by solvents. In all runs, therefore, the amount of water in the solvents was carefully determined every time prior to the preparation of stock solution for kinetics on a Hiranuma Aquameter AQ-1 using Karl-Fischer Reagent SS "Mitsubishi" (f = 0.3 mg/mL) with Standard Water Methanol Solution (f = 0.5 mg/mL at 20 °C) for Karl-Fischer Reagent, Mitsubishi Chemical Industries Ltd., Tokyo. For CTAP, the amount of water was determined after the preparation of stock solution.

Kinetic Measurements. Reaction rates were determined spectrophotometrically by monitoring the liberation of p-nitrophenol. The absorption maximas and molar extinction coefficients in DAP reversed micelles using different bulk solvents are as follows: ϵ_{311} = 10200 M^{-1} cm^{-1} in hexane, ϵ_{311} = 12000 in cyclohexane, ϵ_{311} = 11600 in carbon tetrachloride, ϵ_{317} = 12200 in benzene, ϵ_{313} = 10800 in 1,2-dichloroethane, and ϵ_{312} = 9200 in methanol. The molar extinction coefficient of p-nitrophenol was found to somewhat change with the water content in reversed micelles. Values cited above are for systems containing 0.20 M water. A reaction solution (3.0 mL) containing given amounts of DAP, water, and an organic solvent was placed in a thermostated cell. To this solution were injected 30 μL of the substrate dissolved in the same solvent to give an initial substrate concentration of 2×10^{-5} M. The reaction mixture in the cuvette was rapidly mixed using a slim Teflon rod and the increase of absorbance was followed on a Shimadzu UV-140 double beam spectrophotometer connected with a Riken SP-G3S recorder. An absorbance of the reaction mixture at infinite time was in good agreement with the value estimated from the molar extinction coefficient of p-nitrophenol independently obtained under the same condition. Good first-order kinetics were assured in all runs.

Partition Coefficients. Partition coefficients of **1a** between the aqueous and organic phases were determined for different solvent systems. A 12.5-mL solution of **1a** (8×10^{-4} M) in the solvent was vigorously shaken with the same amount of water. After the separation of both phases, aliquots withdrawn from each phase were subjected to the spectroscopic determination. Substrate concentrations partitioned in both phases were obtained by the aid of the known extinction coefficient. Partition coefficients ($K_p = [\mathbf{1a}]_{water}/[\mathbf{1a}]_{organic\ solvent}$) thus obtained were 0.110 (hexane), 0.089 (cyclohexane), 0.013 (carbon tetrachloride), and 0.001 (1,2,-dichloroethane), respectively. Spectroscopic determination of the benzene phase was impossible because of the overlapping of absorptions of substrate and solvent. The K_p value was, therfore, estimated from only the absorbance of the aqueous phase. Most of **1a** was found to be distributed in the benzene layer ($K_p \doteqdot 0$ for benzene).

Results

Product Analysis. After the completion of the p-nitrophenol release, the reaction mixture was subjected to the high-speed liquid chromatography on a Toyo Soda HLC-802UR. Using a LS-310 column (30 cm in length) with hexane as eluant under the pressure of 10 kg cm^{-2}, only p-nitrophenol and methanol were detected at R_ts' of 9.5 and 11 min, respectively, and no aminolyzate[11] with dodecylamine was detected. This means that the reaction of carbonate esters in the



DAP reversed micelles is simple and normal hydrolysis. In the alkaline hydrolysis of aryl alkyl carbonates, generally, the first stage of phenol liberation is the rate-determining step and the subsequent alcohol formation is very rapid.[12] No efforts, therefore, were made to follow the formation and/or decay of the intermediate monoalkyl carbonates.

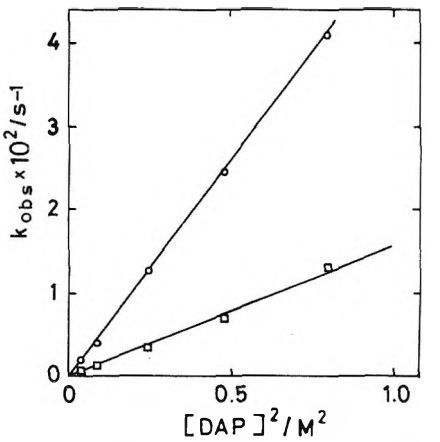


Figure 2. Plots of the observed first-order rate constants against squares of DAP concentration in the hydrolysis of **1a** in benzene (□) and in carbon tetrachloride (○) at 25.0 °C. Initial concentrations of substrate and water were 1.96×10^{-5} and 0.495 M, respectively.

Rate Dependence on the DAP Concentration. Spontaneous hydrolyses of substrates, **1a** and **1b**, in organic solvents, such as benzene, hexane, or carbon tetrachloride, saturated with water were negligibly slow. The addition of DAP, however, drastically enhanced the hydrolysis rates in these solvents, and the reaction rate increased parabolically with respect to the detergent concentration. For the case of **1b** this situation is typically exemplified in Figure 1 with three different water concentrations. When the rate was plotted against the square of DAP concentrations, a good linear relationship was attained as shown in Figure 2. These correlations were kept throughout all the experiments, irrespective of substrates and solvents:

$$\text{rate} = k_3[\text{DAP}]^2[\text{substrate}] \quad (1)$$

Effect of Water Concentration. Decomposition rates of the carbonate esters in DAP reversed micelles were found to be very sensitive to the water content of the system. As shown in Figure 3, between 1 and 0.1–0.2 M water in the 0.2 M DAP/benzene system, the rates are proportional to the reciprocal of water concentration:

$$\text{rate} \propto 1/[H_2O] \quad (2)$$

When the water concentration is lower than about 0.1 M (about 0.2 M for **1a**), however, the rates are almost irrespective of water content. As a result, the rate eq 3 was valid though

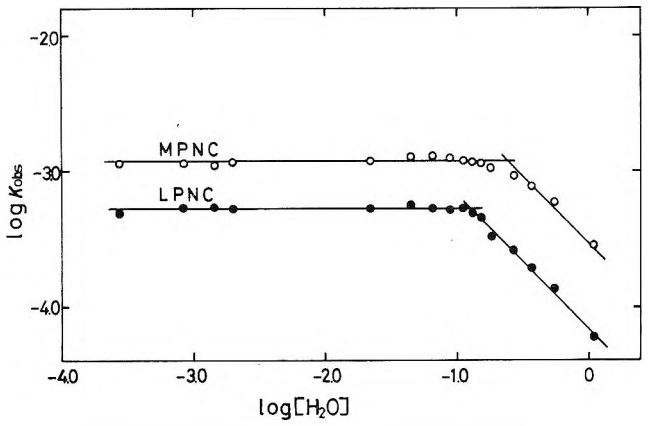


Figure 3. Water concentration dependency of the observed first-order rate constants in the hydrolysis of **1a** (○) and **1b** (●) at 25.0 °C with 0.198 M DAP in benzene. The initial concentrations of **1a** and **1b** were 1.96×10^{-5} and 1.97×10^{-5} M, respectively.

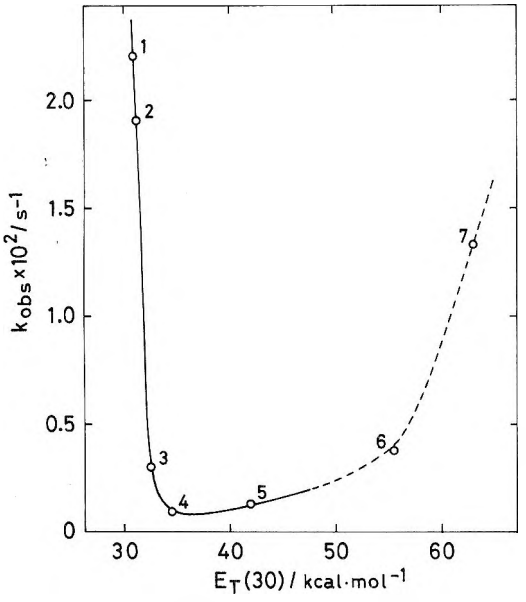


Figure 4. Effect of solvent polarity on the hydrolysis rates of **1a** (1.96×10^{-5} M) with 0.198 M DAP containing 0.198 M water at 25.0 °C.

over a limited range of water concentrations:

$$\text{rate} = k_2 \frac{[\text{DAP}]^2}{[\text{H}_2\text{O}]}[\text{substrate}] \qquad (3)$$

The present findings for the effect of water on the reaction rate were in accordance with the preceding findings by Seno and his co-workers for ATP hydrolyses in the DAP micelles.[6]

Solvent Effect. The rate of *p*-nitrophenol release from **1a** in the DAP reversed micelles was largely affected also by the sort of bulk solvents. When apparent first-order rate constants obtained in various solvents were, at first, plotted against the solvent polarity scale, Dimroth's $E_T(30)$,[13] there exists a minimum point around the polarity corresponding to that of benzene (Figure 4). Since DAP may not form reversed micelles in methanol and water, both polar solvent systems are discarded from further discussion. When rate constants for **1a** in five nonpolar solvents were, then, plotted against the partition coefficients (K_p), a good linear correlation between both parameters has been established as shown in Figure 5. This means that the hydrolysis rate of **1a** decreases when the substrate is more partitioned into the bulk solvent.

Thermodynamic Parameters of Activation. For the hydrolysis of **1a** in the DAP reversed micelles containing different concentrations of water, thermodynamic parameters

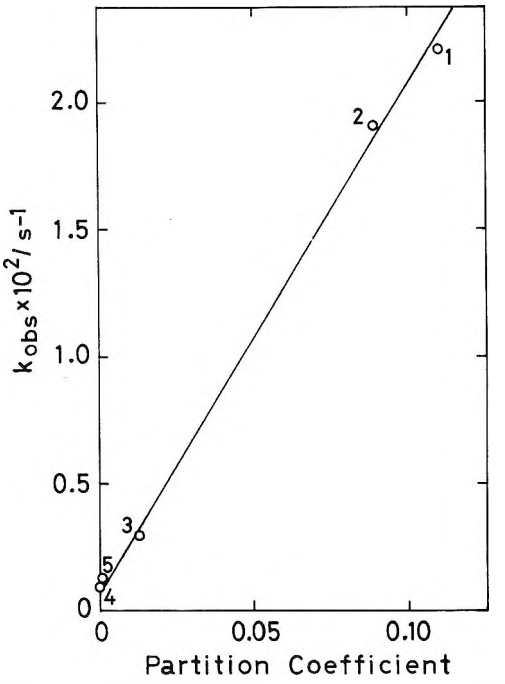


Figure 5. Plots of the rate constants for the hydrolysis of **1a** in the DAP reversed micelles against the partition coefficients of the substrate between aqueous and organic phases. Numbers 1, 2, 3, 4, and 5 in the figure denote hexane, cyclohexane, carbon tetrachloride, benzene, and 1,2-dichloroethane, respectively.

Table I. Thermodynamic Parameters of Activation for the 1a Hydrolysis as Catalyzed with DAP Reversed Micelles [a]

solvent	$[H_2O]$, M	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal mol^{-1}
	reversed micellar catalysis			
benzene	0.051	7.6 ± 0.5	−39.9 ± 0.1	19.5 ± 0.6
	0.495	9.6 ± 0.1	−34.0 ± 0.0	19.7 ± 0.1
	0.693	10.4 ± 0.2	−31.7 ± 0.0	19.9 ± 0.2
	0.891	10.6 ± 0.2	−31.5 ± 0.0	20.0 ± 0.2
carbon	0.051	8.3 ± 0.5	−36.1 ± 0.1	19.1 ± 0.6
tetra-	0.198	8.5 ± 0.1	−35.1 ± 0.0	19.0 ± 0.1
chloride	0.495	10.7 ± 0.2	−29.1 ± 0.0	19.3 ± 0.2
hexane	0.198	1.9 ± 0.3	−53.1 ± 0.1	17.7 ± 0.4
	hydroxide ion catalysis [b]			
		8.4	−26	16.1

[a] Parameters were calculated using the third-order rate constants (k_3) obtained at 25.0 °C. [b] Parameters were calculated using the second-order rate constants. Initial concentration of **1a** was 9.90×10^{-6} M in 9.9% (v/v) EtOH–1.0% (v/v) CH_3CN aqueous solution containing different amounts of sodium hydroxide at 25.0 °C.

of activation were evaluated using the third-order rate constants, k_3 of eq 1, which are listed in Table I. Table I also includes the parameters for the simple hydroxide ion catalysis of the **1a** hydrolysis. There exists a good isokinetic relationship between enthalpies and entropies of activation. The increase of water content results in the increases of both enthalpy and entropy of activation. Isokinetic temperatures (β) obtained were 348 ± 13 and 351 ± 20 K for DAP/benzene and DAP/carbon tetrachloride systems, respectively. The change of bulk solvent from hexane to carbon tetrachloride and then benzene reveals again the increases of enthalpy and entropy of activation, which provides $\beta = 385 \pm 27$ K.

Discussion

The structure of reversed micelles can be visualized as the aggregates of detergents with their ionic heads orienting into

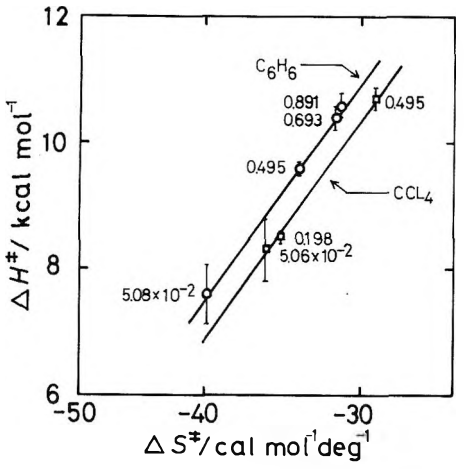


Figure 6. Isokinetic relationship of the **1a** hydrolysis as catalyzed with DAP reversed micelles in benzene and carbon tetrachloride containing different concentrations of water at 25.0 °C. Numbers in the figure refer to the water concentration.

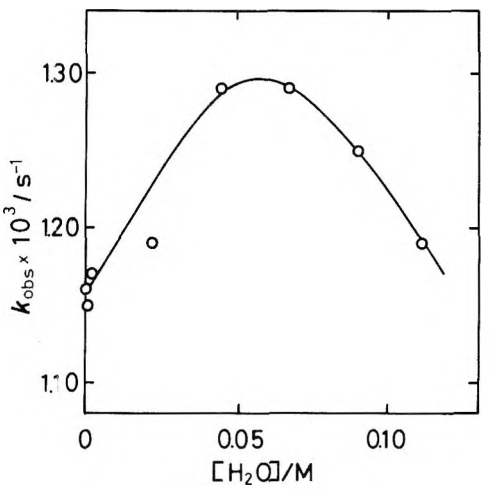


Figure 7. Enlarged view of the correlation between the observed first-order rate constants of **1a** hydrolysis and relatively low concentrations of water in 0.198 M DAP–benzene reversed micelles at 25.0 °C.

Table II. The Observed First-Order Rate Constants of 1a Hydrolysis in Different Reversed Micelles at 25.0 °C[a]

detergent	k_{obsd}/s^{-1}
DAP	9.98×10^{-4}
CTAP	2.60×10^{-4}
CBDACl	~0

[a] The initial concentration of the substrate was 1.96×10^{-5} M in 0.099 M detergent–0.15 M water–benzene system.

the interior core.[2] The aggregation number of DAP in benzene, hexane, or carbon tetrachloride was estimated to be 2–5 by the NMR[14,15] or VPO method.[16] There remain, however, some controversies concerning the concept of cmc in reversed micelles.[17,18] It is generally true that the cmc in reversed micelles is largely affected by the presence of solutes.[3,7]

In the DAP reversed micelles, generally, ionic head groups of the DAP molecule participate in reactions occurring in the interior core. The most common fashion of the catalysis with DAP reversed micelles is the general acid–base catalysis with the ammonium and/or carboxylate groups.[2-7] The reaction rate of the carbonate hydrolyses increased with the increase in the detergent concentration (Figures 1 and 2). This suggests that the detergent molecules must participate directly as the catalyst also in our present case. Since the rate equation indicates the second-order dependence on the DAP concentration, the ternary aggregate of two molecules of DAP and one of the substrate must be involved in the reaction. In CTAP reversed micelles, the hydrolysis rate was decreased by about 3.8 times compared with that in the case of DAP micelles, while CBDACl micelles completely inhibited the reaction (Table II). The former detergent is expected to behave only as a general base catalysis because of the lack of acidic proton, meanwhile the latter is considered not to be the functional detergent for the present reaction since it bears neither an acidic proton nor an effective base. Judging from these results, in the present system DAP may be involved as general acid–base catalysts.

Solvent Effect. For hydrolyses of both esters the same kinetic relationship (eq 1–3) was established for all solvent systems used. Furthermore, even if the bulk solvent was altered, a good isokinetic relationship was attained (Table I and Results). These results were certain evidences indicating that the reaction occurs according to an identical mechanism.

A linear correlation between the hydrolysis rates and partitioning coefficients of the substrate **1a** in different solvents (Figure 5) suggests that partitioning of the substrate into the water core is an important preequilibrium process. This is also proven by the relative rate ratio of the less hydrophobic substrate **1a** to the more hydrophobic **1b**: $k_{(1a)}/k_{(1b)} = 4.65$ in 0.198 M DAP–1.10 M H_2O–benzene and 2.35 in 0.198 M DAP–2.78×10^{-3} M H_2O–benzene, respectively, at 25.0 °C. Quite similar results have been published by Menger and his co-workers for the hydrolysis of PNPA as catalyzed with imidazole in AOT/octane reversed micelles.[19]

The importance of incorporation of substrates into the interior core was pronounced by the effect of water concentration. Over the range where the rate eq 3 is valid, the decrease of water concentration caused the significant enhancement of hydrolysis rate, which is brought about mostly by the enthalpy of activation (Table I and Figure 6). When the substrate is more concentrated in the water pool, the substrate will have more chance to interact directly with the detergent molecules. This should result in the decrease in the enthalpy of activation. Of course, meantime, the substrate may largely lose the motional freedom by being encapsulated in the restricted field,[20] resulting in the decrease of entropy of activation. These are revealed in the isokinetic relationship of Figure 6.

When the substrate is anchored very closely to the catalyst, the catalyst will work most effectively. In addition, the dehydration from the ammonium and carboxylate ions (the hydrophobic ion pair[21]) will provide more powerful catalysts compared to those in the bulk aqueous media. Anyway, the entrapment of substrates in the rigid interior core of reversed micelles brings about the convenient proximity effect, which undergoes anchoring of substrates at the reaction site in a very similar manner to what enzymes do.

At first glance, under the extremely low concentration of water, it seems that the rate of hydrolysis is irrespective of the water content. However, the enlarged view of the relationship between the rates and amounts of water at relatively low concentration revealed the existence of a rate maximum around the point where the molar ratio of DAP to water is about 3–4 (Figure 7). Under the circumstances, the reactivity of water may be much different from that in the bulk solution.[3,22,23] The increase of water amount must enlarge the core size[19,24,25] and increase the hydration of detergent ions and start to form hydrogen bondings by water molecule itself.[26] This will decisively make the catalyst and water less effective.[23]

Acknowledgment. We thank Professor Toyoki Kunitake, Kyushu University, for measurements of trace water.

Registry No.—**1a**, 17175-16-5; **1b**, 66398-02-5; DAP, 17448-65-6; CTAP, 41349-78-4; CBDACl, 122-18-9; methyl-*n*-dodecylurethane, 66769-57-1; methyl chlorocarbonate, 79-22-1; dodecylamine, 124-22-1.

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Application of Molecular Mechanics to Predict Solvolysis Rates of Polycyclic Secondary Derivatives

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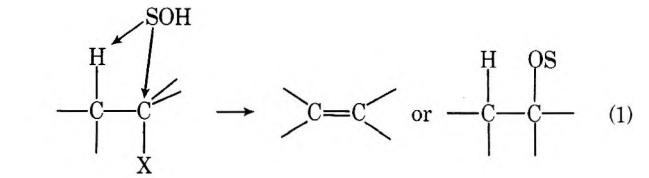
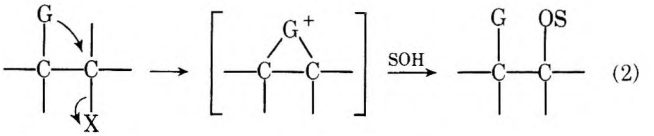
The molecular mechanics method of Schleyer is shown to predict accurately acetolysis rates of rigid, polycyclic secondary derivatives reacting by a k_c mechanism. Calculated rates are compared with experimental rates for substrates which may potentially react with σ assistance, and such assistance is shown to be important for several reactions. Six of these assisted reactions involve either degenerate rearrangement or rearrangement to a less stable carbon skeleton. These six reactions, consequently, cannot be downhill processes for which σ assistance is not controversial, but rather must involve formation of σ-bridged, nonclassical intermediates. In addition, calculated carbocation bond angles are shown to correlate well with the corresponding infrared carbonyl stretching frequencies.

A long-standing goal of organic chemistry has been to predict rates of carbocation formation and rearrangement in solvolysis reactions. The development of molecular-mechanical or empirical-force-field calculations has been a major step toward achieving this goal. The successful calculation of heats of formation, geometries, and strain energies for stable molecules has become practically routine with major efforts now being directed toward parameterization for more atoms.[1-3] Applications to reactivity problems have not been common, but the following reactions have been studied: ester hydrolysis,[4] aldol condensation,[5] nucleophilic addition to ketones,[6] solvolysis reactions,[7-9] carbocation rearrangements,[9,10] alcohol oxidation,[11] alkene dimerization,[12] and free-radical substitution.[13]

Application of the molecular mechanics method to solvolysis reactions is particularly interesting because it presents the possibility of separating steric effects from the other factors governing these reactions. Solvolytic heterolysis of the bond between carbon and leaving group can be assisted by nucleophilic or basic solvent attack (a k_s process,[14] eq 1), or by nucleophilic neighboring group attack (a k_Δ process,[14] eq 2), or it may be assisted or retarded by steric effects.[15-18] One





of the prime questions of solvolysis chemistry concerns the extent to which these various factors affect the reaction rates of secondary derivatives. The reactions of primary and tertiary derivatives are relatively simple, since these compounds react by competitive k_s and k_Δ processes in the former case and by a simple ionization mechanism (a k_c process)[14] in the latter case.[19] Secondary systems are more complex in that k_c, k_s, or k_Δ processes may be involved, and it has proven extremely difficult to determine which is operating.[18,19] Since methods have been developed recently for detecting k_s processes,[20]

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much of the remaining uncertainty concerns distinguishing between k_c and k_Δ processes. This problem could be solved if rates of reaction by a simple, unassisted k_c process could be calculated, since k_Δ processes are assisted and would be readily revealed by reaction rates greater than the calculated unassisted ionization rates. Unfortunately, the several attempts at predicting unassisted solvolysis rates have not been wholly successful.[18,21-25] The purpose of the present work is to describe the application of the method of molecular mechanics to the calculation of unassisted solvolysis rates of secondary derivatives.

Molecular mechanics has been applied to the study of carbocations and their rates of formation primarily by Schleyer and his co-workers.[7-12] Since the calculation of force fields for solvolytic leaving groups was still in the developmental stage, Schleyer used hydride as a leaving-group model, eq 3, and further assumed that the carbocation would serve as a transition state model; little experimental information was available for carbocations, so parameterization for carbocations required estimation of several terms.[7d]

$$RH \rightarrow R^+ + H^- \quad (3)$$

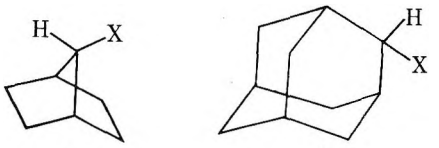
$$\delta \text{ strain} = (\text{strain energy})_{R^+} - (\text{strain energy})_{RH} \quad (4)$$

The validity of this approach (which ignores variation in solvation and entropy contributions) is evidenced by the fact that δ strain was found to correlate solvolysis rates for polycyclic bridgehead alkyl chlorides.[7c,d] The bridgehead chlorides chosen for this initial test are particularly suitable in that there can be no interference from k_s or k_Δ processes, and inductive effects are essentially constant (an isoinductive series).

The goal of the present work is to ascertain whether the Schleyer treatment can be extended to the study of the more complicated secondary derivatives. First it is necessary to provide a rigorous test of whether the Schleyer force field is applicable to secondary carbocations as it is to bridgehead carbocations.[26] Such a test is performed by determining the degree to which the solvolysis rates of a series of rigid, polycyclic, isoinductive secondary derivatives known to react by a k_c mechanism can be correlated with δ-strain values calculated with the Schleyer force field. A test for more flexible secondary derivatives will be the subject of a future report.

The Test Series

Few secondary derivatives have been clearly shown to react by a k_c mechanism. Two compounds which approach reaction by this unassisted process are 7-norbornyl (**1**) and 2-adamantyl (**2**) tosylates.[20] There is evidence that there may be weak assistance in the reaction of these substrates,[7b,27,28] but there is no question that their reaction mechanisms closely approach the k_c limit.[29] Compounds forming an isoinductive series with **1** and **2** must have two "essential" isopropyl groups attached to the reactive center as in **3**; the term "essential" isopropyl group is used here because substitution further down the chain (e.g., isobutyl rather than isopropyl) should cause only minor differences in inductive effects, so such groups can be considered to be isoinductive with an isopropyl group. Acetolysis rates for 21 compounds (other than **1** and **2**) belonging to series **3** were obtained from the literature; these are compounds **4**–**16** (in these structures, the leaving group position is represented as E for exo, N for endo, Ax for axial, Eq for equatorial, and X when epimers are not possible).



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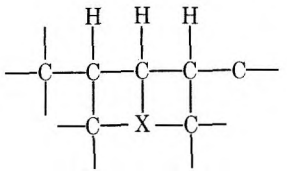

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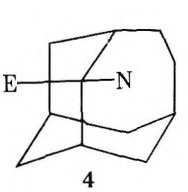
There is evidence that five compounds in this series (**4**-N, **5**-N, **6**-Ax, **9**-N, and **10**-N) react by a k_c mechanism. A review of this evidence follows.

Publication of detailed studies of the 2-homoadamantyl derivatives (**4**) has not appeared, but Grunwald–Winstein m values of 0.86 and 0.99 have been measured for the exo and endo derivatives, respectively.[30] Such a sensitivity to variations in solvent polarity has been shown to be characteristic of reaction by k_c mechanisms,[14,20b] so **4**-N seems clearly to be a k_c substrate. The slightly lower m value for the exo derivative, **4**-E, indicates involvement of a charge delocalization mechanism not operating in the reaction of **4**-N.



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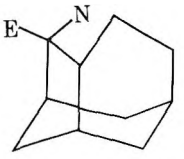

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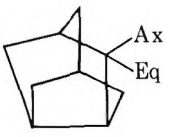

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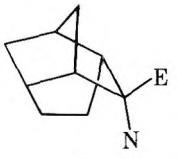

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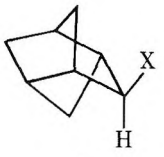

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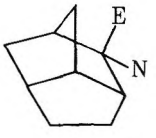

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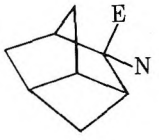

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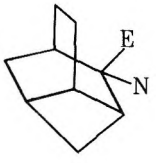

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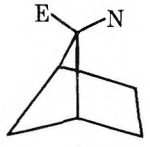

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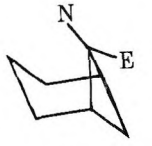

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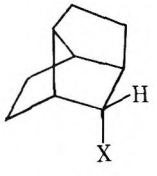

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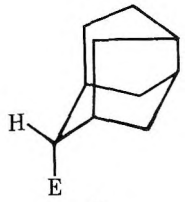

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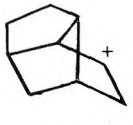

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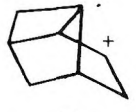
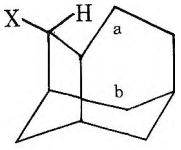


18

Spurlock[31] has studied the solvolysis of the 2-protoadamantyl derivatives, **5**-E and **5**-N, and has obtained evidence indicating that **5**-E reacts either by a k_Δ or a k_c mechanism and that **5**-N reacts by a k_c mechanism. The evidence is similar to that observed for the solvolysis of *exo*- and *endo*-2-norbornyl derivatives. First, a large exo–endo rate ratio (**5**-E/**5**-N) of 2512 is found for acetolysis. Also, the acetolysis products were the same for both exo and endo and included *exo*-2-protoadamantyl acetate and seven other tricyclic products;

endo-2-protoadamantyl acetate was not formed. Attack from the exo side was shown to be kinetically favored (e.g., reduction of 2-protoadamantanone with $LiAlH_4$ gave only *endo*-2-protoadamantanol). The rearranged products can be obtained from concerted displacement by bonds a or b (**19**) of the leaving group in **5**-E followed by various 1,2 carbon–carbon shifts and 1,3 hydride shifts, or by unassisted ionization of **5**-E and **5**-N to give the 2-protoadamantyl cation which then rearranges. There are two bonds in **5**-N which are approximately antiperiplanar to the leaving group (**20**), but participation by these bonds would give cyclobutyl carbinyl cations, not the products observed. The possibility of a k_Δ process for **5**-N solvolysis can, therefore, be eliminated. It appears that **5**-N must react by a k_c mechanism to give the 2-protoadamantyl cation which enters the same manifold of cations formed by **5**-E. The major question unanswered in this study is whether or not the large exo–endo rate ratio is the result of an accelerated k_Δ process for **5**-E or is of steric origin. Both events seem reasonable in that two carbon–carbon bonds are in the antiperiplanar positions necessary for effective anchimeric assistance (a and b of **19**) of **5**-E solvolysis, and the endo C_5



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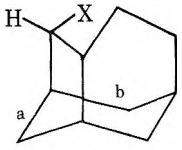

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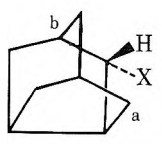
proton is well situated to sterically impede departure of the leaving group from **5**-N. We will comment on these two possibilities later, but our current interest lies with determining the k_c or k_Δ nature of **5**-N solvolysis, and this is clearly indicated to be k_c.

Acetolysis of axial and equatorial 2-noradamantanols, **6**-Ax and **6**-Eq, shows a similar pattern:[32] (1) the axial–equatorial rate ratio is 1190, (2) both derivatives give the same product mixture (95.5% equatorial acetate and 4.5% *exo*-4-brendyl acetate for **6**-Eq, and 92.7 and 7.3%, respectively, for **6**-Ax), (3) rearrangement of carbon–carbon bonds antiperiplanar to the leaving group gives the observed products for **6**-Eq but not for **6**-Ax (**21** and **22**), and those for **6**-Ax give highly improbable strained structures, and (4) reduction of the ketone shows that approach across the equatorial face is kinetically favored (reduction with $LiAlH_4$ gives 98% axial alcohol and 2% equatorial alcohol). Two additional pieces of information are available from deuterium labeling experiments. First, 91.9% of the products from **6**-Eq solvolysis derive from the degenerate rearrangement of bond b of **21**, and the remaining 8.1% derive from rearrangement of bond a to give the 4-brendyl cation, **23**. And second, acetolysis of C_4 or C_2 monodeuterium



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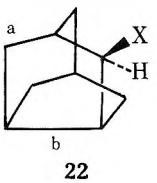

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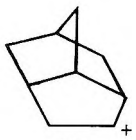

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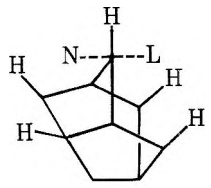
labeled **6**-Ax gives 10–13% less deuterium scrambling than observed for **6**-Eq. The sum of these experiments indicates either a k_c or a k_Δ mechanism for **6**-Eq acetolysis and either a k_c or a k_s mechanism for **6**-Ax acetolysis. The reduction in deuterium scrambling for **6**-Ax acetolysis is consistent with some nucleophilic solvent assistance for this reaction. That such assistance must, however, be weak can be determined from the observation that products other than inverted, unrearranged acetate are formed and from consideration of the transition state for this displacement process, **24**. As can be seen, the transition state closely resembles that for 2-adamantyl tosylate, a known k_c substrate,[14] in that there are several severe nonbonded interactions between hydrogens and both nucleophile and leaving group.



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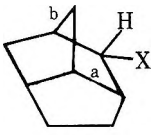
Acetolysis of 2-brendyl derivatives (**9**-E and **9**-N) yields the same product mixture and an exo–endo rate ratio of 1870.[33] Again there are no carbon–carbon bonds antiperiplanar to the endo leaving group which can participate to give the observed products; rather, highly strained cyclobutylcarbinyl cations would be formed by participation of a or b of **25**. As in the



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previous case, reaction of the exo derivatives by a k_c or k_Δ mechanism and of the endo derivatives by a k_c mechanism is indicated.

The final member of series **3** which is indicated to react by a k_c mechanism is *endo*-2-tricyclo[3.2.1.$0^{3,6}$]octyl tosylate, **10**-N, for which we suggest the trivial name *endo*-2-norbrendyl tosylate. Sauers, Parent, and Damle[34] studied the acetolysis of **10**-E and **10**-N and found an exo–endo rate ratio of 192, 85% endo and 15% exo alcohol from $LiAlH_4$ reduction of the ketone, and exo acetate as the only reaction product from both **10**-E and **10**-N. Deuterium labeling studies revealed that there were no hidden degenerate rearrangements. These data are consistent with reaction of **10**-N by a simple k_c mechanism and with reaction of **10**-E by a k_Δ mechanism; a k_Δ mechanism is indicated for **10**-E because derivation of products from a classical cation would be expected, on the basis of the ketone reduction, to give some endo product.

The available evidence is, therefore, consistent with the seven compounds **1**, **2**, **4**-N, **5**-N, **6**-Ax, **9**-N, and **10**-N as constituting an isoinductive k_c series. If the Schleyer force field accurately represents the strain energy present in secondary carbocations, the solvolytic rates for this series of k_c substrates should be well correlated by δ-strain values, eq 3 and 4. Table I contains the requisite strain energies and rate constants for all the molecules considered in this work. As models for tosylates we have used both hydrogen and methyl (i.e., R–H and R–Me) since methyl would seem more likely to represent differences in strain energies for epimeric pairs; however, in the present work, no advantage results from using the larger model. Actually, as Dubois has shown, the methyl is probably also too small to model a tosylate group properly.[8]

Figure 1 is a plot of δ strain, using the R–Me model, against acetolysis rate for the seven k_c compounds, and Figure 2 is the corresponding plot using the R–H model. With the exception of *endo*-2-protoadamantyl tosylate (**5**-N) a good correlation results (correlation coefficients of 0.97 in each case); the expressions for the correlations are given in eq 5 and 6. The deviation of the point for **5**-N can be rationalized.

$$-\log k = 0.44(\delta \text{ strain}) + 8.06 \qquad \text{L = Me} \qquad (5)$$

$$-\log k = 0.44(\delta \text{ strain}) + 7.22 \qquad \text{L = H} \qquad (6)$$

We have used the carbocation as a transition state model, and this model can be expected to work as long as there is no increase in nonbonded interactions with the leaving group upon

Table I. Strain Energies for a Series of Carbocations and Hydrocarbon Precursors and Acetolysis Rates for the Series of Alkyl Tosylates 1–16

compd	registry no.	strain energy, kcal/mol[r] R–Me	R–H[a]	R+	δ strain L = H	L = Me	−log k, s^{-1}	assistance[q]
1	10265-27-7	18.77	16.98	30.79	13.81	12.02	13.68[c]	0
2	25139-43-9	8.56	6.87	9.21	2.34	0.65	8.23[b]	0
4-E	66687-78-3	15.80	14.59	15.12	0.53	−0.68	6.69[d]	1.06
4-N	66748-94-5	16.09	14.59	15.12	0.53	−0.97	8.08[d]	0
5-E	66687-79-4	19.10	18.29	20.51	2.22	1.41	6.50[e]	2.18
5-N	66748-95-6	21.84	18.29	20.51	2.22	−1.33	9.90[e]	−2.43
6-Ax	66687-80-7	22.76	20.07	25.70	5.63	2.94	9.66[f,p]	0
6-Eq	66748-96-7	21.85	20.07	25.70	5.63	3.84	6.58[f,p]	3.17
7-E	66687-81-8	37.42	34.17	40.34	6.17	2.92	5.65[g,p]	3.69
7-N	66748-97-8	39.79	34.17	40.34	6.17	0.55	4.74[g,p]	3.56
8	63561-18-2	45.90	(36.86)	54.68	17.82	8.78	4.50[h,p]	7.40
9-E	66687-82-9	22.94	22.57	26.03	3.46	3.09	5.24[i,j,p]	4.18
9-N	66748-98-9	24.78	22.57	26.03	3.46	1.25	8.50[j,p]	0
10-E	6738-62-6	42.46	41.46	48.10	6.64	5.64	7.04[k,p]	3.50
10-N	6239-91-4	43.26	41.46	48.10	6.64	4.84	9.32[k,p]	0
11-E	66687-83-0	41.30	(40.04)	42.79	2.75	1.49	3.83[g,p]	4.88
12-E	3097-76-5	43.05	41.21	69.74	28.53	26.69	10.65[l]	9.17
12-N	10437-83-9	44.36	41.21	69.74	28.53	25.38	2.58[l]	16.66
13-E	6621-20-1	36.34	35.85	51.28	15.43	14.94	9.00[m]	5.64
13-N	6621-28-9	38.49	35.85	51.28	15.43	12.34	2.35[m]	11.15
14	66687-84-1	27.47	25.47	30.98	5.51	3.51	4.79[j]	4.81
15-E	58918-47-1	20.03	18.29	15.03	−3.26	−5.00	6.99[n]	−1.20
16	15291-16-4	117.65	118.13	133.10	14.97	15.45	8.07[o]	6.83
17	66687-85-2			29.18				
18	66687-86-3			51.71				

[a] Values in parentheses from this work, others from ref 3a. [b] Reference 21b. [c] R. K. Lustgarten, J. Lhomme, and S. Winstein, *J. Org. Chem.*, **37**, 1075 (1972). [d] Reference 30. [e] Reference 31. [f] Reference 32. [g] Reference 37. [h] Reference 38. [i] Reference 33b. [j] Reference 33a. [k] Reference 34. [l] Reference 42. [m] Reference 41. [n] Reference 39. [o] Reference 44. [p] OBs/OTs = 3.0. [q] Deviation in rate from the k_c line of Figure 4. [r] Strain energies were calculated using the force fields described in ref 3a and 7d.

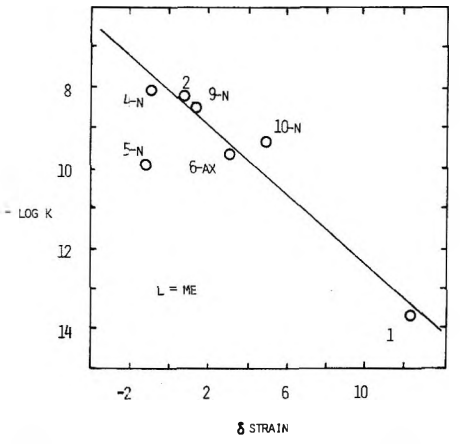


Figure 1. A plot of log k against δ strain for a series of proposed k_c substrates where the leaving group is modeled by methyl. Excluding 5-N correlation coefficient = 0.97, standard deviation in log k = 0.48 (1.0 including 5-N).

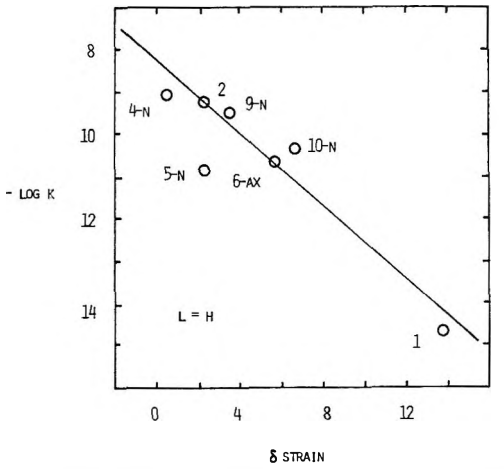


Figure 2. A plot of log k against δ strain for a series of proposed k_c substrates where the leaving group is modeled by hydrogen. Excluding 5-N correlation coefficient = 0.97, standard deviation in log k = 0.50 (0.79 including 5-N).

proceeding from the reactant to the transition state. Such interactions would not be reflected in the carbocation and if severe would cause our model to fail. As Spurlock has noted,[31] 5-N is just such a case; leaving group departure is severely hindered in this molecule by the endo hydrogen at C_5, **20**. Nonbonded hindrance to ionization is not reflected by the molecular-mechanical calculation but can be readily detected by examination of molecular models, or (we propose) by a negative deviation from Figures 1 or 2. Also, it is important to note that deviations of this sort may cause a k_Δ substrate to be classified as a k_c substrate but not vice versa; because of the inability of the present method to detect large increases in nonbonded strain in the transition state, molecules may appear to react too slowly but not too rapidly.

The correlation of unassisted solvolysis rates with strain values in Figures 1 and 2 indicates that the Schleyer molecular-mechanics method accurately calculates the strain energies of polycyclic secondary carbocations, and further, that employing hydrocarbons as tosylate models and carbocations as solvolytic-transition-state models is legitimate for these reactions. A further test of the method follows.

Correlation of Infrared Carbonyl Absorptions

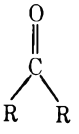
Since both ketones and the corresponding secondary carbocations (**26** and **27**) are trigonal and approximately sp^2 hybridized, their infrared carbonyl stretching frequencies and carbocation stabilities exhibit similar dependencies upon conformation (upon bond angles in particular) about the trigonal center.[35] If it can, therefore, be assumed that infrared

Table II. Infrared Carbonyl Absorption Frequencies (ν_{CO}) for Ketone 26 and C–C⁺–C Bond Angles (θ) for 27

Compd	$1715 - \nu_{CO}$, cm^{-1} [a]	θ, deg	ref
1	−58	112.9	21
2	−12	118.5	21
4	15	120.3	*b*
5	−28	116.7	31
6	−40	115.5	32
7	−38	114.5	37
8	−55	112.6	38
9	−32	116.2	*c*
10	−35	115.5	34
11	−20	117.7	37
12	−83	110.4	*d*
13	−60	112.6	41
14	−36	115.0	*c*
15	4	120.1	39
16	−42	112.7	44
17	−34	116.3	37

[a] The absorption at 1715 cm^{-1} is that for cyclohexane.[21] [b] R. K. Murray, Jr., K. A. Babiak, and T. K. Morgan, Jr., *J. Org. Chem.*, **40**, 2463 (1975). [c] A. Nickon, H. Kwasnik, T. Swartz, R. O. Williams, and J. B. DiGiorgio, *J. Am. Chem. Soc.*, **87**, 1613 (1965). [d] K. B. Wiberg, B. R. Lowry, and T. H. Colby, *ibid.*, **83**, 3998 (1961).

carbonyl stretching frequencies are proportional to CCC bond angle, and further, that the CCC bond angle of a ketone will be similar to the same bond angle in the corresponding secondary carbocation, then a further test of the accuracy of the Schleyer force field for calculation of structure and energy of secondary carbocations is provided. Thus, a direct correlation should exist between experimental infrared carbonyl absorption frequencies and calculated C–C⁺–C bond angles. We have collected in Table II the carbonyl infrared absorptions and the appropriate bond angles from molecular mechanical calculation for the 16 carbocations considered in the present study. These data are plotted in Figure 3, and with the exception of the homocubyl point (**16**) an excellent correlation results.



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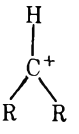


27

The success with which molecular-mechanical calculations using the Schleyer force field correlate with infrared carbonyl absorption and with solvolysis rates for known secondary k_c systems justfies the following conclusions: (1) these calculations accurately predict the structure and energy of secondary carbocations; and (2) differences in strain energies between hydrocarbons and carbocations approximate the energies of activation for unassisted solvolysis of polycyclic alkyl tosylates. In the following section these concepts are applied to identify the operation of neighboring carbon assistance.

Neighboring Carbon Assistance

As discussed earlier, it is often very difficult to distinguish between k_c and k_Δ processes. In the present study of polycyclic alkyl derivatives, neighboring group assistance can potentially be provided by σ electrons of carbon–carbon bonds. There is, of course, much debate about the existence of σ-bridged or nonclassical intermediates,[18] but there is no doubt regarding the importance of σ bridging in the transition states for secondary solvolyses. Actually, σ bridging is common in transition states for processes in which rearrangement to a more stable ion occurs (a so-called downhill process).[36]

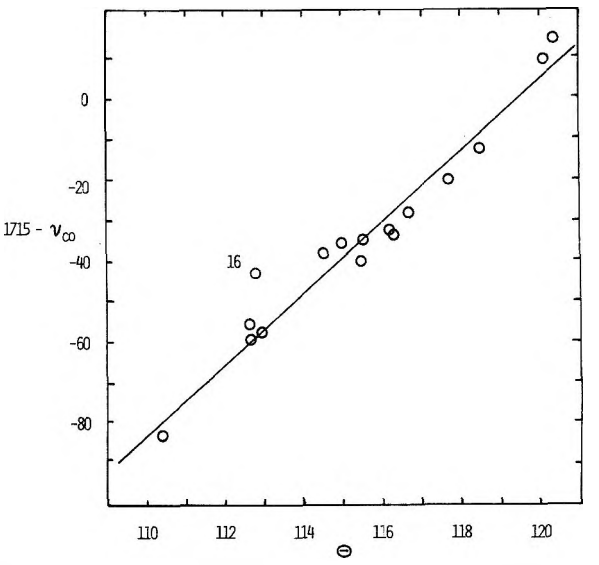


Figure 3. A plot of infrared carbonyl absorption frequency ($1715 - \nu_{CO}$) against calculated C–C⁺–C bond angles (θ) for compounds **1–17**. Correlation coefficient = 0.97, standard deviation in carbonyl absorption = 5.7 cm^{-1}.

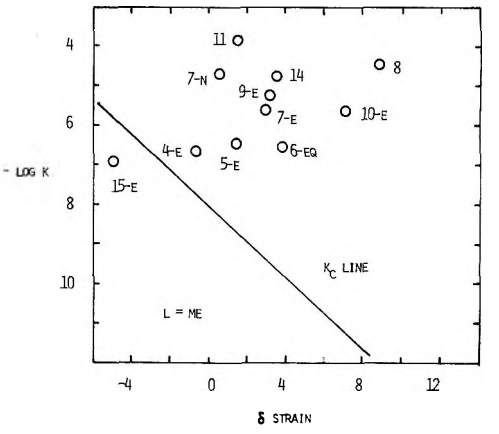


Figure 4. A plot of log k against δ strain for substrates other than the k_c models.

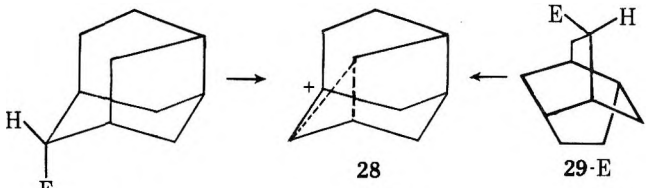
In Figures 1 and 2 the relationship between unassisted acetolysis rates and δ strain is defined. If a secondary substrate, isoelectronic with **3**, undergoes acetolysis by a k_c mechanism, it should lie on the correlation lines of Figures 1 and 2 unless nonbonded interaction involving the leaving group increases significantly upon proceeding to the transition state; in this latter case the point should be below the line defined by the other k_c substrates. In addition to the seven model k_c substrates, we have performed strain calculations for 16 other isoinductive compounds which are either known not to be k_c substrates or for which there is insufficient evidence available to specify reaction by a k_c or a k_Δ mechanism. Figure 4 is a plot of acetolysis rate against δ strain for 11 of these additional 16 substrates; included in the plot is the line defined by the k_c substrates. Five substrates were not included in the plot because their points were so far above the k_c line that they distorted the figure. These five substrates are discussed below.

In Figure 4 the points for ten compounds lie above the k_c line as would be expected for k_Δ processes. One compound, *exo*-10-protoadamantyl tosylate (**15-E**), lies slightly below the k_c line and is thus indicated to be a k_c substrate. Table I contains an assistance column in which is presented the rate acceleration for each compound relative to the predicted k_c rate (i.e., the amount the point is above or below the k_c line).

To discuss the implications of Figure 4 for each compound

would be prohibitively lengthy, but it should be noted that in the cases of 4-E,[30] 5-E,[31] 6-Eq,[32] and 9-E[33] the available evidence was not sufficient for the original authors to distinguish between k_c and k_Δ processes. Figure 4 clearly shows that, with the possible exception of 4-E, each of these compounds reacts by a k_Δ mechanism. The amount of assistance calculated for 4-E is only $10^{1.06}$, Table I, and one of the k_c substrates is this far above the k_c line.

The other seven compounds of Figure 4 (7-E and 7-N,[9,38] 8,[38] 10-E,[34] 11,[37] 14,[37] and 15-E[39]) were said by the original authors either to ionize with neighboring carbon assistance (7-E, 8, and 10-E) or to form bridged ions (7-N, 11, 14, and 15-E); of course, formation of a bridged ion implies a neighboring-carbon-assisted process. The results of Figure 4 support the original analyses in every case except that of 15-E, *exo*-10-protoadamantyl tosylate.[40] The solvolysis of 15-E has been studied by Tichy, Kniezo, and Hapala[40] who found that both 15-E and *exo*-4-twistly tosylate (29-E) gave the same product mixtures of approximately three parts 15-OS and one part 28-OS in 70% acetone, acetic acid, and ethanol, eq 7. A

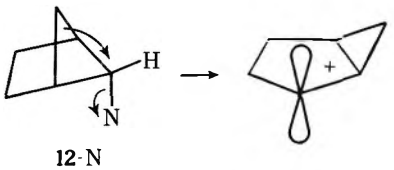


(7)

15-E-OS + 29-E-OS

deuterium labeling experiment was consistent with the scrambling expected from the bridged ion 28 and not with that expected from a series of equilibrating classical ions. Regarding the discrepancy between our study of this solvolysis and that of Tichy et al., one possibility is that 15-E does react with assistance to form a bridged ion, but the assistance is too small to detect with our method. It should be recalled that theoretical studies indicate there may be little difference in stability between bridged and classical ions.[41]

Four compounds not included in Figure 4 because of the large degree of deviation from the figure are the cyclobutyl compounds 12-E, 12-N, 13-E, and 13-N. Wiberg and his co-workers have extensively studied the reactions of these compounds and have found that the endo compounds undergo acetolysis by k_Δ mechanisms.[41-43] Both endo compounds react much faster than cyclobutyl tosylate (12-N/cyclobutyl = 880, 13-N/cyclobutyl = 1467), and both compounds have available a symmetry-allowed disrotatory pathway to a highly stable cyclopropylcarbinyl cation, eq 8. The concerted rearrange-



(8)

12-N

ment is not possible for the exo derivatives, 12-E and 13-E, and they react much more slowly than cylobutyl (12-E/cyclobutyl = 7.46×10^{-6}, 13-E/cyclobutyl = 3.37×10^{-4}). Consequently, Wiberg and his co-workers described the exo isomers as having "particularly low reactivity".[43] Actually, the exo isomers only appear to be unreactive when compared to the highly reactive parent cyclobutyl system. Examination of Table II shows that the C–C$^+$–C bond angles in the carbocations 12 and 13 are far less than the desired 120°, and examination of Table I shows that the strain increase upon ionization of the compounds 12 and 13 is tremendous and is higher than that for any other compound treated, including the notoriously unreactive 7-norbornyl derivative. Comparison of the rates of 12-E and 13-E with the more appropriate model 7-norbornyl shows 12-E and 13-E reacting 3.51×10^3 and 1.58×10^5 times as fast, respectively, as 7-norbornyl. Thus, our 5-strain prediction that 12-E and 13-E receive neighboring carbon assistance of $10^{9.17}$ and $10^{5.64}$, respectively (Table I), appears to be quite reasonable.

A final compound not included in Figure 4 is 9-homocubyl tosylate, 16. Experimental[44,45] and theoretical[46] studies of the acetolysis and accompanying degenerate rearrangements of this system have been performed. Schleyer used the approximate relationship between infrared carbonyl absorption frequency and solvolysis rate to predict that the acetolysis of 16 was accelerated by a factor of approximately 400 (see discussion of the Foote–Schleyer relationship below).[44] According to Figure 4 the assistance is even greater, amounting to $10^{6.83}$, Table I.

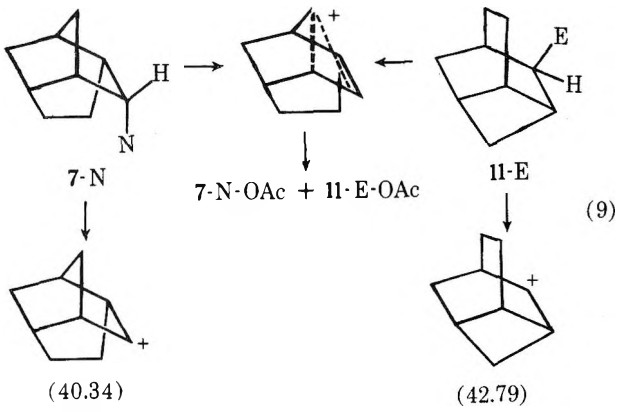
Intermediacy of Nonclassical Ions

In addition to the downhill process discussed above, two other mechanisms can result in a solvolytic reaction which appears to be accelerated relative to appropriate models under the same conditions. These mechanisms are neighboring group assistance to yield a bridged ion and enhanced hyperconjugation. Several workers have noted[18,47,48] that highly strained bent σ bonds can provide an exceptional degree of hyperconjugative stabilization to a developing carbocation, and thus lead to solvolytic rate enhancement. The cyclopropylcarbinyl system has been identified as having this property,[18] while the 2-norbornyl system has been identified as not having it.[49] It appears, therefore, that a high degree of strain such as is present in cyclopropyl systems is necessary for enhancement of hyperconjugative ability. Since none of the systems examined in the present study has cyclopropyl groups, it appears unlikely that reaction of any of these systems involves enhanced hyperconjugation; however, it should be noted that the importance of this phenomenon remains to be clearly delineated.

The importance of neighboring carbon participation to yield a σ-bridged or nonclassical intermediate is a matter of long-standing debate.[18] The molecular mechanics method permits the identification of several reactions which are clearly assisted yet which are not downhill processes; i.e., rearrangement to a more stable carbocation does not occur. If there is σ bridging in the transition states for these processes (indicated by accelerated rates if enhanced hyperconjugation is ruled out, as it seems to be for the molecules under consideration in the presented study), and if rearrangement to a more stable classical cation can be ruled out, then it must be concluded that these σ-bridged transition states are leading to σ-bridged, nonclassical intermediates.

Compounds 10-E and 16 fit the above description in that both compounds react at greatly accelerated rates, Table I, and both give products in which the original carbon skeleton is retained.[33,44,45] Also, reaction of 10-E yields only the exo product, and as discussed earlier, the results of ketone reduction by $LiAlH_4$ indicate that nucleophilic attack on the classical cation (10^+) should yield some endo product as well as exo product; it should be recalled, however, that $LiAlH_4$ is a rather unselective reagent.[18] The reaction of 14-X is similar to that of 10-E or 16 in that an accelerated rate is observed, yet the reaction involves several degenerate rearrangements followed by a hydride shift to give the same nonclassical ion (below) as 9-E; a downhill process is not occurring.[37]

The reaction of 7-N, eq 9, provides another example of acceleration without downhill rearrangement. In this instance some rearrangement does occur, but it is uphill to yield products derived from cation 11 (in eq 9 the strain energies

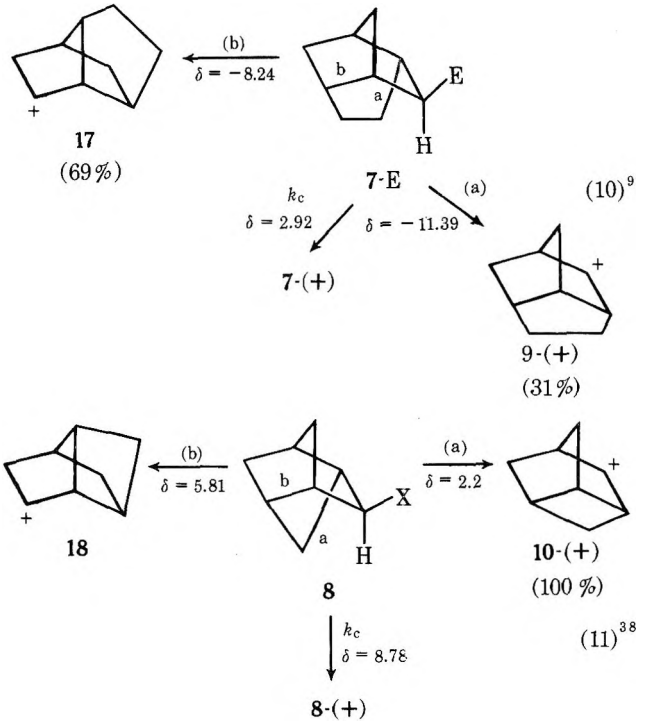


of the two cations are given in parentheses below the structure).[37] Reaction of 11-E yields the same product mixture as does reaction of 7-N. Also, $LiAlH_4$ reduction of the ketone corresponding to 7 (i.e., 2-twistbrendanone) results in less than 1% of attack from the endo direction to give *exo*-2-twistbrendanol.[37] In contrast, solvolytic substitution of 7-N proceeds entirely from the sterically disfavored endo direction. Similarly, $LiAlH_4$ reduction of the ketone corresponding to 11 favors approach from the endo direction over approach from the exo direction by a factor of approximately 2. Again, the solvolytic results are in contrast, with attack coming exclusively from the exo direction to yield 11-E-OAc. These results are consistent only with formation of a nonclassical ion as shown in eq 9.

As a final example, the reaction of 9-E is analogous to that of 7-N in that the reaction is accelerated, and unrearranged acetate (9-E-OAc) and a more strained *exo*-4-brexyl acetate (17-OAc) are formed;[33] formation of a nonclassical ion is indicated from reaction of 9-E and 17-E.

These results indicating formation of nonclassical ions, combined with those of Coates,[50] Brown,[51] and Schleyer,[7b] demonstrate that nonclassical ions can be formed in solvolysis reactions. Much debate in this area has centered on deciding the classical or nonclassical nature of the 2-norbornyl cation, and this question still has not been settled.[18-25] However, the present results and those referenced above show that whether the norbornyl cation is classical or nonclassical does not affect the following general principle: carbocations generated in solvolytic processes *can* have positive centers (carbonium carbons)[52] which are pentacoordinate; such nonclassical cations[52] are more stable than their classical counterparts, in which the positive centers are tricoordinate, and they will thus be formed at accelerated rates relative to the rate of formation of the corresponding classical carbocations.

Prediction of Rearrangement Rates. The molecular mechanics method permits accurate calculation of relative energies of carbocations and their precursors, and therefore offers the possibility of predicting the relative formation rates of isomeric carbocations. For example, the k_Δ substrates 7-E and 8 are known[9,38] to rearrange as shown in eq 10 and 11 (in these equations the experimentally observed yields are given beneath the figure and δ-strain values [in kcal/mol] calculated from differences between the cation formed and the neutral precursor are given below the reaction arrows). According to the δ-strain values presented in eq 10, compound 7-E should rearrange upon acetolysis to give 9-(+). Nickon has shown that the favored cation is actually 17, the less stable isomer.[9] Also, if the δ-strain value for the rearrangement process is used to predict the rate of reaction according to Figure 4, the predicted rate is approximately 10^3 times too slow. The reason for this failure, as has been made clear for this specific case by Nickon and co-workers[9] and for the general case by Schleyer and co-workers,[10] is the result of competition between bond-alignment control and product-stability control. As these workers



have pointed out, rearrangement pathways are controlled not only by product stabilities but also by the geometric alignment of the involved bonds and orbitals, with dihedral angles of zero and 180° being preferred. The rearrangement of 7-E is unusual in that considerations of bond alignment and product stability lead to opposite predictions; since formation of the less stable product is favored by bond alignment, bond alignment is seen to be the dominant factor.[9]

In the case of rearrangement of 8, bond-alignment and product-stability predictions are the same: 10^+ is 3.61 kcal/mol more stable than 18, and the a–x dihedral angle is 165.2° and the b–x dihedral angle is 158.8° (for the methyl derivative). Again, however, using the rearrangement δ strain of 2.20 kcal/mol in conjunction with Figure 4, one fails to obtain the observed rate; instead, a predicted rate which is $10^{4.5}$ times too fast is obtained.

Thus it appears that the δ-strain method in its present, simple formulation is useful for accurately predicting k_c rates but not k_Δ rates. As others have noted,[9,10] prediction of k_Δ rates requires consideration of both bond alignment and energy factors.

Foote–Schleyer Correlation. Foote has shown that the rate of acetolysis for a large number of secondary tosylates can be correlated with the infrared carbonyl absorption frequency of the corresponding ketones.[21] More recent research has shown that k_s (e.g., cyclohexyl[20]), k_c (e.g., 7-norbornyl[20]), and k_Δ (3-methyl-2-butyl[20a]) substrates lie on the correlation line, implying that compensating factors must be involved in producing the correlation. As noted above, carbonyl frequencies are primarily a function of C–C(O)–C bond angle, and it is surprising that a parameter which depends only on this one factor should be so well correlated with rates. Inclusion of our seven k_c substrates (1, 2, 4-E, 5-N, 6-Ax, 9-N, and 10-N) in the Foote plot, Figure 5, shows poor agreement between experimental and calculated rates (compounds 1 and 2 were part of the original correlation).

Schleyer expanded the Foote correlation to include, in addition to carbocation angle strain, contributions from reactant torsional strain, differences in nonbonded strain in ground and transition states, and inductive effects, eq 11. In applying this Schleyer treatment to the isoinductive k_c substrates, the inductive contribution can be ignored. The third term in the equation, (GS − TS)/1.36, accounts for differences in non-

Table III. Foote–Schleyer Parameters for Calculation of Acetolysis Rates.[22]

Compd	$1715 - \nu_{CO}$, cm^{-1}	ϕ_i	$(-\log k_{calcd})^a$	$(-\log k_{exptl})^a$	(exptl − calcd)
1	−58	60.60	7.25	6.37	0.88
2	−12	60,60	1.50	0.92	0.58
4-N	15	60,50	−2.05	0.77	−2.82
5-N	−28	60,30	3.5	2.59	0.91
6-Ax	−40	60,51	4.86	2.35	2.51
9-N	−32	60,24	2.27	1.19	1.08
10-N	−35	59,55	4.33	2.01	2.32

[a] Relative to cyclohexyl tosylate.

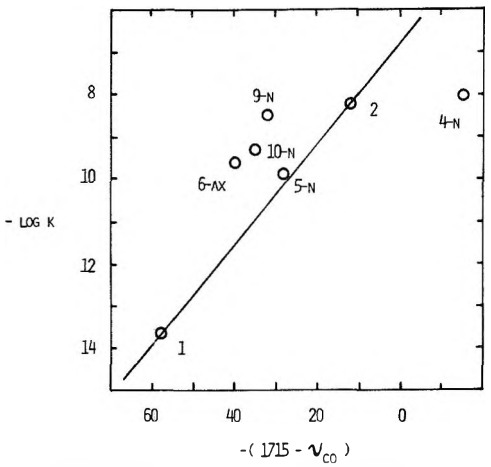


Figure 5. A Foote plot for seven k_c substrates (points 1 and 2 were on Foote's original plot).[21]

bonded strain and is estimated by referring to model systems. There is a degree of arbitrariness in the assignment of the strain values, and we have omitted this term from our calculations. The results of applying eq 11 to our seven k_c substrates are given in Table III, and, as is evident, there are significant discrepancies between calculated and observed rates. Inclusion of the term for nonbonded strain would give calculated rates slightly closer ($<10^{0.5}$) to the experimental rates in every case except 4-N, for which the calculated rate is already too large; relief of nonbonded strain, of course, gives larger calculated rates.

$$\log k_{rel} = (1715 - \nu_{CO})/8 + 1.32 \sum_i (1 + \cos 3\phi_i) + (GS - TS\ strain)/1.36 + inductive\ term \quad (12)$$

It should be noted that Schleyer has pointed out that the Foote–Schleyer correlation is not expected to work for crowded substrates such as those considered in the present study.[53] Our purpose in applying the method to these molecules is not intended as a criticism of the Foote–Schleyer treatment, since its limitations have already been discussed by one of the original authors, but rather to emphasize that prior to the present work the Foote–Schleyer approach was the best available method for predicting acetolysis rates of polycyclic secondary tosylates. The present molecular-mechanical method should be superior since it accounts, with a high degree of accuracy, for differences of all four components of strain energy in both reactant and product carbocation.

Conclusions

The present work demonstrates that the molecular mechanics method of Schleyer can be used to predict accurately the acetolysis rates of rigid, polycyclic secondary derivatives reacting by a k_c mechanism. Comparison of these calculated k_c rates with experimental rates for several substrates permits the identification of accelerated reactions and involvement of σ assistance. Operation of σ assistance for substrates in which there is no downhill rearrangement is consistent only with the formation of nonclassical, σ-bridged intermediates for these substrates, and several such intermediates are identified.

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Synthesis and Reactions of Chloroalkene Epoxides

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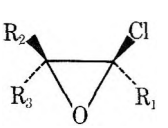
The chloroalkene epoxides, vinyl chloride oxide (1), trichloroethylene oxide (2), tetrachloroethylene oxide (3), *cis*- and *trans*-1-chloropropene oxide (4 and 5), and *cis*- and *trans*-1,3-dichloropropene oxide (6 and 7), were synthesized from their respective chloroalkenes via either autooxygenation (in the case of 2 and 3) or *m*-chloroperbenzoic acid oxidation (in the case of 1 and 4–7). Dichlorobenzene was a byproduct in the synthesis of both 6 and 7. In the case of 6, its formation was determined to be a result of a bimolecular reaction involving an intermediate in the synthesis of 6. Kinetics of hydrolysis at pH 7.4 and 37 °C were determined for compounds 2–7. Kinetics of thermal decomposition in dilute hydrocarbon solution were determined for compounds 2, 4, 5, and 7. The hydrolysis and thermolysis rates are discussed with respect to structure and mechanism of product formation.

Halogenated alkenes are widely employed as insecticides, industrial monomers, as solvents, and for other uses. Vinyl chloride has been shown to be carcinogenic to animals and man.[1] Trichloroethylene has been shown to be carcinogenic to mice.[1] These compounds and others including *cis*- and *trans*-1,3-dichloropropene are potent mutagens.[2] Vinyl chloride and trichloroethylene have been shown to bind covalently to cellular macromolecules.[3] This binding requires metabolic oxidation of the compounds and there is some evidence which suggests that epoxides may be intermediates involved in the binding.[4] Such epoxides have been proposed as potential activated carcinogenic intermediates[5] based on their structural similarity to known epoxide and chloroether carcinogens.[6] We have undertaken the synthesis and characterization of a number of such epoxides including vinyl chloride oxide (1), trichloroethylene oxide (2), tetrachloroethylene oxide (3), *cis*- and *trans*-1-chloropropene oxide (4 and 5), and *cis*- and *trans*-1,3-dichloropropene oxide (6 and 7). We determined and compared the rates and products of hydrolysis of these epoxides at physiological conditions. In addition, we have carried out thermal degradations of several of these epoxides and determined the rate of degradation and the nature of the products formed.



1, $R_1 = R_2 = R_3 = H$
2, $R_1 = H$; $R_2 = R_3 = Cl$
3, $R_1 = R_2 = R_3 = Cl$
4, $R_1 = R_3 = H$; $R_2 = CH_3$
5, $R_1 = R_2 = H$; $R_3 = CH_3$
6, $R_1 = R_3 = H$; $R_2 = CH_2Cl$
7, $R_1 = R_2 = H$; $R_3 = CH_2Cl$

Trichloroethylene oxide (2), synthesized by the autooxidation of trichloroethylene,[7] has been previously characterized in this laboratory.[8] Frankel et al.[9] had reported the synthesis of tetrachloroethylene oxide (3) by the chlorine-initiated photooxygenation of tetrachloroethylene. We modified this procedure by eliminating the chlorine initiator (which was found to catalyze the decomposition of the product) and allowing the reaction to go to completion. In this way the yield was improved and the purification of the product was greatly simplified.

Kirrman and co-workers synthesized 1-chloropropene oxide via dehydrohalogenation of 1,1-dichloro-2-hydroxypropane.[10] They obtained an unseparated mixture of cis and trans epoxides in low yield. Pure 4 and pure 5 were obtained in excellent yield by the *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of the respective *cis*- and *trans*-1-chloropropenes. The NMR spectrum of each of the pure compounds was superimposable on the NMR spectrum of the mixture obtained by the method of Kirrman.

cis- and *trans*-1,3-dichloropropene oxide (6 and 7) were likewise synthesized by the *m*-CPBA oxidation of the corresponding alkenes. NMR, IR, and mass spectra of the major products were consistent with two possible structures, i.e., the assigned epoxide structure (A) or the cyclic ether (B). Incremental addition of the lanthanide shift reagent Eu(fod)^{TM} to compound 6 moved the chemical shifts of the methine (CH_2) protons (H(b), assigned on the basis of peak shape and integration) at a rate slower than that of either of the other protons H(a) or H(c) (Table I). The lanthanide reagents are known to

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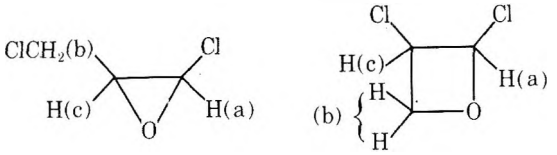
Table I. NMR of Compound 6

proton(s)	chemical shift, δ (ppm)	no. of protons	peak shape	coupling constant, Hz	slope of lanthanide-induced shift[a]
H(a)	5.28	1	d	3.5	1.56
H(b)	3.81	2	2-d, d	*b*	0.92
H(c)	3.40	1	m		1.96

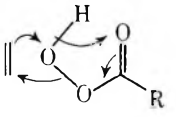
[a] Slope of a plot of $\Delta\delta$ vs. weight of added Eu(fod). [b] Second-order effects did not allow determination of coupling constant.

complex with epoxide oxygens but not with chlorine.[11] Such a shift, therefore, is consistent with A where the oxygen is proximal to proton H(a) and H(c) and distal to protons H(b). The chemical shift data were inconsistent with structure B



where the reverse is true. In addition, the NMR pattern of protons H(b) and H(c) in **6** was strikingly similar to that of the corresponding protons in epichlorohydrin (as determined in this laboratory), thus confirming that compound **6** was indeed *cis*-1,3-dichloropropene oxide.

A byproduct from the oxidation of both *cis*- and *trans*-1,3-dichloropropene was an aromatic compound of molecular weight 146 containing two chorine atoms, i.e., dichlorobenzene (substitution pattern not known). In addition, the cis oxide **6** contained some trans oxide (25%) and the trans oxide **7** contained a trace (5%) of the cis oxide after epoxidation of the corresponding alkenes. Dichlorobenzene may be formally thought to arise from bimolecular addition and cyclization of the parent olefin and epoxide followed by loss of 2 mol of HCl and 1 mol of water. However, when *cis*-1,3-dichloropropene was heated with *cis*-1,3-dichloropropene oxide, dichlorobenzene was not formed. The possibility that a reaction between *cis*-1,3-dichloropropene and **6** is acid catalyzed (by the *m*-chloroperbenzoic acid byproduct) or involves free radicals (from *m*-chloroperbenzoic acid) was explored by heating the compounds in the presence of catalytic amounts of either 1,4-dinitrobenzoic acid or benzoyl peroxide or both. In no case was dichlorobenzene a product. This compound, therefore,



probably arises from a reaction involving an intermediate in the synthesis of **6** from the parent olefin. Peracid oxidations, however, are believed to involve a concerted, bimolecular mechanism (i.e., involving no detectable intermediate) between olefin and peracid.[12] The dichlorobenzene must therefore be formed in the course of a second oxidative pathway involving an intermediate such as CH_2Cl–$CHOH$–$CHCl^+$. This would also account for the slight degree of nonstereospecificity during the course of the oxidation resulting in small amounts of trans oxide from the cis olefin and vice versa. The unoxidized olefin remained stereochemically pure so that formation of **7** from *cis*-1,3-dichloropropene, for example, did not involve preliminary isomerization of cis olefin to trans olefin.

Vinyl chloride oxide (**1**) was also synthesized in good yield by *m*-CPBA oxidation of vinyl chloride. It was identified by its NMR spectrum which was identical with the published spectrum.[13] Previously this compound had been synthesized by the chlorination of ethylene oxide.[13] However, our procedure was easier to carry out and gave higher yields.

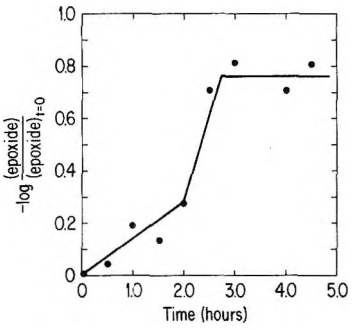
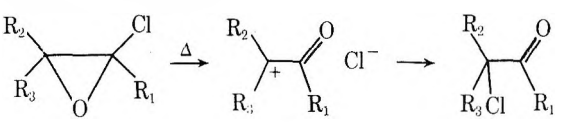


Figure 1. First-order plot for the decomposition of *cis*-1-chloropropene oxide (**4**) in xylene at 200 °C.

Since epoxides are potential metabolites of haloalkenes,[4,5] it was of interest to determine their stability under physiological conditions. Thus, pseudo-first-order hydrolysis rates were measured at 37 °C in aqueous solution buffered at pH 7.4, data which should be indicative of the epoxide reactivity toward cellular nucleophiles in vivo. All of the compounds tested gave good pseudo-first-order kinetics. As indicated in Table II, the presence of chlorine on the α position greatly increases the hydrolytic reactivity of aliphatic epoxides. Hydrolyses at pH 7.4 of the α-chloroepoxides **1**–**7** occur with chlorine migration, yielding α-chlorocarbonyl compounds (Table II). Kirrman[10b] reported that other α-chloroepoxides hydrolyzed under neutral conditions to mixtures of α-chloro- and α-hydroxycarbonyl compounds. In the case of **2**, it is clear that hydroxyl attacks at the less hindered monochlorinated carbon. An examination of products formed from hydrolyses of the α-chloroepoxides **1** and **4**–**7**, which contain only one chlorine, does not indicate the site of hydroxyl attack since addition at either the chlorinated or nonchlorinated carbon can lead to the same products. The rates of hydrolysis of the monochloroepoxides **1** and **4**–**7** decrease as the substituent at C-2 changes in the order H > CH_3 ≫ CH_2Cl. Molecular models show that the presence of a large substituent on C-2 will not sterically hinder the approach of OH toward C-1, but the substituent effects indeed indicate that C-2 is the position of attack. Reactions of α-chloroepoxides with secondary amine nucleophiles are also believed to proceed via attack at C-2.[14]

Compounds **1**–**7** rearrange thermally to α-chlorocarbonyl compounds (Table II), a reaction generally believed to occur with intramolecular chlorine migration.[15] Thermolysis rates of compounds **2**, **4**, **5**, and **7** were determined in dilute toluene or xylene solutions (Table II). Compounds **2**, **5**, and **7** showed good first-order kinetics with respect to epoxide decomposition.[16] The decomposition of **4** is complex (see Figure 1). The early stages of the reaction exhibit roughly first-order kinetics. HCl evolved during the early course of the reaction may catalyze the reaction during its later stages. The rate of thermolysis of **2** in solution was reasonably close to that reported for its thermolysis in the gas phase (1.0×10^{-2} min^{-1} compared with 5×10^{-3} min^{-1} [17] at 130 °C).

There is evidence to suggest that the thermal rearrangement of α-chloroepoxides proceeds through an α-carbonyl carbonium ion intermediate:[15]



I II

The fivefold decrease in the rate of thermolysis of **7** with respect to **5** is consistent with the expected inductive effect ex-

Table II. Hydrolysis and Thermolysis of α-Chloroepoxides

compd	registry no.	hydrolysis rate constant[a] min^{-1}	hydrolysis products	thermolysis rate constant,[b] min^{-1} (temp, °C)	thermolysis product
ethylene oxide		2.1×10^{-5} [c]	ethylene glycol		
epichlorohydrin		6.9×10^{-4} [d]	1,2-dihydroxy-3-chloropropane[d]		
vinyl chloride oxide (1)	7763-77-1	4.6×10^{-1} [e]	chloroacetaldehyde[e]		chloroacetaldehyde[f]
cis-1-chloropropene oxide (4)	21947-75-1	6.3×10^{-2}	polymer presumably from 1-chloropropanal	5.8×10^{-3} (200)[g]	1-chloropropanal[h]
trans-1-chloropropene oxide (5)	21947-76-2	1.6×10^{-1}	polymer presumably from 1-chloropropanal	3.2×10^{-2} (200)[i]	1-chloropropanal[h]
cis-1,3-dichloropropene oxide (6)	66826-72-0	2.4×10^{-3}	α-chloroacrylaldehyde	[j]	
trans-1,3-dichloropropene oxide (7)	66826-73-1	2.3×10^{-3}	α-chloroacrylaldehyde	6.1×10^{-3} (200)[i]	2,3-dichloropropanal, α-chloroacrylaldehyde
trichloroethylene oxide (2)	16967-79-6	5.3×10^{-1}	dichloroacetic acid[k]	1.0×10^{-2} (130)[l]	dichloroacetyl chloride[m]
tetrachloroethylene oxide (3)	16650-10-5	6.0×10^{-2} [c]	trichloroacetic acid[n]	7.2×10^{-3} (100)[n,o]	trichloroacetyl chloride

[a] Pseudo-first-order rate constant determined at 37 °C, pH 7.4. [b] First-order rate constant determined in solution. [c] J. N. Brönsted, M. Kilpatrick, and M. Kilpatrick, *J. Am. Chem. Soc.*, **51**, 428 (1929). Pseudo-first-order rate constant was determined at 20 °C, pH 7.0. [d] W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950). [e] Reference 21. [f] H. Gross and J. Freiberg, *J. Prakt. Chem.*, **311**, 506 (1969). [g] First-order rate constant calculated for initial (linear) portion of reaction. [h] Reference 10b. [i] In xylene. [j] See Experimental Section. [k] Reference 7. [l] In toluene. [m] Reference 17. [n] Reference 9. [o] First-order rate constant determined in neat liquid phase.

erted on a carbonium ion center by a CH_2Cl substituent relative to a CH_3 substituent.[18] The large increase of the rate of thermolysis of **2** with respect to **5** (which was too slow to quantitate at 130 °C) at first sight might appear to argue against such an intermediate carbonium ion since carbonium ions are stabilized by a chlorine to about the same extent as a methyl substituent.[19] However, one must also consider the effects of the formation of new functionalities on $\Delta G^{\ddagger}$. In particular, C-1 is transformed in the transition state (which may be approximated by II) from a saturated carbon to an acyl chloride in the case of **2** or an aldehyde in the case of **5**. One may roughly estimate that the transition state energy for **2** is 15 kcal/mol lower than that for **5**.[20] The increased rate of isomerization of **2** relative to **5** is thus likely controlled by the energetically favorable formation of an acylhalide compared to an aldehyde functionality attached to the cation center.

Finally, it may be noted that epoxides **4** and **5** appear to be thermally more stable than originally reported,[10b] decomposing at an appreciable rate only at temperatures above 180 °C.

Experimental Section

Infrared spectra were determined using a Perkin-Elmer Model 421 spectrophotometer. Proton magnetic resonance spectra were recorded using a Varian Model T-60A spectrometer. Visible absorbances were read from a Gilford Model 240 spectrometer. Gas chromatographic analyses for hydrolysis kinetics of compounds **2** and **3** were performed on a Jarrel-Ash Model 28-710 gas chromatograph. Mass spectra were obtained on a DuPont Model 21-492 double-focusing high-resolution mass spectrometer. Chemical ionization mass spectrometry was performed using isobutane as the ionizing gas. Gas chromatography–mass spectrometry were carried out using a Varian Model 2740 gas chromatograph with a 5 ft × ⅛ in. 3% SE30 column coupled to the mass spectrometer. High performance liquid chromatography (LC) was done on a Waters 6000A chromatograph using a Waters C_{18} μ-Bondapak column. Incubations at 37 °C were done using a Dubnoff Metabolic Shaking Incubator. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Trichloroethylene Oxide (2). This compound was synthesized by the benzoyl peroxide initiated oxygenation of trichloroethylene as previously described by us.[8]

Tetrachloroethylene Oxide (3). Tetrachloroethylene (100 mL, 0.978 mol) was heated to 90 °C in a photochemical immersion flask under a dry ice condenser. The liquid was irradiated with a Hanovia 250 W medium pressure mercury lamp while oxygen was bubbled through at a rate of 300 mL/min. Infrared spectra taken during the course of the reaction showed absorptions corresponding to tetrachloroethylene, trichloroacetyl chloride, and tetrachloroethylene oxide.[9] No unidentifiable absorptions were observed. The reaction was monitored by IR by observing the disappearance of the tetrachloroethylene absorption at 905 cm^{-1} and the concomitant increase of absorptions at 1753 and 975 cm^{-1} belonging respectively to the acid chloride and the epoxide. During the reaction the ratio of the absorptions at 975 and 1020 cm^{-1} belonging respectively to the epoxide and acid chloride did not change. After 35 h the absorption at 905 cm^{-1} was negligible and the photooxygenation was terminated.

The product mixture (87.2 g, 0.506 mol) was partially esterified by the dropwise addition of 24 mL (0.40 mol) of ethanol at 0 °C. IR showed that the trichloroacetyl chloride was completely converted to the corresponding ethyl ester while **3** remained largely unreacted. This mixture was distilled at 87 mm and material boiling at 39–55 °C was collected. This was redistilled at 70 mm and 11.2 g (12%) of a colorless liquid boiling at 33–35 °C was collected: IR (salt plate) 1320, 1365, 961, 869, 693, and 602 cm^{-1}; mass spectrum (electron impact) *m/e* 180. Anal. Calcd for C_2Cl_4O: C, 13.21; Cl, 78.00. Found: C, 13.24, Cl, 78.08.

***cis*-1-Chloropropene Oxide (4).** A solution of 10.0 mL (0.145 mol) of *cis*-1-chloropropene and 35.0 g (0.172 mol) of 85% *m*-chloroperbenzoic acid in 150 mL of methylene chloride was refluxed for 16 h. An NMR spectrum at this time showed no starting material. The solution was cooled at −20 °C overnight and filtered. The filtrate was washed first with 100 mL of 5% sodium sulfite and then with 100 mL of 10% sodium bicarbonate and the organic layer dried over anhydrous magnesium sulfate. Methylene chloride was removed by distillation at atmospheric pressure. The residue was distilled at 180 mm and the fraction which boiled at 40–55 °C was collected. The heated oil bath was kept below 90 °C. The material was redistilled at 130 mm and 5.0 g (37%) of a colorless liquid boiling at 32–34 °C was collected: IR (CH_2Cl_2) 1478, 1445, 1401, 1380, 1300, 1267, 1220, 1140, 1071, 1012, 964, and 845 cm^{-1}; NMR (neat) δ 5.08 (d, 1 H, H_1, $J_{1,2}$ = 3.5 Hz), 3.08 (d, q, 1 H, H_2, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 5.0 Hz), 1.18 (d, 3 H, H_3, $J_{2,3}$ = 5.0 Hz); mass spectrum (chemical ionization) $(M + H)^+$ *m/e* 93. Anal. Calcd for C_3H_5ClO: C, 38.95; H, 5.45; Cl, 38.31. Found: C, 38.75; H, 5.38; Cl, 38.25.

Compound **4** was stable in 15% methylene chloride solution. When left neat at 4 °C, however, it decomposed to a viscous material after 2 weeks.

***trans*-1-Chloropropene Oxide (5).** This compound was prepared from 10.0 mL (0.145 mol) of *trans*-1-chloropropene using the same procedure that was used to prepare the cis compound. The product

was distilled twice at 190 mm. In the second distillation 4.0 g (32%) of a colorless liquid boiling at 42–44 °C was collected: IR (salt plate) 1450, 1407, 1381, 1288, 1256, 1134, 1065, 1025, 965, and 880 cm^{-1}; NMR (neat) δ 4.82 (d, 1 H, H_1, $J_{1,2}$ = 1.5 Hz), 3.13 (d, q, 1 H, H_2, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 5.0 Hz), 1.22 (d, 3 H, H_3, $J_{2,3}$ = 5.0 Hz); mass spectrum (chemical ionization) $(M + H)^+$ *m/e* 93. Anal. Calcd for C_3H_5ClO: C, 38.95; H, 5.45; Cl, 38.31. Found: C, 38.84; H, 5.37; Cl, 38.29. Compound **5** when stored at 4 °C decomposed to the extent of 20% over 1 month.

***cis*-1,3-Dichloropropene Oxide (6).** A solution of 15.0 mL (0.162 mol) of *cis*-1,3-dichloropropene and 36.8 g (0.181 mol) of 85% *m*-chloroperbenzoic acid in 170 mL of carbon tetrachloride was refluxed for 7 h after which time subsequent NMR spectra showed little change. The mixture was cooled to −20 °C overnight and filtered. The filtrate was washed with 100 mL of 5% sodium bisulfite and 100 mL of 10% sodium bicarbonate and then dried over anhydrous magnesium sulfate. Solvent was removed by distillation at atmospheric pressure. The remainder was distilled in three fractions: Fraction 1 boiled at 34 °C at 163 mm and contained 4.8 g (27%) of *cis*-1,3-dichloropropene. Fraction 2 (**6**) boiled at 78–80 °C at 130 mm and, after a second distillation, yielded 5.0 g (24%) of a colorless liquid: IR (salt plate) 1308, 1270, 1255, 1084, 907, 681, and 645 cm^{-1}; NMR (neat) δ 5.28 (d, 1 H, H_1, $J_{1,2}$ = 3.5 Hz), 3.81 (2-d, d, 2 H, H_3 and H_4), 3.40 (m, 1 H, H_2). Additional absorptions at δ 5.17 (s) and 3.67 (m) were superimposable on a spectrum of **7** and integrated to 25% of **6**; mass spectrum (gas chromatography–MS, chemical ionization) $(M + H)^+$ *m/e* 127 containing 2Cl. Fraction 3 boiled at 48–50 °C at 15 mm and contained 3.0 g (12%) of a colorless liquid: NMR (neat) δ 7.30 (m); mass spectrum (gas chromatography–MS, chemical ionization) $(M + H)^+$ *m/e* 147 containing 2Cl.

NMR Spectra of Compound 6 in the Presence of a Lanthanide Shift Reagent. Eu(fod) was added in 10–20-mg increments to a solution of 20 mg of **6** in 0.5 mL of carbon tetrachloride. NMR spectra were recorded and integrated after each addition.

***trans*-1,3-Dichloropropene Oxide (7).** This compound was prepared from 19.0 mL (0.205 mol) of *trans*-1,3-dichloropropene using a procedure identical to that for *cis*-1,3-dichloropropene oxide. The product mixture was distilled in three fractions: Fraction 1 boiled at 32–34 °C at 150 mm and contained 5.0 g (22%) of *trans*-1,3-dichloropropene. Fraction 2 (**7**) was distilled twice collecting 6.0 g (23%) of a colorless liquid boiling at 95–96 °C at 132 mm: IR (salt plate) 1464, 1413, 1295, 1270, 918, 805, 790, 745, and 694 cm^{-1}; NMR (neat) δ 5.17 (broad s, 1 H), 3.67 (m, 3 H). An additional absorption at δ 5.28 (d, J = 3.5 Hz) integrated to about 5% of **7** was superimposable on a spectrum of **6**; mass spectrum (gas chromatography–MS, chemical ionization) $(M + H)^+$ *m/e* 127 containing 2Cl. Fraction 3 boiled at 60–62 °C at 30 mm and contained 4.0 g (13%) of a colorless liquid whose NMR and gas chromatography–mass spectra were identical to those of the byproduct from the synthesis of *cis*-1,3-dichloropropene oxide.

Formation of Dichlorobenzene during the Synthesis of 6. Six 3-mL glass ampules were sealed containing 50 μL of carbon tetrachloride plus the following compounds: (1) *cis*-1,3-dichloropropene (25 μL) and **6** (25 μL); (2) **6** (50 μL); (3) *cis*-1,3-dichloropropene (25 μL), **6** (25 μL), and 1,4-dinitrobenzoic acid (1 mg); (4) *cis*-1,3-dichloropropene (25 μL), **6** (25 μL), and benzoyl peroxide (1 mg); (5) *cis*-1,3-dichloropropene (50 μL) and benzoyl peroxide (1 mg); and (6) *cis*-1,3-dichloropropene (50 μL), **6** (10 μL), benzoyl peroxide (1 mg), and 1,4-dinitrobenzoic acid (1 mg). These were heated at 85 °C for 40 h after which time NMR spectra were recorded in CCl_4. Spectra for reactions 1–3 and 6 showed no change from starting materials. Reaction 4 showed a new absorbance at δ 7.35 as well as absorbance characteristic of **6**. No *cis*-1,3-dichloropropene remained. Reaction 5 showed a diminished quantity of *cis*-1,3-dichloropropene as well as a new absorbance at δ 7.35. IR's of reactions 4 and 5 showed new absorptions in each case superimposable on a spectrum of chlorobenzene.

***m*-Chloroperbenzoic Acid Oxidation of Vinyl Chloride.** Vinyl chloride (100 mg, 1.62 mmol) and 35.0 mg (1.72 mmol) of 85% *m*-chloroperbenzoic acid were dissolved in 3 mL of chloroform-*d* and sealed in a 5-mL glass ampule. After heating at 55 °C for 3.5 h an NMR revealed, in addition to *m*-chloroperbenzoic acid and *m*-chlorobenzoic acid, vinyl chloride (34%) and two new products A (55%) and B (11%). The major product (A) had an NMR δ 5.00 (d, d, 1 H, H_1, $J_{1,2}$ = 2.5 Hz, $J_{1,3}$ = 1.5 Hz) and 2.96 (m, 2 H, H_2 and H_3), consistent for vinyl chloride oxide (**1**). The minor product B had an NMR δ 9.50 (t, 1 H, J = 1.5 Hz) and 4.02 (d, 2 H, J = 1.5 Hz), consistent for chloroacetaldehyde.

Base-Catalyzed Hydrolysis of Compounds 6 and 7. A solution containing 10 μL of either **6** or **7** and 10 mg of sodium bicarbonate in 0.8 mL of a 1:1 mixture of D_2O and acetone-d_6 was allowed to stand overnight. NMR's of both mixtures after this time were identical, δ 9.53 (s, 1 H), 6.80 (d, 1 H, J = 6.5 Hz), 6.73 (d, 1 H, J = 6.0 Hz); mass spectra (gas chromatography–MS, chemical ionization) $(M + H)^+$ *m/e* 91. These data were consistent for α-chloroacrylaldehyde.

Hydrolysis Kinetics of 2 and 3. A solution of 0.2 mL of acetone in 1.5 mL of 0.5 M sodium phosphate buffer, pH 7.4, was warmed to 37 °C after which 10 μL of either **2** or **3** were added along with an equal volume of a suitable internal standard: chlorobenzene for **2** or ethyl trichloroacetate for **3**. Incubation was continued for 3 half-lives. After incubation for various time intervals, 0.3 mL of ether was added and the phases vigorously mixed for 45 s. An aliquot of the ether layer was immediately analyzed by GLC using a 6 ft × 0.25 in. diameter column packed with 10% Apiezon on Chromosorb W for compound **2** or a 6 ft × 0.25 in. diameter column packed with 10% SE 30 on Chromosorb W for compound **3**. The relative concentration of epoxide was determined from the ratio of its chromatogram peak area relative to that of the respective internal standard. The rates of hydrolysis were calculated from these data.

Hydrolysis Kinetics of Compounds 4–7 at pH 7.4. Following a procedure of Bartsch,[21] 50 mL of a 2:1 solution of 0.2 M tris–HCl buffer, pH 7.4, and acetone were warmed to 37 °C. To this was added 10 μL of epoxide. Incubation was continued for 3 half-lives. At various times 1.5-mL aliquots of this solution were removed and immediately added to a solution containing 30 mg of *p*-nitrobenzylpyridinium chloride in 2.0 mL of ethylene glycol, shaken vigorously for 30 s and warmed at 37 °C for 30 min in the case of **4** and 5 or 1 h in the case of **6** and **7**. After this time 2.5 mL of a 1:1 mixture of triethylamine and acetone were added and the solutions were shaken. After an additional 1 min the absorbance of the solutions at 575 nm was read against a reference containing 1.0 to 0.5 mL tris–HCl (pH 7.4), 0.5 mL of acetone, and 2.0 mL of ethylene glycol. A prior experiment confirmed that the concentration of the epoxide was proportional to the absorbance of the *p*-nitrobenzylpyridine adduct formed in this procedure. Rates of hydrolysis were calculated based on these data. Duplicate experiments show that rate constants were all within ±10%.

Thermal Isomerization of Compound 7. Compound **7** (20 μL) was sealed in a 10-mL ampule and heated in an oil bath to 200 °C for 40 h. An NMR spectrum ($CDCl_3$) showed three components, A, B, and C, in a ratio of 18:23:59. A: NMR δ 5.10 (s, 1 H), 3.63 (m, 3 H); mass spectrum (chemical ionization) $(M + H)^+$ *m/e* 127. B: NMR δ 9.07 (s, 1 H), 6.67 (d, 1 H, J = 2.0 Hz), 6.50 (d, 1 H, J = 2.0 Hz); mass spectrum (gas chromatography–MS, chemical ionization) $(M + H)^+$ 91. C: NMR δ 9.13 (d, 1 H, J = 1.7 Hz), 4.47 (d, t, 1 H, J = 1.7, 6.0 Hz). 3.95 (d, 2 H, J = 6.0 Hz); mass spectrum (chemical ionization) $(M + H)^+$ *m/e* 127. Compounds A and B had NMR and mass spectra identical to *trans*-1,3-dichloropropene oxide and the product from hydrolysis of **7** (α-chloroacrylaldehyde). Compound C had NMR and mass spectrum consistent with 2,3-dichloropropanal.

Thermal Isomerization of Compound 2 in Solution. Into a 3-mL ampule was sealed 0.5 mL of a solution containing 15 mg of **2** in 4.0 mL of xylene (dried and distilled over phosphorus pentoxide). The ampule was heated to 130 °C for 8 h (4 half-lives). Methanol (100 μL) was added to the solution to convert acyl chloride to its corresponding methyl ester. The resultant solution was analyzed using LC on a C_{18} reverse-phase column, eluting with 50% methanol–water. A single peak eluted at a retention time identical to methyl dichloroacetate. No peak corresponding to trichloroacetaldehyde was observed. Comparison of the peak area from isomerized **2** with that from an identical injection sample of a solution of 15 mg of dichloroacetyl chloride and 100 μL of methanol dissolved in 4.0 mL of xylene indicated that **2** isomerized to dichloroacetyl chloride in a yield of 80%. Dichloroacetyl chloride dissolved in xylene was itself unchanged upon heating at 130 °C for 8 h.

Thermal Isomerization of Compounds 2, 4, 5, 6, and 7 in Solution. Into 3-mL ampules were sealed 0.5 mL of a solution containing 10 μL of epoxide in 10 mL of either toluene or xylene (distilled and stored over phosphorus pentoxide). The ampules were heated to the desired temperature in an oil bath and cooled after various times. Samples were heated over a period of at least 3 half-lives. No HCl was detected upon breaking the ampules, although the pH of the solutions was slightly acidic. The contents of the ampules were added to a solution containing 30 mg of *p*-nitrobenzylpyridinium chloride in 2.5 mL of acetone, 1.0 mL of ethylene glycol, and 0.5 mL of 0.2 M tris–HCl buffered at pH 7.4. After these were warmed at 37 °C for either 30 min for **2**, **4**, and **5** or 1 h for **6** and **7**, 2.5 mL of a 1:1 mixture of triethylamine and acetone was added. The absorbance was read at 540 nm for compound **2** or at 575 nm for **4–7** against a reference containing acetone, ethylene glycol, and tris–HCl in the above proportions. Rates of thermolyses were calculated from these data. Duplicate experiments show rates were constant to ±10%. A subsequent experiment confirmed that the absorbance of the *p*-nitrobenzylpyridine adduct

formed in this procedure was proportional to the concentration of epoxide for all compounds tested except **6**. The thermolysis rate could therefore not be calculated from **6** from these data. Thermal isomerization kinetics of compounds **2** and **5** were repeated in the presence of 2 mg of solid sodium bicarbonate added to each ampule to absorb any generated HCl. pH at all times remained slightly basic to indicator paper. Rate constants for isomerization were seen to be unaffected by this addition.

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Registry No.—Tetrachloroethylene, 127-18-4; *cis*-1-chloropropene, 16136-84-8; *trans*-1-chloropropene, 16136-85-9; *cis*-1,3-dichloropropene, 10061-01-5; *trans*-1,3-dichloropropene, 10061-02-6; vinyl chloride, 75-01-4.

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(20) $\Delta G_2^{\ddagger} - \Delta G_5^{\ddagger} \approx \Delta H_2^{\ddagger} - \Delta H_5^{\ddagger} \approx (\Delta H_f^{II} - \Delta H_f^{I})_2 - (\Delta H_f^{II} - \Delta H_f^{I})_5 \equiv \Delta_2^5(\Delta H^{\ddagger})$. The substituents at C-2 (R_2 and R_3) as well as the dihedral angle between them remain constant going from I to II. The stabilizing effects of R_2 on the carbonium ion center are similar in **2** and **5** and therefore may be ignored in a discussion of relative transition state energies. Thus, the substituents about C-2 should have a negligible effect on $\Delta_2^5(\Delta H^{\ddagger})$. Therefore, we may roughly estimate $\Delta H_2^{\ddagger} \sim \Delta H_f(CH_3COCl) - \Delta H_f(CH_3CHCl_2)$. $\Delta H_5^{\ddagger} \sim \Delta H_f(CH_3CHO) - \Delta H_f(CH_3CH_2Cl)$. $\Delta H_f^{298K}(CH_3COCl) = -58.7$ kcal/mol (Devore and O'Neal, *J. Phys. Chem.*, **73**, 2644 (1969)). $\Delta H_f^{298K}(CH_3CHCl_2) = -30.7$ kcal/mol (Lacher et al., *Trans. Faraday Soc.*, **63**, 1608 (1967)). $\Delta H_f^{298K}(CH_3CHO) = -39.7$ kcal/mol (Vasil'ev and Vvendenskii, *Zh. Fiz. Khim.*, **39**, 2052 (1965)). $\Delta H_f^{298K}(CH_3CH_2Cl) = -26.7$ kcal/mol (Green and Holder, *J. Chem. Soc.*, 1974 (1962). Therefore $\Delta_2^5(\Delta H^{\ddagger}) \sim -15$ kcal/mol.
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Notes

Zwitterionic Meisenheimer Complex Reactivity. Influence of Cyano and Nitro Groups on Ortho Substituent Attack vs. Meta Bridging

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Anionic σ complexes (Meisenheimer complexes) formed from electron deficient aromatic compounds and a variety of organic and inorganic bases have been extensively studied and well characterized.[1-6] We previously reported evidence for zwitterionic σ complexes like **3a** as intermediates in the formation of the bicyclic zwitterion **4a** from reaction of *sym*-trinitrobenzene (**1a**) and α-phenyl-*N,N*-dimethylacetamidine in ethanol[7,8] and Me_2SO. It was of interest to study the effect of diminished electron deficiency of the starting aromatic in this reaction sequence. Surprisingly we have found that an entirely different reaction occurs when the aromatic substrate is 3,5-dinitrobenzonitrile (**1b**). Although related bicyclic ions in which the cyano group is part of the anionic function are well known,[9] the bicyclic zwitterions **4b** or **4c** *were not formed.* Instead, a green solid crystallized from the ethanolic reaction solution which had visible maxima at 469 and 596 nm, characteristic of σ complexes of **1b**.[10] The ^1H NMR and elemental analyses confirm the structure as **2** (see Experimental Section). Compound **2** appears remarkably stable. The diminished electrophilicity of the ring in **3b** relative to **3a** may make the **3b** to **4b** conversion less favorable than that of **3a** to **4a**.

While the ^1H NMR spectrum of **2** is easily recorded in Me_2SO-d_6 at room temperature, heating this solution to 50–60 °C causes absorptions for **2** to diminish as new peaks appear. The latter are identical to those obtained from the reaction product of **1b** and α-phenyl-*N,N*-dimethylacetamidine in Me_2SO. The ^1H NMR spectrum of this product, as well as the elemental analyses, confirm the structure as **5**. A distinction between **5a** and **5b** cannot be made on the basis of the ^1H NMR spectrum.

Although no absoprtions other than those of **2** and **5** appear in the heated Me_2SO solution of **2**, it is unlikely that **2** is a direct precursor to **5**. Cyclization of carbon-bonded σ complexes like **2** does not occur in ethanol or Me_2SO even in the presence of excess amidine.[7,8]

A likely mechanism for the formation of **5** would be dissociation of **2** to amidine and **1b** as the solution is warmed. Attack of amidine on the cyano group or a ring carbon of **1b** can then occur, with eventual cyclization to **5**. It seems clear that amidine attack on **1b** in Me_2SO proceeds differently than in ethanol (i.e., amidine nitrogen attack on the ring or cyano group). In any case, if subsequent cyclization–aromatization is rapid relative to initial complex formation, no intermediates would be observed by NMR. We have no definitive explana-

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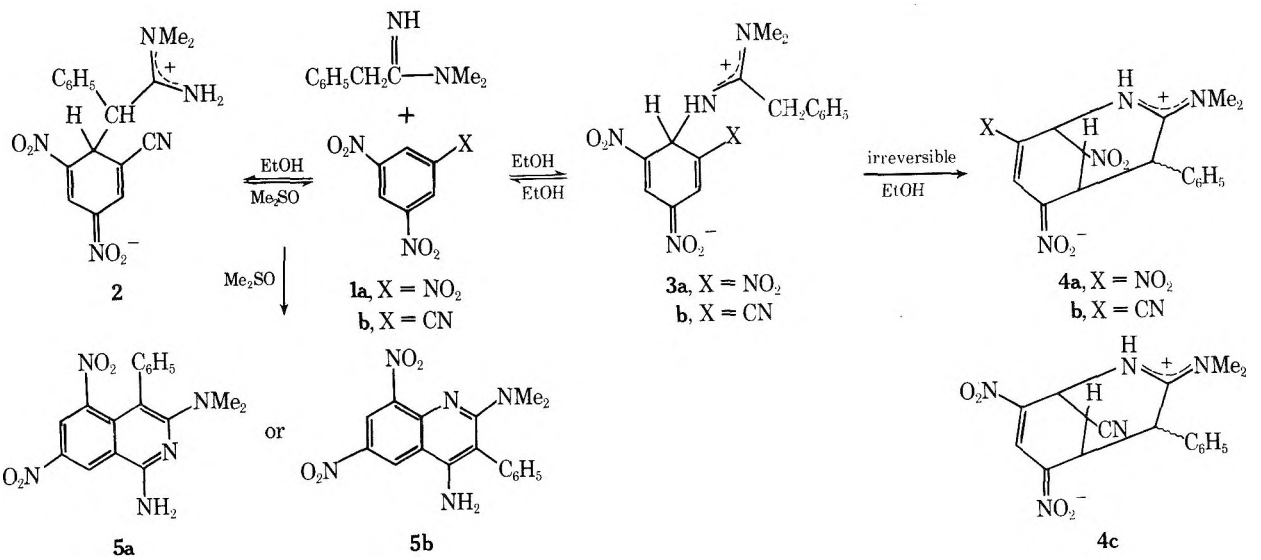

Table I

	δ C, ppm, from Me_4Si									
	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
quinoline		151.1	121.7	136.2	128.5	127.0	129.9	130.3	149.1	128.9
isoquinoline	153.3		144.0	121.0	127.0	130.7	127.7	128.1	129.3	136.2
nitrobenzene	148.3	123.4	129.5	134.7						
N,N-dimethylaniline	151.3	113.1	129.7	117.2						
aniline	147.9	116.3	130.0	119.2						
2-aminopyridine		158.9	108.5	137.5	113.3	147.7				

tion for the solvent effect observed in changing the reaction medium from ethanol to Me_2SO.

Structures **5a** and **5b** differ in the number of aromatic carbons bonded to two nitrogen atoms (i.e., 2 for **5a** and 1 for **5b**) indicating that the ^{13}C NMR spectrum of **5** might afford a distinction between these isomers.[11] The chemical shifts of the aromatic ring carbons of quinoline,[12] isoquinoline,[12] nitrobenzene,[12] *N,N*-dimethylaniline,[12] aniline,[12] and 2-aminopyridine[14] are summarized in Table I. The heteroaromatic ring carbons of **5** show absorptions at δ 102.3, 111.3, 121.8, 133.0, 135.4, 137.0, 143.3, 156.9, and 160.7. The peaks at 156.9 and 160.7 ppm point strongly to carbon atoms bonded to two nitrogens (similar to C-2) in 2-aminopyridine [with additional peaks at 130 (2), 128 (2), 127, and 125 for the C_6H_5 group].[14] Careful examination of the shift data shown above shows that only **5a** is consistent with the recorded spectrum of **5**.

It is quite apparent that in addition–cyclization reactions of amidines with electron-deficient aromatics, the solvent and electron-withdrawing ability of the ring substituents play a major role in directing the course of the reaction.

Experimental Section

All melting points are uncorrected. ^1H NMR spectra were run on JEOL C-60-HL and MH-100 spectrometers with Me_4Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 UV–visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237B infrared spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and G. I. Robertson Laboratories, Florham Park, N.J.

Aromatics and Amidines. *sym*-trinitrobenzene (**1a**) was purchased from J. T. Baker and recrystallized three times from ethanol. 3,5-Dinitrobenzonitrile (**1b**) was purchased from Aldrich Chemical Co. and dried over P_2O_5 before use. α-Phenyl-*N,N*-dimethylacetamidine was prepared as reported previously.[8]

Preparation of 2. A solution of 0.67 g (0.004 mol) of α-phenyl-*N,N*-dimethylacetamidine in 10 mL of ethanol and a solution of 0.63 g (0.003 mol) of **1b** in 50 mL of ethanol were mixed. The solution was filtered after 24 h to give 0.56 g (1.58 mol) of crystalline **2**: mp 178–181 °C; UV visible maxima (Me_2SO) 288, 469, and 596 nm; IR (KBr) 3560, 3375, 3200–2000, 1620, 1575, 1505, 1375, 1290, and 1135 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.11 (s, 3 H, NCH_3), 3.39 (s, 6 H, NCH_3 and H_2O of hydration), 4.90 (d, J = 6 Hz, 1 H, CHC_6H_5), 5.22 (d, J = 6 Hz, 1 H, sp^3 anionic ring proton), 6.98 (m, 2 H, C_6H_5), 7.50 (m, 3 H, C_6H_5), 8.00 (d, J = 2 Hz, 1 H, para to CN), 8.23 (d, J = 2 Hz, 1 H, para to NO_2), 9.27 (br, 1 H, NH), and 9.54 (br, 1 H, NH). Anal. Calcd for $C_{17}H_{17}N_5O_4 \cdot H_2O$: C, 54.68; H, 5.12; N, 18.75. Found: C, 54.54; H, 5.05; N, 18.64.

Preparation of 5. This compound was prepared by two methods. A solution of 0.1 g of **2** in 1 mL of Me_2SO was stirred at 60 °C for 48 h. The mixture was added to water and the solid was filtered, washed with water, dried, and chromatographed (silica gel–chloroform). The solvent was removed from the major fraction under vacuum and the residue was recrystallized from methanol to yield 0.075 g (74%) of red crystalline **5**: mp 263–265 °C; UV–visible maxima (Me_2SO) 275, 430, and 514 nm; IR (KBr) 3470, 3370, 3080, 2920, 1630, 1605, 1570, 1530, 1465, 1385, 1330, 1290, 1250, 1165, 930, 915, 855, 785, 730, and 705 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.67 (s, 6 H, NCH_3), 7.32 (m, 5 H, C_6H_5), 7.79 (br, 2 H, NH), 8.40 (d, J = 2 Hz, 1 H, ortho to both NO_2 groups), and 9.26 (d, J = 2 Hz, 1 H, peri proton). Anal. Calcd for $C_{17}H_{15}N_5O_4$: C, 57.78; H, 4.28; N, 19.82. Found: C, 57.70; H, 4.28; N, 19.41.

Compound **5** was also prepared by mixing solutions of 0.52 g of **1b** in 1 mL of Me_2SO and 0.88 g of α-phenyl-*N,N*-dimethylacetamidine in 1 mL of Me_2SO. The mixture was stirred for 30 min at 35 °C and at room temperature for 4 h and then added to anhydrous ether with continued stirring. After a few minutes the ether layer was decanted off and 30 mL of water was added to the residue. Filtration of this slurry yielded a red powder which was chromatographed (silica gel–chloroform). Evaporation of solvent from the major fraction and crystallization of the residue from methanol–chloroform yielded **5**, identical in all respects with the compound obtained by heating **2** in Me_2SO (vide supra).

Acknowledgment. The authors thank the National Institute of Drug Abuse for support of this work; Grant No. PHS R01 00450-02.

Registry No.—**1b**, 4110-35-4; **2**, 66922-38-1; **5a**, 66922-39-2; 2-phenyl-*N,N*-dimethylacetamidine, 56776-16-0.

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A Convenient Preparation of Deuterated Aromatic Compounds

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The classical procedures for the deuteration of polycyclic aromatics are tortuous and inconvenient,[1] involving heating the arene in D_2O to 350 °C in the presence of a Pt catalyst or exchange with benzene-d_6.[2] A more convenient procedure for the deuteration of benzo[*a*]pyrene was recently published.[3] There also exists an excellent method developed by Makabe, but since it was published in Japanese it has not been used widely in the west.[4] Their elegant method uses a mixture of BF_3·D_3PO_4 and is useful with a variety of organic compounds. This experimental procedure was improved by Heredy and co-workers.[5] The use of liquid deuteriohalides has also been reported.[6] We have developed another technique for preparing deuterated aromatic compounds which is very rapid and convenient, requiring only BF_3 and D_2O.

The liquid acid prepared by blowing BF_3 gas into D_2O to prepare a 1:1 molar solution is a fascinating, strong acid system[7,8] whose chemistry we are exploring. Its preparation is rapid and easy. It can be used for preparing deuterated aromatics simply by stirring the neat aromatic with the BF_3·D_2O system. Reactions with deactivated benzenes are too slow to be useful. The reaction proceeds nicely with polycyclic aromatics and others whose electrophilic reactivity is as great as or greater than benzene. The system has obvious advantages over D_2SO_4. Since the proton is the only electrophile, competing electrophilic reactions such as sulfonation do not occur. Since BF_3 and D_2O are commonly available, the procedure is much more convenient than the use of deuteriohalides such as DBr and $AlBr_3$ or DF or DCl in CF_3COOD.[6] Results with a variety of aromatics are given in Table I.

Experimental Section

All compounds were purchased and were used without further purification.

Preparation of BF_3·D_2O. A weighed amount of D_2O (99.8%) was cooled in a ice–water bath and BF_3 was bubbled into the liquid until a 1:1 molar ratio was reached as measured by the weight increase. BF_3·D_2O is a fuming liquid and was stored in a polyethylene bottle.

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Table I. Deuteration of Aromatic Compounds

compd	registry no.	temp, °C	time, h	H–D exchange, %
benzene	71-43-2	25	61	45
toluene	108-88-3	25	24	74
chlorobenzene	108-90-7	25	120	14
o-xylene	95-47-6	25	48	81
m-xylene	108-38-3	25	48	85
p-xylene	106-42-3	25	48	81
cumene	98-82-8	25	41	78
tert-butylbenzene	98-06-6	25	30	dealkylates
n-butylbenzene	104-51-8	25	48	70
tetralin	119-64-2	25	61	78
naphthalene	91-20-3	90	23	76
phenanthrene	85-01-8	105	20	81

Deuterium Exchange. The hydrocarbon was placed in a flask and a ca. 10 M excess of D_2O·BF_3 was added. A condenser was connected and the reaction mixture was stirred at room temperature. Naphthalene and phenanthrene exchanges were carried out at 90 and 105 °C, respectively, in fuming, slowly decomposing acid. After completion, the organic layer was separated, washed twice with water, and dried with silica gel. Naphthalene and phenanthrene were dissolved in CCl_4 after the reaction, the CCl_4 layer was separated, washed with water, and dried over silica gel, and the CCl_4 was evaporated.

Analysis of Deuterium Exchange. The possibility of deuterium incorporation into the aliphatic groups was examined by looking for aliphatic C–D stretching bands in the IR spectrum. While a diminution of the C_{ar}–H stretch at about 3030 cm^{-1} and a new intense band at 2260 cm^{-1} due to C_{ar}–D stretch was observed, no bands attributable to C_{al}–D stretch were observed. Mass spectra indicated that a mixture of deuterated compounds was present in each reaction product. The extent of deuterium incorporation was measured by comparing the areas of the aromatic and aliphatic NMR peaks in the deuterated products. With benzene, chlorobenzene, naphthalene, and phenanthrene, D incorporation was estimated by adding a known amount of a standard compound (cyclohexane) to the CCl_4 solution of deuterated product and comparing peak areas. Reproducibility of the NMR technique was ±5% of the measured conversion.

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Registry No.—D_2O, 7789-20-0; BF_3, 7637-07-2; BF_3·D_2O, 33598-66-2.

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An Improved General Synthesis of 1-Aryl-1-cyclopropanols

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The most general procedure for the synthesis of 1-aryl-1-cyclopropanol previously available was that of De Puy and his co-workers[2] (eq 1). An alternative procedure, based on 1-

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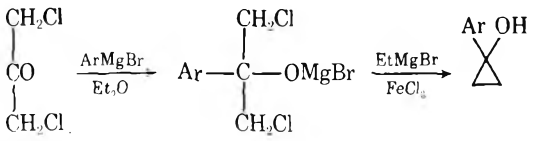
Table I. Synthesis of 1-Aryl-1-cyclopropanols[a]

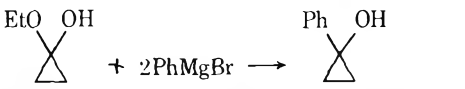
1-Aryl-1-cyclopropanol[b]	Registry no.	Bp (mm) or mp, °C	Yield,[c] %	3,5-DNB[b] mp, °C	Registry no.
p-(Dimethylamino)phenyl	66826-74-2	113–114	57 (0)	137–138	66826-75-3
[5-Coumaranyl]	66859-36-7	130–132 (0.3)	51 (0)	147–148	66826-76-4
p-Methoxyphenyl	15973-65-6	75–78 (0.5)[d]	52 (35)	109–110[g]	65109-90-2
p-Methylphenyl	40122-37-0	38–39[e]	71 (55)	114–115[g]	65109-92-4
Phenyl	29526-96-3	106–107 (20)[f]	75 (48)	104–105[g]	66826-77-5

[a] Complete spectral characterization confirms the structural assignments. [b] Satisfactory microanalytical data were obtained for all of the 1-aryl-1-cyclopropanols and their 3,5-DNB derivatives. [c] The figures in parentheses indicate the percent yields obtained using the De Puy method.[2,5] [d] Lit.[5] bp 75–78 °C (0.5 mm). [e] Lit.[2] mp 39–40 °C. [f] Lit. bp 119–121 °C (26 mm): S. Murai, T. Aya, and N. Sonoda, *J. Org. Chem.*, **38**, 4354 (1973). [g] Melting point is identical with those of products prepared earlier by the De Puy procedure.[5]



(1)

ethoxycyclopropanol, has recently become available[3,4] (eq 2).

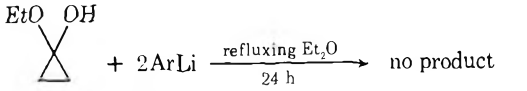


(2)

In our hands the De Puy synthesis proved satisfactory for the preparation of a series of 1-aryl-1-cyclopropanols containing moderately activating substituents in the aryl group (*p*-CH_3, *p*-SCH_3, *p*-OCH_3).[5] However, in attempting to synthesize 1-aryl-1-cyclopropanols containing even more activating substituents (*p*-$N(CH_3)_2$, 5-coumaranyl), this synthetic procedure failed, in spite of considerable experimental effort.

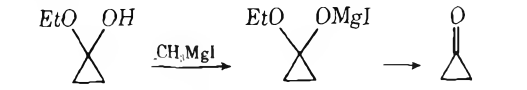
First, these reactive aryl derivatives are converted into the Grignard reagents only with difficulty. The corresponding lithium compounds are far more accessible. However, these aryllithiums failed to add to 1,3-dichloro-2-propanone over a variety of conditions. Instead, preferential enolization of the ketone invariably occurred.

Attempts to use 1-ethoxycyclopropanol with these aryllithiums likewise failed. Apparently the lithium salt of 1-ethoxycyclopropanol is formed, but further reaction does not occur even in refluxing ether over 24 h (eq 3).

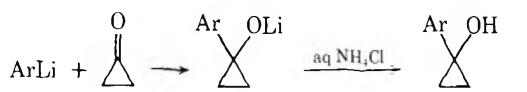


(3)

Experiments revealed a simple solution to the difficulty. Treatment of the reagent, 1-ethoxycyclopropanol, with an equimolar amount of methylmagnesium iodide converted it into a species which readily reacts with the desired aryllithium to give the desired products in high purity and satisfactory yields. Although we did not attempt to identify the intermediate, we believe that the magnesium salt readily breaks down into cyclopropanone, whereas the intermediate lithium salt does not (eq 4 and 5). A further advantage of this procedure



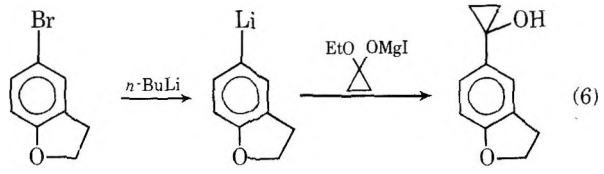
(4)



(5)

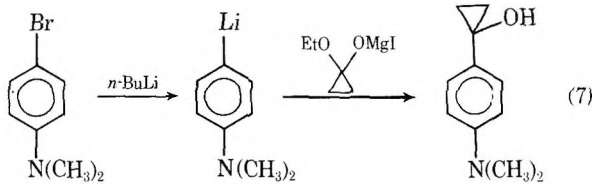
is the fact that it requires only 1 mol of the desired aryllithium.

In this way we successfully synthesized 1-[5-coumaranyl]-1-cyclopropanol (eq 6), which had previously eluded us in spite



(6)

of exhaustive efforts.[5] Similarly, we were successful in extending the procedure to the synthesis of the highly activated *p*-(dimethylamino)phenyl derivative (eq 7). This method



(7)

appears to provide a highly convenient general synthetic route to the 1-aryl-1-cyclopropanols.

Experimental Section

Melting and boiling points are uncorrected. ^1H NMR spectra were determined on a Varian T-60 spectrometer.

Synthesis of 1-ethoxycyclopropanol was done from 1-ethoxy-1-trimethylsiloxycyclopropane[6] according to the method of Salaün[3] in 90% yield, bp 60–61 °C (18 mm) [lit.[7] bp 60–62 °C (20 mm)].

Preparation of Aryllithiums. The aryllithiums were made by the treatment of the corresponding aryl bromides with *n*-butyllithium.[8]

Synthesis of 1-Aryl-1-cyclopropanols: 1-[*p*-(Dimethylamino)phenyl]-1-cyclopropanol. To an oven-dried, nitrogen-flushed, 250-mL three-neck flask fitted with a septum inlet, a magnetic stirring bar, a pressure equalizing dropping funnel, and a reflux condenser and topped with a connecting tube leading to a mercury bubbler was added magnesium (0.243 g, 10 mmol) and diethyl ether (20 mL). To this stirred suspension was added dropwise methyl iodide (1.42 g, 10 mmol) in ether (20 mL). After all of the magnesium was dissolved, the flask was cooled in an ice bath. To this was added dropwise 1-ethoxycyclopropanol (1.02 g, 10 mmol) in ether (20 mL). A gas, presumably methane, evolved, and a white suspension was observed. To a 100-mL flask fitted with a septum inlet and a magnetic stirring bar and topped with a connecting tube leading to a mercury bubbler was added *p*-(dimethylamino)bromobenzene (2.0 g, 10 mmol) and diethyl ether (20 mL). To this stirred solution at room temperature was added dropwise a solution of 10 mmol of *n*-butyllithium in hexane (1.9 M, 5.3 mL) with the help of a syringe. Stirring was continued for 2 h.[9] This solution was added dropwise with a double-ended needle to the white suspension prepared above, maintained at 0 °C. After the addition was over, the reaction mixture was brought to room temperature (30 min) and then maintained (oil bath) under reflux for 12 h. It was cooled to 0 °C and saturated ammonium chloride solution added. After the usual workup and removal of solvents, the solid obtained was recrystallized from a 90:10 mixture of hexane–ethyl acetate. There was obtained 1.01 g (57%) of pale yellow crystals, mp 113–114 °C.

This procedure was applied to the synthesis of a representative group of 1-aryl-1-cyclopropanols, and these were converted into the corresponding 3,5-dinitrobenzoates.[5] The results are summarized in Table I.

Registry No.—1-Ethoxycyclopropanol, 13837-45-1; *p*-(dimethylamino)bromobenzene, 586-77-6; 5-bromocoumarin, 66826-78-6; *p*-(methoxy)bromobenzene, 104-92-7; *p*-(methyl)bromobenzene, 106-38-7; bromobenzene, 108-86-1.

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Preparation of Optically Pure *N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine and Its Antipode

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O-Benzyl-L-serine derivatives are useful in peptide synthesis. The currently available methods for preparing these compounds are laborious and not convenient for large-scale preparation. Okawa[1] prepared *O*-benzyl-L-serine via bromination of methyl acrylate and resolved the racemate of the *N*-acetyl derivative by acylase. The other method is benzylation of N-*tert*-butyloxycarbonyl-L-serine in sodium–liquid ammonia[2] or in sodium hydride–dimethylformamide.[3] The acylase method can obtain optically pure *O*-benzyl-L-serine but the amino-protecting group should be introduced again for peptide synthesis. The enzyme, however, is not cheap and is hard to obtain. The second method, benzylation of *N-tert*-butyloxycarbonyl-L-serine, is only around 50% in yield and racemization might occur in the benzylation process.

The direct resolution of *N-tert*-butyloxycarbonyl derivatives of racemic amino acids would be a better way of preparing optically pure protected amino acids rather than incorporating the protecting group onto optically active amino acids or derivatives.

We present here a new method for the preparation of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode. Both enantiomers appeared optically pure and the yields are higher than the published values.

Starting from methyl acrylate, *O*-benzyl-DL-serine obtained[1] was converted to *N-tert*-butyloxycarbonyl derivative[4] and then methylated by diazomethane.[5] The butyloxycarbonyl group might be introduced to the amino acid methyl ester prepared by thionyl chloride in methanol. The racemic acyl amino acid methyl ester was then hydrolyzed under papain catalysis to afford the L acid in 72% yield; its antipode was recovered in 81% yield from the unreacted D ester by mild alkaline treatment.

The same approach to other amino acids including threonine derivative, which has two optical centers, is under investigation.

Experimental Section

***N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine Dicyclohexylammonium Salt.** *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine (mp 90–91 °C, from ether/*n*-hexane) (5.9 g, 20 mmol) prepared from *O*-benzyl-DL-serine was dissolved in ether (100 mL). The ethereal solution of diazomethane[7] was dropped in until the solution remained pale yellow. The mixture was then washed twice with 20-mL portions of 1 N $NaHCO_3$, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to dryness. The oily ester (6.0 g, 98%) obtained was dissolved in 10 mL of dimethylformamide and then added to a phosphate buffer solution (0.05 M, pH 6.0) containing 5 mmol of β-mercaptoethanol, 5 mmol of EDTA and 500 mg of crude papain. The mixture was kept at 35 °C with stirring and the pH was maintained at 6.0 by addition of 1 N NaOH. After 4 h and with no decrease in pH, the mixture was extracted twice with 50-mL portions of ether to recover the unreacted ester. The aqueous solution was then acidified to pH 3.0 with 3 N HCl and extracted three times with 50-mL portions of ethyl acetate. The combined ethyl acetate was washed with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure to give a colorless oil. The oil was dissolved in 30 mL of ether/*n*-hexane (1:1 v/v) followed by addition of dicylcohexylamine (1.6 mL). The precipitates formed after cooling were collected by filtration to give the title compound (3.4 g, 72%): mp 135–136 °C; R_f 0.78 (system A), 0.20 (system B); $[\alpha]^{25}_D$ +25.0 (c 2, MeOH) [lit.[7] mp 135.5–136 °C, $[\alpha]^{25}_D$ +24.3 (c 2.94, MeOH)].

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 8.92; N, 6.03.

***N-tert*-Butyloxycarbonyl-*O*-benzyl-D-serine Dicyclohexylammonium Salt.** The unreacted ester obtained above in ether was washed with water, dried, and evaporated to give an oil (3.4 g, 11 mmol), which was further digested with papain (50 mg) in the same way as described above (in 100 mL of solution) for 4 h and the unreacted ester was isolated again (2.5 g, 8.1 mmol): R_f 0.88 (system B); $[\alpha]^{25}_D$ +2.5 (C 2, MeOH). It was hydrolyzed by stirring in a mixture of dioxane–1 N NaOH (1:1 v/v) (30 mL) with 1.5 equiv of alkali for 20 min. The solution was then acidified and followed by extraction to prepare the dicyclohexylammonium salt of *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine (3.8 g, 8 mmol): mp 133–134 °C; $[\alpha]^{25}_D$ −24.2 (c 2, MeOH) [lit.[7] mp 130–131 °C; $[\alpha]^{25}_D$ −23.6 (c 2.28, MeOH)]; TLC data were the same as for the L isomer.

Anal. Calcd for $C_{15}H_{21}NO_5 \cdot C_{12}H_{23}N$: C, 68.03; H, 9.24; N, 5.88. Found: C, 67.90; H, 9.11; N, 6.06.

The Steric Purity. An aliquot of *N-tert*-butyloxycarbonyl-*O*-benzyl-L-serine and its antipode obtained by the above procedure were dissolved in 5 mL of 2 N HCl–AcOH, respectively. After 1 h at room temperature, the reaction mixture was evaporated under reduced pressure at 25 °C to yield a residue which was then diluted to 5 mL with 1 N HCl for optical rotation determination. The samples showed the same optical rotation in absolute value, respectively, as a sample of *O*-benzyl-L-serine[1] similarly treated, $[\alpha]^{25}_D$ =7.4 (c 2, 1 N HCl).

Registry No.—*N-tert*-Butyloxycarbonyl-*O*-benzyl-L-serine dicyclohexylammonium salt, 30200-52-3; *N-tert*-butyloxycarbonyl-*O*-benzyl-DL-serine, 53317-22-9; *O*-benzyl-DL-serine, 5445-44-3; dicyclohexylamine, 101-83-7; *N-tert*-butyloxycarbonyl-*O*-benzyl-D-serine dicyclohexylammonium salt, 10342-02-6.

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Synthesis of β-Dihydrothebaine

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The 6,14-*endo*-etheno and 6,14-*endo*-ethanotetrahydrooripavines are among the most potent analgesics known.[1]

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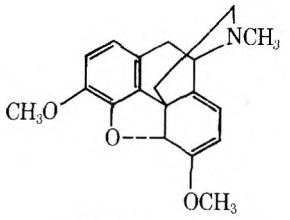
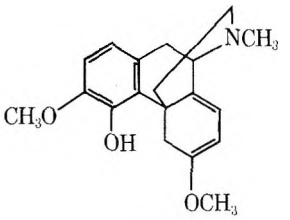
They were discovered by Bentley and co-workers during a study of the Diels–Alder reaction of thebaine with various dienophiles. β-Dihydrothebaine (2) is a diene related to thebaine which could thus give Diels–Alder products of interest as potential analgesic intermediates. Earlier attempts to pursue this approach were limited because compound 2 was not readily available.[2b,3] In spite of the report by Schmid and Karrer[4] that β-dihydrothebaine (2) can be prepared from



thebaine 1



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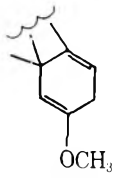

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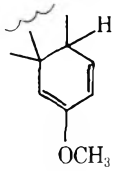

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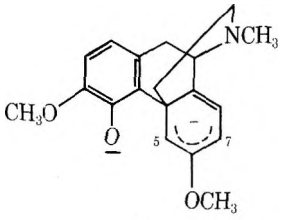

5

thebaine (1) in 42% yield by reduction with $LiAlH_4$ in C_6H_6/ether, it has been pointed out on several occasions that 2 is still essentially inaccessible.[2,3,5,6] Bentley and co-workers[6] reexamined the reaction and noted that the reaction was "capricious and slow and considerable amounts of thebaine were found in solution after 48 h reflux". Furthermore, these authors studied the reaction utilizing mixtures of $LiAlH_4$/$AlCl_3$ and found that ratios of 1:1, 1:3, or 1:4 of the reagents, respectively, gave mainly a rearranged product neodihydrothebaine, whereas ratios of 4:1 or 3:1 yielded thebainone-A enol methyl ether 4 as the major product with traces of neodihydrothebaine and β-DHT (2). Bentley, Robinson, and Wain[5a] had earlier carried out the reduction of thebaine with Na/liquid NH_3 and found it to form the unconjugated diene, φ-DHT (3) in 95% yield with no trace of 2. This was confirmed by Birch and Fitton[3] who also reported that the isomerization *of 3 to 2 cannot be accomplished by the usual basic reagents.*

We have found that the reaction of thebaine with K/liquid NH_3 gives a 1:1 mixture of 2 and 3 in 95% yield. The procedure is reproducible and provides pure β-DHT (2), mp 167–168 °C (lit.[4] 170–171 °C), after one crystallization (isolated yield 34%). A comparative study of various amounts of K and other metals is shown in Table I. It was also observed that treatment of φ-DHT (3) with K/liquid NH_3 in the presence of a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$[7] gave a 1:1 mixture of 2 and 3 in 79% yield. These results suggest that an intermediate dianion 5 is formed which is protonated either at C_5 or C_7. However, in our hands attempts to increase the yield of 2 by modification of quenching conditions were not successful. On occasion enriched mixtures of 2 were obtained but the results were not reproducible.

Table I. Reaction of Thebaine with Alkali Metals in Liquid NH_3

no.	elements	equiv	% thebaine converted	% 2	% 3
1	K	1.0	50[a]	50	50
2	K	2.3	95	50	50
3	Ca	2.3	50[a]	0	100
4	Li	2.3	62	0	100
5	K/$FeCl_3$[b]	2.3	95	0	100
6	Na[c]	2.3	95	0	100
7	Na[d]	2.3	95	25	75

[a] 50% of unreacted thebaine recovered. [b] A few crystals of $FeCl_3$ were added to liquid NH_3 followed by K metal. [c] Following the literature[5a] conditions Na metal was added over 35 min and after stirring for another 10 min the reaction was quenched. [d] Reaction was carried out as described for K metal.

Experimental Section

The following general procedure, as described below using potassium, was used for the reduction of thebaine with various alkali metals. The results are summarized in Table I.

Reaction of Thebaine (1) with K/Liquid NH_3. The apparatus consisted of a 1-L, three-neck flask fitted with a mechanical stirrer, a reflux condenser which was in turn fitted with a KOH drying tube, and a ground glass stopper. The flask was insulated with a heating mantle. Approximately 600 mL of liquid NH_3 was introduced into the flask followed by the addition of 44.0 g (0.141 mol) of thebaine. The sand-colored mixture was stirred and 12.6 g (0.322 mol, 2.3 equiv) of K was added in small pieces over a period of 80 min. As the K was added the resulting mixture became orange in color, which eventually turned dark red. The reaction mixture was stirred for 1 h and quenched by the addition of 24 mL of C_2H_5OH (200 proof). Stirring was then continued for 0.5 h and the NH_3 was allowed to evaporate overnight. Then 500 g of crushed ice followed by 150 mL of H_2O was added slowly. The resultant green solution was treated with solid CO_2 until the mixture was acidic. Ether (2 L) was added and the layers were separated. The ether layer was washed with 4 × 250 mL of H_2O, dried, and concentrated to yield a tan powder. Analysis by NMR ($CDCl_3$) showed it to be a 1:1 mixture of 2 [olefin protons: δ 5.73 (d, 1 H, 4.80 (d, 1 H)] and 3 [olefin protons: δ 6.10 (s, 1 H), 5.57 (t, 1 H)]. The mixture was boiled in 250 mL of ligroin (bp 63–75 °C) and then EtOAc was added until the solution was complete. After filtration while hot, the filtrate was allowed to stand at room temperature overnight and typically 15 g (34%) of 2, mp 167–168 °C dec (lit.[4] 170–171 °C) (free of 3 by NMR), was obtained. The filtrate on concentration and crystallization gave pure 3, mp 150–152 °C (lit.[5a] 154 °C).

Reaction of φ-DHT (3) with K/Liquid NH_3. In a 100-mL three-neck flask, equipped as described above, approximately 65 mL of liquid NH_3 and a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ were added to the flask followed by the slow addition of 750 mg (19.2 mmol, 3 equiv) of K in small portions: the resulting solution, which was steel-gray in color, was then stirred for approximately 0.5 h. After addition of 2.0 g (6.4 mmol) of 3 the reaction mixture (red color) was stirred for 2 h and then quenched by the careful addition of 10 mL of ether followed by 10 mL of H_2O/ether mixture. The NH_3 was allowed to evaporate and an additional quantity of H_2O/ether mixture and an excess of NH_4Cl was added. The ether layer was separated and the aqueous layer was extracted once with ether. The combined ether extract was washed with H_2O, dried, and evaporated to leave 1.58 g (79%) of a red resin, identified as a 1:1 mixture of 2 and 3 (NMR).

Acknowledgment. We thank Mr. T. Melby and Ms. A. Bousquet for technical assistance and Miles Laboratories, Elkhart, Indiana, for financial support.

Registry No.—1, 115-37-7; 2, 63944-52-5; 3, 6878-93-9.

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Synthesis of *dl*-α-Lipoic Acid from a Butadiene Telomer

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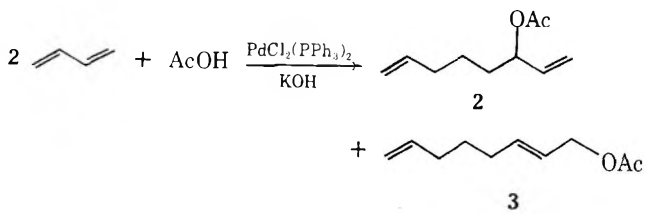
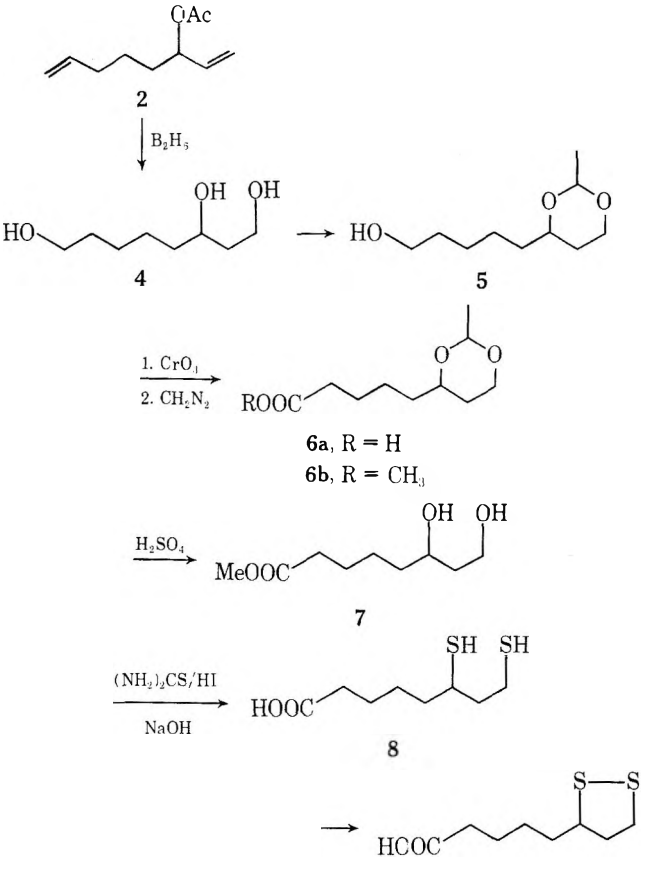
α-Lipoic acid has been recognized as a cofactor involved in the biochemical decarboxylation of α-keto acids and as a growth factor for a variety of microorganisms.[1] This naturally occurring sulfur containing vitamin was isolated by Reed et al.[2] from liver in 1951 and identified as 1,2-dithiolane-3-valeric acid (1). Because of its important physiological properties, numerous synthetic studies of this acid have been carried out.[1]

In designing an efficient synthesis of *dl*-α-lipoic acid, two problems have to be considered. The first one is the selection of proper building blocks for the eight-carbon chain, and there are still many possibilites. In the first synthesis by Bullock et al.,[3] ethylene and adipic acid half ester acid chloride were used as building blocks of the eight-carbon chain. In another synthesis by Braude et al.,[4] 6-heptenoic acid was subjected to Prins reaction. Other starting materials were 2-hydroxyethylanisole[5] and 2-acetoxyethylcyclohexanone[6] which were cleaved to give the eight-carbon chain with necessary functional groups. The second problem in the α-lipoic acid synthesis is the method of forming the dithiolane system. For this purpose, usually 1,3-diols, tosylates, and halides were converted to the dithiols by the reaction of sulfur compounds such as sodium disulfide,[7] thioacetic acid,[8] benzylmercaptane,[8] and thiourea.[3-5]

We now wish to report a new simple synthetic method for *dl*-α-lipoic acid using a butadiene telomer as a very suitable starting material, offering a new solution to the first problem mentioned above. Palladium-catalyzed telomerization of butadiene with various nucleophiles affords a number of useful telomers. In our continuous effort to utilize these telomers in organic synthesis, we have already synthesized a number of natural products starting from various butadiene telomers. In the present synthesis of *dl*-α-lipoic acid, we used 3-acetoxy-1,7-octadiene (**2**), a telomer obtained easily with 1-acetoxy-2,7-octadiene (**3**) from butadiene and acetic acid.[9,10] The ester **3** can be rearranged to **2** with the palladium catalyst.



We have already utilized these easily available telomers for simple syntheses of 2,15-hexadecanedione,[11,12] 1-octen-3-ol (Matsutake alcohol),[13,14] and diplodialide.[15] The compound **2** has the eight-carbon chain necessary for *dl*-α-lipoic acid synthesis. In addition, its functional groups, namely two double bonds and one acetoxy group, are located at the right positions and very suitable for conversion to *dl*-α-lipoic acid. The synthesis has been carried out by the following sequence of reactions.



The first step of the synthesis is hydroboration of two terminal double bonds. At first the reaction was carried out with 9-borabicyclo[3.3.1]nonane. Although the hydroboration proceeded smoothly with this hydroborane, the separation of cyclooctanediol, formed by the oxidation of the reagent, from desired 1,3,8-octanetriol (**4**) was not easy. Therefore the hydroboration of **2** was carried out using B_2H_6 to give the triol **4** which is very soluble in water. The triol was isolated using a continuous extractor. Then in order to differentiate one hydroxy group from the 1,3-diol system, the latter was protected by six-membered acetal formation using paracetaldehyde to afford **5** in 64% yield from **2**. The oxidation of the unprotected terminal alcohol was carried out with Jones reagent to give carboxylic acid **6a** in 73% yield. Although the oxidation was carried out under acidic conditions, the protecting group of the 1,3-diols was not attacked. The carboxylic acid was methylated with diazomethane in order to avoid lactone formation in the next step. The protecting group was removed by heating with sulfuric acid in dry methanol to give methyl 6,8-dihydroxyoctanoate (**7**) in 92% yield. The ester **7** is a known compound and the conversion of the ester to *dl*-α-lipoic acid has been carried out already. Following the method of the literature,[3] the ester was treated with thiourea in hydroiodic acid and 6,8-dimercaptooctanoic acid (**8**) was isolated in 80% yield. The final step is the oxidative ring closure to form the dithiolane ring by bubbling oxygen in the presence of ferric chloride. By this way, *dl*-α-lipoic acid was obtained as a yellow crystalline compound which was identified by its melting point and spectral data.

Experimental Section

All boiling points and melting points were uncorrected. IR spectra were recorded as neat films on a JASCO IR-2 spectrometer. NMR spectra were recorded in CCl_4 on a HITACHI R-24 A, (60 MHz) with Me_4Si as an internal standard.

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3-Acetoxy-1,7-octadiene (2). A mixture of $PdCl_2(PPh_3)_2$ (400 mg, 0.57 mmol), KOH (200 mg, 3.56 mmol), acetic acid (21.0 g, 0.35 mol), and triethylamine (35.4 g, 0.35 mol) was placed in a 100-mL autoclave and then butadiene (29 mL, 0.35 mol) was introduced. The autoclave was placed in an oil bath kept at 90 °C and stirred with a magnetic stirrer. After 10 h, ether (20 mL) was added to the resulting mixture and the solution was acidified with 3 N HCl and washed with brine. The organic layer was dried over magnesium sulfate and evaporated. The crude oil was distilled to give a mixture of 3-acetoxy-1,7-octadiene (2) and 1-acetoxy-2,7-octadiene (3) (1:2.7) (25 g, 85% based on butadiene). The fractional distillation of the mixture gave pure 3-acetoxyl-1,7-octadiene (2) (92 °C (24 Torr)): NMR (CCl_4) δ 1.52 (4 H, m), 1.80–2.27 (2 H, m), 2.00 (3 H, s), 4.78–6.13 (7 H, complex m); IR 1742, 1640, 1375, 1242 cm^{-1}.

1,3,8-Octanetriol (4). A solution of 3-acetoxy-1,7-octadiene (2) (3.36 g, 20.0 mmol) in dry tetrahydrofuran (15 mL) was placed in a flask under nitrogen atmosphere. Next the flask was placed in an ice bath and a 2.4 M solution of B_2H_6 in tetrahydrofuran (15 mL) was added slowly. The solution was stirred for 2 h at room temperature. A mixture of 5 N NaOH (15 mL) and 28% hydrogen peroxide (10 mL) was added dropwise to the flask at 0 °C and the mixture was stirred for 3 h at room temperature. The reaction mixture was poured into a cooled aqueous sodium thiosulfate solution to remove excess hydrogen peroxide. The solution was concentrated to 10 mL and continuous extraction with ethyl acetate was carried out. The extract was evaporated to give a crude triol 4 (2.59 g). The triol 4 was used in the next step without purification.

1-Hydroxy-5-(2-methyl-1,3-dioxan-4-yl)pentane (5). A mixture of the crude triol 4 (2.59 g), paraldehyde (5 mL), and a catalytic amount of *p*-toluenesulfonic acid dissolved in dry dichloromethane (10 mL) was placed in a flask under nitrogen atmosphere. The reaction was carried out for 2 h at room temperature. An aqueous sodium bicarbonate solution was added to the resulting mixture. The solution was extracted with dichloromethane and the extract was washed with brine. Dichloromethane and excess paraldehyde were removed under reduced pressure to give a crude oil. The oil was purified by column chromatography (silica gel, *n*-hexane/ether, 5:1) to afford alcohol 5 (2.40 g, 63.8% from 2): NMR (CCl_4) δ 1.24 (3 H, d, J = 5 Hz), 1.40 (10 H, broad), 3.31 (1 H, s), 3.40–4.23 (5 H, m), 4.65 (1 H, q, J = 5 Hz); IR 3450, 2945, 2870, 1135, 960 cm^{-1}.

Methyl 5-(2-Methyl-1,3-dioxan-4 yl)valerate (6b). The alcohol 5 (1.88 g, 10 mmol) dissolved in acetone (5 mL) was placed in a flask at 0 °C. Then Jones reagent (CrO_3–H_2SO_4) was added to the flask slowly. The color of a solution turned to green. The Jones reagent was added dropwise until its red-brown color remained. After water was added to the flask, the resulting mixture was extracted with ether. An aqueous sodium carbonate solution was added to the extract to remove neutral compounds. The aqueous layer was extracted with ether and acidified with 3 N HCl. The solution was extracted with dichloromethane and the extract was dried over magnesium sulfate. The solvent was removed to give the desired carboxylic acid 6a (1.46 g, 72%): NMR (CCl_4) δ 1.22 (3 H, d, J = 5 Hz), 1.48 (8 H, broad), 2.32 (2 H, m), 3.20–4.22 (3 H, m), 4.60 (1 H, q, J = 5 Hz), 10.67 (1 H, s); IR 1720 cm^{-1}.

The crude carboxylic acid was converted to the methyl ester **6b** with diazomethane. The product was purified by column chromatography (silica gel, *n*-hexane/ether, 10:1) to give the pure methyl ester **6b** (1.40 g, 65% from 5): NMR (CCl_4) δ 1.21 (3 H, d, J = 5 Hz), 1.42 (8 H, broad), 2.25 (2 H, m), 3.10–4.20 (3 H, m), 3.60 (3 H, s), 4.55 (1 H, q, J = 5 Hz); IR 2950, 1740 cm^{-1}.

Methyl 6,8-Dihydroxyoctanoate (7). A mixture of the protected product **6b** (1.00 g, 4.63 mmol) and dry methanol (50 mL) was refluxed in the presence of a catalytic amount of concentrated sulfuric acid. After 24 h, the solution was concentrated to 10 mL and the residue was diluted with water. The solution was extracted with ether. From the extract, unchanged ester (258 mg) was recovered. The aqueous solution was neutralized with sodium hydrogen carbonate solution and concentrated under reduced pressure. The residue was extracted with boiling ethyl acetate. The extract was dried over magnesium sulfate and evaporated to give methyl 6,8-dihydroxyoctanoate (7) (605 mg, 92.8% based on the consumed ester **6b**): NMR (CCl_4) δ 1.46 (8 H, m), 2.28 (2 H, t), 3.49–4.15 (5 H, m), 3.60 (3 H, s); IR 3370, 2925, 1740 cm^{-1}.

6,8-Dimercaptooctanoic Acid (8). A mixture of methyl 6,8-dihydroxyoctanoate (7) (500 mg, 2.63 mmol), thiourea (1.8 g, 23.6 mmol), and 57% HI (4 g) was heated under reflux for 24 h. After cooling, KOH (4 g) in water (10 mL) was added and the mixture was refluxed for 12 h under nitrogen. The mixture was then extracted with ether, acidified with 3 N HCl, and extracted with dichloromethane. The extract was washed with water, dried over magnesium sulfate, and evaporated to give a yellow oil (522 mg). The oil was distilled under reduced pressure (170–175 °C bath temperature (8.3×10^{-2} Torr)) to give 6,8-dimercapotooctanoic acid (8) (438 mg, 80%): NMR δ 3.08 (2 H, t, J = 6 Hz), 3.49 (1 H, m), 11.31 (1 H, s); IR 2925, 1710, 1410, 1285 cm^{-1}.

dl-α-Lipoic Acid (1). A mixture of dithiol acid 8 (190 mg, 0.913 mmol) and water (6 mL) containing NaOH (31 mg, 0.775 mmol) and ferric chloride (2 mg) was placed in a flask. The color of the solution turned to dark red. A stream of oxygen was bubbled through the solution until the reddish color changed to pale yellow. After 9 h, the resulting pale yellow solution was washed with dichloromethane. The aqueous layer was acidified with 3 N HCl and extracted with dichloromethane. The extract was dried over magnesium sulfate and evaporated to give a yellow oil, which solidified upon trituration with pentane. Crystallization from hexane gave *dl*-α-lipoic acid (1) (132 mg, 70%) as yellow needles: mp 60–61 °C (lit. mp 60 °C,[4] 60–60.5 °C,[5] 61 °C,[3] 61–62 °C[6,8]); NMR (CCl_4) δ 1.60 (8 H, broad), 2.37 (2 H, m), 3.08 (2 H, t, J = 6 Hz), 3.50 (1 H, m), 12.00 (1 H, s); IR 3300–2400, 1690, 1250, 945 cm^{-1}.

Acknowledgment. This work was supported financially by the Grant-in-aid administered by the Ministry of Education, Japanese Government (203510).

Registry No.—**1**, 1077-28-7; **2**, 66859-02-7; **3**, 3491-27-8; **4**, 66859-03-8; **5**, 66859-04-9; **6a**, 66859-05-0; **6b**, 66859-06-1; **7**, 66859-07-2; **8**, 7516-48-5; butadiene, 106-99-0; acetic acid, 64-19-7.

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Stereoselective Synthesis of 1-Substituted (*E,E*)- and (*E,Z*)-2,4-Decadienyl Derivatives

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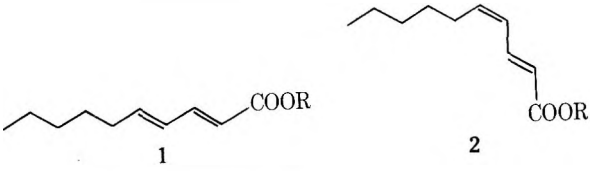
Recently we required the ethyl esters of (*E,E*)-2,4-decadienoic acid (1, R = H) and the corresponding (*E,Z*)-2,4-decadienoic acid (2, R = H). Since these compounds were to serve as starting materials in a synthesis of the prostaglandin nucleus, it was imperative that our syntheses be stereoselec-



1 2

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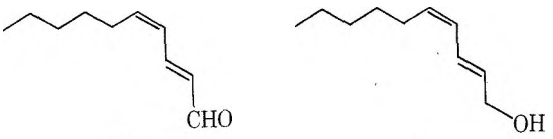
tive. The *N*-isobutylamide of **1** (pellitorine) is an insecticidal compound from *Anacyclus pyrethrum*. A number of syntheses of pellitorine have proceeded via acid **1** or its esters,[2-6] which in turn were prepared by a number of different routes. However, the ready availability of (*E,E*)-2,4-decadienal[7] led us to consider it as a precursor of acid **1** (R = H). Following the suggestion of Ohloff and Pawlak,[4] we oxidized (*E,E*)-2,4-decadienal to the ethyl ester **1** (R = Et) in 80% yield using MnO_2–NaCN in ethanol–acetic acid.[8] VPC analysis of this product indicated that the ratio of the *E,E* ester **1** (R = Et) to the *E,Z* ester **2** (R = Et) was 93:7 which was the same as the ratio of isomers in the starting aldehyde.[7] Thus it would appear that the oxidation is stereoselective.

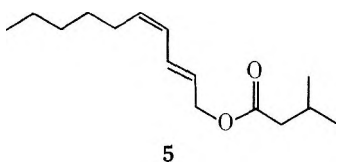
Next we turned to the preparation of the *E,Z* compounds **2**, **3**, and **4**. The ethyl ester **2** (R = Et) is one of the flavor



3 4

constituents of Bartlett pears.[9] This ester has also been synthesized by a number of different routes.[4,5,10] The methyl ester **2** (R = Me, methyl stillingate)[11] has also been synthesized.[2] Unfortunately these syntheses proceed with either low yield or low stereoselectivity. Our route to ester **2** (R = Et) is shown in Scheme I.

The dianion of propargyl alcohol[12] was alkylated with 1-bromopentane in liquid NH_3 to give 2-octyn-1-ol in 50% yield. This alcohol was oxidized to 2-octynal in 83% with MnO_2[13] in CH_2Cl_2. Condensation of the 2-octynal with the anion of triethyl phosphonoacetate[14] produced ethyl (*E*)-2-decen-4-ynoate[2] in 97% yield. The acetylene was reduced with hydrogen and Lindlar's catalyst[15] to give the desired ethyl (*E,Z*)-2,4-decadienoate (**2**, R = Et) in 94% yield. This was contaminated with 4% starting material and <2% of the *E,E* isomer. The spectral data of the above ester **2** (R = Et) were identical with those reported from previous syntheses of this ester and for the product isolated from Bartlett pears.[4,5] The ester **2** (R = Et) was reduced with diisobutylaluminum hydride in hexane to produce (*E,Z*)-2,4-decadien-1-ol (**4**) in 90% yield. This can be oxidized with MnO_2 to the corresponding aldehyde **3** which is one of the flavor constituents of black tea.[16] Finally the (*E,Z*)-2,4-decadien-1-ol was acylated with isovaleryl chloride and triethylamine to give, in 98% yield, (*E,Z*)-2,4-decadienyl isovalerate (**5**) which has recently been isolated from cypress oil.[18] The spectral data of our synthetic material were identical with those reported for the natural product.[18]



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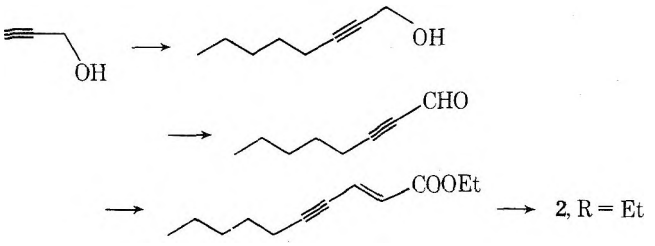
Experimental Section

All IR spectra were taken in chloroform solution on a Perkin-Elmer Model 700 spectrophotometer and were calibrated with the 1601 cm^{-1} band of polystyrene. The ^1H-NMR spectra were taken in deuteriochloroform on Varian Model T-60 or Model XL-100 spectrometers. Tetramethylsilane was used as an internal standard. Chemical shifts are reported on the δ scale. Coupling constants are quoted in hertz and the multiplicity of the signal is designed as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). The mass spectra were recorded with either an Atlas CH-4b or, for high resolution, on AEI-MS-50 mass spectrometer. In both cases, the spectra were obtained at 70 eV. Gas chromatography was carried out on a Hewlett Packard Model 5830A using helium as the carrier gas, 6 ft × ⅛ in. OV-1 and OV-17 as the columns and flame ionization detector.

Scheme I. Synthesis of Ethyl (*E,Z*)-2,4-Decadienoate (2, R = Et)



Ethyl (*E,E*)-2,4-Decadienoate (1, R = Et). To 25 mL of ethanol was added 0.164 g (1.08 mM) of (*E,E*)-2,4-decadienal, 1.952 g of MnO_2,[13] 0.277 g (12 mM) of sodium cyanide, and 0.098 mL of acetic acid. This mixture was allowed to stir at room temperature overnight. The MnO_2 was then filtered off and the ethanol was removed under reduced pressure. The resulting solid was dissolved in 25 mL of water and this solution was extracted with 3 × 25 mL of ethyl ether. The organic layer was dried and the solvent removed under reduced pressure giving 0.143 g (80%) of ester **1** (R = Et). GC analysis showed this ester to be 95% pure with no trace of starting aldehyde. A small quantity was isolated by gas chromatography: IR 1710, 1640, and 1620 cm^{-1}; NMR 6.9–7.4 (m, 1 H), 5.5–6.2 (m, 3 H), 4.13 (q, *J* = 7, 2 H), 2.0–2.4 (m, 1 H), 0.7–1.6 (m, 9 H); MS *m/e* 197 (8), 196 (43), 151 (28), 128 (11), 127 (15), 126 (13), 125 (100), 123 (13), 122 (13), 121 (8), 114 (8), 112 (6), 111 (10), 109 (6), 108 (10), 107 (8), 99 (18), 98 (30), 97 (53), 96 (13), 95 (13), 94 (10), 93 (10), 84 (6), 83 (10), 82 (10), 81 (50). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.29.

2-Octyn-1-ol. In a 2-L flask was condensed 1 L of ammonia and a catalytic amount of $Fe(NO_3)_3$ was added. To the solution was slowly added 12.55 g (1.8 mol) of lithium. After the blue color had disappeared, 54.6 mL (.92 mol) of propargyl alcohol in 200 mL of tetrahydrofuran was added over 15 min. The mixture was left for 1 h and then 124 mL (1.0 mol) of 1-bromopentane dissolved in 100 mL of dry tetrahydrofuran was added. After 45 min the reaction was quenched with solid ammonium chloride. The ammonia was evaporated and the resulting solution was washed with brine and dried and the solvent removed under reduced pressure. The 2-octyn-1-ol distilled at 90 °C (8 mm) yielding 57.2 g (50%) of product: IR 3700, 3500, 2330, and 2250 cm^{-1}; NMR 4.16 (m, 2 H), 3.67 (s, 1 H), 2.0–2.36 (m, 2 H), 1.0–1.8 (m, 6 H), 0.7–1.0 (m, 3 H); MS *m/e* 126 (1), 95 (39), 93 (44), 91 (13), 83 (52), 82 (17), 81 (30), 79 (39), 77 (22), 70 (74), 69 (48), 68 (22), 67 (83), 66 (13), 65 (17), 57 (26), 55 (91), 54 (22), 53 (35), 52 (30), 51 (22), 43 (44), 42 (39), 41 (100), 40 (22), 39 (78), 31 (13), 29 (74), 38 (44), 27 (52). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.33; H, 11.10.

2-Octynal. In a 500-mL flask was placed 250 mL of methylene chloride, 25 g of active MnO_2, and 3.64 g (28.9 mM) of 2-octyn-1-ol. The mixture was left at room temperature for 4 h. The MnO_2 was filtered off and the solvent removed under reduced pressure yielding 2.963 g (83%) of 2-octynal which distilled at 49 °C (0.1 mm): IR 2250 and 1670 cm^{-1}; NMR 9.08 (s, 1 H), 2.38 (t, *J* = 6, 2 H), 1.2–1.8 (m, 6 H), 0.7–1.2 (m, 3 H); MS *m/e* 124 (1), 123 (9), 109 (33), 96 (10), 95 (100), 81 (38), 70 (19), 68 (43), 67 (48), 57 (19), 56 (14), 55 (52), 54 (14), 53 (24), 41 (86), 39 (57), 29 (90), 28 (29), 27 (43). Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.45; H, 9.90.

Ethyl (*E*)-2-Decen-4-ynoate. A 0.957-g (19.9 mM) sample of NaH (50% mineral oil) was stirred in 50 mL of dry tetrahydrofuran. To this mixture was added 4.64 g (19.9 mM) of triethyl phosphonoacetate. When the evolution of H_2 stopped, the mixture was cooled to −20 °C (CCl_4 and dry ice) and 2.47 g (19.9 mM) of 2-octynal was added slowly and the reaction was left at −20 °C for 2 h. The mixture was then extracted with ethyl ether and the ether layer dried. The solvent was removed under reduced pressure yielding 3.77 g (97%) of the desired ester: IR 2250, 1705, 1620, and 960 cm^{-1}; NMR 6.67 (d t, *J* = 16 and 2, 1 H), 6.03 (d, *J* = 16, 1 H), 4.15 (q, *J* = 7, 2 H), 2.2–2.5 (m, 2 H), 1.0–1.6 (m, 9 H), 0.6–1.0 (m, 3 H); MS *m/e* 194 (2), 179 (17), 169 (5), 166 (12), 165 (48), 151 (21), 149 (55), 148 (17), 147 (21), 138 (5), 137 (21), 133 (21), 125 (7), 124 (10), 123 (41), 121 (48), 120 (36), 119 (59), 111 (10), 110 (43), 109 (55), 107 (17), 106 (17), 105 (45), 98 (19), 96 (26), 95 (21), 94 (69), 93 (38), 92 (35), 91 (62), 83 (17), 82 (35), 81 (52), 80 (14), 79 (71), 78 (19), 77 (50), 57 (17), 55 (83), 53 (27), 51 (28), 41 (78), 39 (58), 29 (100), 28 (55), 27 (50). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.10; H, 9.43.

Ethyl (*E,Z*)-2,4-Decadienoate (2, R = Et). In a 50-mL flask was placed 0.115 g of freshly prepared Lindlar's catalyst,[15] 2 drops of quinoline, 0.906 g (4.67 mM) of the above ester, and 25 mL of hexane.

A slight positive pressure of hydrogen was applied to the flask. When 1 equiv (103 mL) of H_2 was taken up the catalyst was filtered off. The solution was washed with mild acid and dried and the solvent was removed under reduced pressure yielding 0.900 g of product shown to be 94% pure by GC analysis. A small sample was isolated by gas chromatography: IR 1710, 1630, and 1605 cm^{-1}; NMR 7.55 (d, d, J = 16 and 10, 1 H), 5.80 (d, J = 16, 1 H), 5.5–6.3 (m, 2 H), 4.18 (q, J = 7, 2 H), 2.0–2.2 (m, 2 H), 1.0–1.7 (m, 9 H), 0.7–1.0 (m, 3 H); MS m/e 197 (9), 196 (61), 167 (6), 151 (42), 129 (48), 128 (26), 127 (29), 126 (16), 125 (100), 123 (19), 122 (32), 121 (16), 114 (10), 108 (19), 98 (26), 97 (29), 81 (61), 79 (32), 67 (68), 55 (29), 53 (23), 41 (42), 29 (90). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.45; H, 10.27. Found: C, 73.50; H, 10.20.

(*E,Z*)-2,4-Decadien-1-ol (4). To 4.66 mL (4.5 mM) of DIBAL (20% in hexane, Aldrich) was added 15 mL of hexane and this solution was cooled to 0 °C (N_2 atmosphere) with stirring. Then 0.378 g (1.92 mM) of ethyl (*E,Z*)-2,4-decadienoate (**2**, R = Et) dissolved in 5 mL of hexane was slowly added to the DIBAL solution. The reaction was left at 0 °C for 2 h. To the reaction was added 3 mL of methanol and after 10 min 10 mL of aqueous dilute HCl was added and the mixture was left for 1 h. The resulting solution was then extracted with ethyl ether and the organic layer was dried and the solvent removed yielding 0.266 g (90%) of the alcohol **4**. The spectral data of the crude alcohol **4** were identical to that reported by Tabacchi et al.[18] for (*E,Z*)-2,4-decadien-1-ol: IR 3400 and 980 cm^{-1}; NMR 5.2–6.7 (m, 4 H), 3.79 (d, J = 6, 2 H), 1.9–2.4 (m, 3 H, one exchanges on addition of D_2O), 1.0–1.8 (m, 9 H), 0.7–1.0 (m, 3 H).

(*E,Z*)-2,4-Decadien-1-yl Isovalerate (5). In a 25-mL flask was placed 0.235 g (1.53 mM) of (*E,Z*)-2,4-decadien-1-ol (**4**) dissolved in 10 mL of dry tetrahydrofuran. To this solution of the alcohol was added 0.22 mL (1.6 mM) of triethylamine and then 0.30 mL (2.5 mM) of isovaleryl chloride.[17] The solution was refluxed for 2 h and left at room temperature for 12 h. Then 25 mL of ethyl ether was added and the resulting solution was extracted with aqueous saturated $NaHCO_3$. The organic layer was dried and the solvent removed under reduced pressure yielding 0.364 g (98%) of the desired ester **5**: IR 1730 and 980 cm^{-1}; NMR 6.4–6.8 (d, d, J = 7.5 and 5.5, 1 H), 5.4–6.2 (m, 3 H), 4.57 (d, J = 6, 2 H), 1.8–2.4 (m, 4 H), 1.1–1.7 (m, 7 H), 0.7–1.0 (d, J = 3, 9 H); MS m/e 238 (6), 137 (5), 136 (5), 111 (4), 110 (8), 99 (4), 85 (100), 83 (7), 82 (8), 81 (12), 80 (14), 79 (20), 77 (7), 71 (8), 69 (13), 68 (10), 67 (22), 57 (79), 55 (18), 54 (104), 43 (29), 42 (7), 41 (40), 39 (12), 29 (26). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.53; H, 10.80.

Acknowledgments. We are grateful to Professor R. Tabacchi and Dr. F. Näf for copies of spectral data and to the National Research Council of Canada for financial support.

Registry No.—**1** (R = Et), 7328-34-9; **2** (R = Et), 3025-30-7; **4**, 16195-71-4; **5**, 56699-32-2; 2-octyn-1-ol, 20739-58-6; 2-octynal, 1846-68-0; ethyl (*E*)-2-decene-4-ynoate, 66901-42-6; (*E,E*)-2,4-decadienal, 25152-84-5; propargyl alcohol, 107-19-7; 1-bromopentane, 110-53-2; triethyl phosphonoacetate, 867-13-0; isovaleryl chloride, 108-12-3.

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Synthesis of Tetrasubstituted Cyclopropenes and Medium to Large Carbocyclic Alkenes by the Intramolecular Reductive Coupling of Diketones with Titanium Trichloride–Lithium Aluminum Hydride

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Low-valent titanium reagents offer a convenient method for the preparation of alkenes from ketones.[1] The intramolecular reductive coupling of dicarbonyls to cycloalkenes has been carried out.[2] Recently, McMurry and Kees have shown[2c] the potential of the method in medium- and large-ring carbocyclic synthesis by preparing cycloalkenes, ring size 4–16, with $TiCl_3$/Zn–Cu. There have been no reports of cyclopropene synthesis by low-valent titanium reagents. 1,2-Diphenylcyclobutene is the only strained-ring alkene to have been previously prepared by reductive coupling of a diketone.[2b,c] We wish to report the first synthesis of cyclopropenes in addition to the synthesis of medium to large carbocyclic alkenes[3] by the intramolecular reductive coupling of dibenzoylalkanes with $TiCl_3$–$LiAlH_4$.

Results and Discussion

Attempts to prepare 1,2-diphenylcyclopropene and 3-methyl-1,2-diphenylcyclopropene by the coupling of dibenzoylmethane and 1,1-dibenzoylethane were unsuccessful.[4] However, complete substitution of alkyl groups for the acidic hydrogens of the 1,3-diketone resulted in the successful preparation of tetrasubstituted cyclopropenes. 3,3-Dimethyl- and 3,3-diethyl-1,2-diphenylcyclopropene (**2** and **4**) were prepared in 40–46% yield by the coupling of dimethyl- and diethyldibenzoylmethane (**1** and **3**) with $TiCl_3$–$LiAlH_4$. A series of 1,2-diphenylcycloalkenes was also investigated. 1,2-Diphenylcycloalkenes of ring size 5, 8, 9, 10, and 12 were prepared in 50–60% yield by the coupling of a series of dibenzoylalkanes with $TiCl_3$–$LiAlH_4$. 1,2-Diphenylcyclobutene and 1,2-diphenylcyclohexene have previously been prepared by the $TiCl_3$–$LiAlH_4$ method.[2b] The results are summarized in Table I.

The yield (46%) of cyclopropene **2** by the $TiCl_3$–$LiAlH_4$ method compares favorably with that (20%) of the procedure of Closs[5] (alkyne, dichloroalkane, alkyllithium) as employed by Friedrich and Fiato[6] in the synthesis of **2**. The $TiCl_3$–$LiAlH_4$ method also has the advantage of producing only one isomer. The $TiCl_3$–$LiAlH_4$ method would appear to be a new general route to 3,3-disubstituted cyclopropenes.[7]

The yields of the large cycloalkenes ranged between 50 and 60%. Little or no drop in yield was noted for the synthesis of the medium rings in contrast to other methods of ring preparation.[8] The apparent lack of variation of yield with ring size is in complete agreement with the results[2c] of McMurry and Kees. McMurry and Kees report higher yields of cycloalkenes by the more elaborate $TiCl_3$/Zn–Cu method.[2c] Titanium reagents apparently overcome effects[8] encountered in the preparation of medium rings. Surprisingly, even rapid addition of the diketones as powders to the $TiCl_3$–$LiAlH_4$ reagent under nitrogen only lowered the isolated yields of 1,2-diphenylcycloalkenes to 35–40%. It is remarkable that large, medium, normal, and strained rings can be prepared by the $TiCl_3$–$LiAlH_4$ method in moderate yield without the need to alter the reaction conditions.

The mechanism of the intermolecular coupling of carbonyls was suggested[1c] to proceed via reduction of a carbonyl to a radical anion followed by coupling to form the pinacol dianion. Judging from the results of Corey,[9] *cis*-pinacol dianions are

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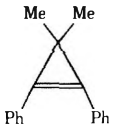
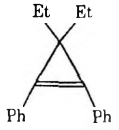
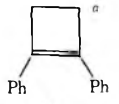
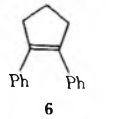
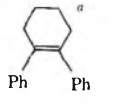
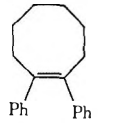
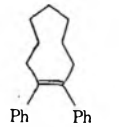
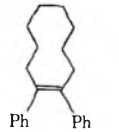
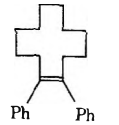
Table I
Yields of Cycloalkenes from the Reductive Coupling of Diketones with $TiCl_3$–$LiAlH_4$

diketone	registry no.	cycloalkene	registry no.	isolated yield, %
$PhCOCMe_2COPh$ (1)	41169-42-0	 2	50555-61-8	46
$PhCOCEt_2COPh$ (3)	66901-96-0	 4	66901-91-1	40
$PhCO(CH_2)_2COPh$[a]	495-71-6		3306-02-3	40–61[a]
$PhCO(CH_2)_3COPh$ (5)	6263-83-8	 6	1485-98-9	62
$PhCO(CH_2)_4COPh$[a]	3375-38-0		41317-87-7	35,[a] 60[b]
$PhCO(CH_2)_5COPh$ (7)	6268-58-2	 8	66901-94-8	61
$PhCO(CH_2)_7COPh$ (9)	28861-21-4	 10	66901-93-7	53
$PhCO(CH_2)_8COPh$ (11)	6268-61-7	 12	66901-92-6	49
$PhCO(CH_2)_{10}COPh$ (13)	66901-95-9	 14	66901-91-5	61

[a] Reference 2b. [b] Heated under reflux 5 days instead of 1 day as reported in ref 2b.

not formed exclusively by the initial reduction. McMurry and Fleming have suggested[2a] that deoxygenation of the pinacol dianion may take place from a five-membered titanium(II) ring intermediate which collapses in nonconcerted manner to TiO_2 and olefin. Several alternative mechanisms for the pinacolic coupling have recently been proposed.[1d,9] The formation of large and medium rings with high efficiency indicates that a titanium species might be simultaneously complexed with both carbonyl groups before reduction.

The synthesis of cyclopropenes by reductive coupling is remarkable when the ring strain (estimated at ~55 kcal[10]) is considered. Corey et al. have shown[9] that the pinacolic coupling of 1,4-hexanedione with titanium(II) yields *cis*-1,2-dimethylcyclobutanediol (estimated strain ~26 kcal[10]). The preparation[2b] of 1,2-diphenylcyclobutene (estimated strain ~31 kcal[10]) by reductive coupling of the 1,4-diketone with $TiCl_3$–$LiAlH_4$ indicated that additional strain could be introduced at the deoxygenation step(s). The preparation of 1,2-diphenylcyclopropanes[11] by the coupling of 1,3-glycols showed that a large amount of strain could be introduced at the deoxygenation stage and indicated that cyclopropenes might be accessable by the $TiCl_3$–$LiAlH_4$ method. For the cyclopropenes, roughly half of the strain is introduced in the initial coupling and the remainder in the deoxygenation step.

For normal and medium rings, the strain energies of the cycloalkenes are similar in value to those of the corresponding cycloalkanes.[10] Thus, unlike the cyclopropene case, the major portion of the strain in the synthesis of normal, medium, and large cycloalkenes is introduced in the initial pinacolic coupling and relatively little is introduced at the deoxygenation step(s). McMurry and Kees have shown[2c] that aliphatic diketones and dialdehydes can be coupled to produce medium and large rings. It remains to be tested if phenyl groups are

required in the final deoxygenation to yield cyclopropenes and cyclobutenes.

In conclusion, the intramolecular reductive coupling of diketones with $TiCl_3$–$LiAlH_4$ is an effective and convenient method for the preparation of moderate amounts of strained, normal, medium and large carbocyclic alkenes.

Experimental Section

3,3-Dimethyl-1,2-diphenylcyclopropene (2). $LiAlH_4$ (MCB) (0.6 g, 16 mmol) was added to 5.7 g (37 mmol) of fresh $TiCl_3$ (Alfra-Ventron) in ~250 mL of dry THF under N_2. The black mixture was heated under reflux for 15 min. Dimethyldibenzoylmethane (1) (2.0 g, 8 mmol) in dry THF (under N_2) was added dropwise over a period of 30 to 60 min. The mixture was heated under reflux for 6 days.[12] The cool reaction mixture was poured into petroleum ether followed by addition of water. The organic layer was separated, washed, and dried. Removal of solvent under reduced pressure yielded 1.5 g of crude product which was purified by column chromatography (alumina/petroleum ether–CH_2Cl_2) to yield 0.8 g of **2** (46%). The oily sample of **2** slowly crystallized upon standing at 4 °C: mp 34–37 °C (lit.[6] mp 43.5–44.0 °C); ^1H NMR ($CDCl_3$) δ 1.50 (s, 6 H) and 7.2–7.7 (m, 10 H); mass spectrum, parent peak 220 (47% of base peak at 205) and a P + 1 of 18.7% consistent with $C_{17}H_{16}$. The UV spectrum was in good agreement with the reported spectrum.[6] The IR spectrum (CCl_4) was identical with that of an authentic sample.[12] Anal. Calcd: C, 92.68; H, 7.32 Found: C, 92.63; H, 7.31.

The procedure described for the preparation of **2** is representative for the cycloalkenes listed in Table I. All compounds gave UV spectra consistent with the structures and showed only one peak on the gas chromatograph (2 m 5% SE 20 column, temperature range 200–240 °C).

3,3-Diethyl-1,2-diphenylcyclopropene (4): ^1H NMR ($CDCl_3$) δ 0.92 (t, 6 H), 2.1 (q, 4 H), 7.1–7.6 (m, 10 H); mass spectrum, parent peak 248 (10% of base peak at 219), P + 1 of 20.8%, peak at 233 (3% of base) consistent with $C_{19}H_{20}$. Anal. Calcd: C, 91.88; H, 8.12. Found: C, 91.80; H, 8.06.

1,2-Diphenylcyclopentene (6): ^1H NMR ($CDCl_3$) δ 2.1 (m, 2 H), 2.9 (t, 4 H), 7.19 (s, 10 H); mass spectrum, base and parent 220. The UV spectrum was in good agreement with the reported spectrum.[14] The ^{13}C NMR spectra (^1H coupled and decoupled) were in excellent agreement with the reported spectra.[15]

1,2-Diphenylcyclooctene (8): mp 74–76 °C (lit.[16] mp 77.5); ^1H NMR ($CDCl_3$) δ 1.5–1.9 (b, 8 H), 2.5–2.9 (b, 4 H), 7.13 (s, 10 H); mass spectrum, parent 262 with P + 1 of 22.2% consistent with $C_{20}H_{22}$. The UV spectrum was in agreement with the published value.[14] Calcd: C, 91.55; H, 9.45. Found: C, 91.29; H, 8.52.

1,2-Diphenylcyclononene (10): mp 42–45 °C; ^1H NMR ($CDCl_3$) δ 1.67 (bs, 10 H), 2.5–2.9 (b, 4 H), 7.13 (s, 10 H); mass spectrum, parent 276 consistent with $C_{21}H_{24}$. Anal. Calcd: C, 91.25; H, 8.75. Found: C, 91.37; H, 8.60.

1,2-Diphenylcyclodecene (12): mp 91–93 °C; ^1H NMR ($CDCl_3$) δ 1.62 (bs, 12 H), 2.5–2.9 (b, 4 H), 7.08 (s, 10 H); mass spectrum, parent 290 with P + 1 of 24.4% consistent with $C_{22}H_{26}$. Anal. Calcd: C, 90.98; H, 9.02. Found: C, 90.88; H, 9.02.

1,2-Diphenylcyclododecene (14): mp 82–84 °C; ^1H NMR ($CDCl_3$) 1.5 (bs, 14 H), 2.3–2.8 (b, 4 H), 7.04 (bs, 10 H); mass spectrum, parent 318 with P + 1 of ~26% consistent with $C_{24}H_{30}$. The ^{13}C NMR ($CDCl_3$, ^1H decoupled) showed a ten-line spectrum consistent with the structure. The stereochemistry was tentatively assigned as cis on the basis of the UV spectrum which was similar to that of **8**. Anal. Calcd: C, 90.51; H, 9.49. Found: C, 90.34; H, 9.58.

The dibenzoylalkanes shown in Table I were prepared in ~50% yield by the Friedel–Crafts acylation[17] of dry benzene ($AlCl_3$ catalyst) with the corresponding diacid chlorides. All the products were recrystallized from methanol and dried. The IR and NMR spectra were consistent with the proposed structures: **1**, mp 95–97 °C;[18] **3**, mp 104–105 °C (lit.[19] mp 104 °C); **5**, mp 60–62 °C (lit.[20] mp 63 °C); **7**, mp 87–89 °C (lit.[21] mp 85 °C); **9**, mp 46–48 °C (lit.[22] mp 44 °C); **11**, mp 90–92 °C (lit.[23] mp 94–96 °C); **13**, mp 94–96 °C (lit.[24] mp 98–99 °C). Contrary to early reports,[18b,19] **1** and **3** have been prepared in moderate yields.[18a] The yields of **1** and **3** were found to be erratic under the present set of conditions and fell in the range of 20–55%.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to the Georgia State University Research Fund. The mass spectra were taken at the Georgia Institute of Technology, on an instrument supported in part by NSF.

Registry No.—$TiCl_3$, 7705-07-09; $LiAlH_4$, 16853-85-3.

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(4) No cyclopropenes were isolated from either reaction. A few percent of 1,2,4,5-tetraphenylbenzene was isolated from the attempted reductive coupling of dibenzoylmethane. Tetraphenylbenzene is the formal dehydrogenation product of a dimer of 1,2-diphenylcyclopropene. [See R. Breslow and P. Dowd, *J. Am. Chem. Soc.*, **85**, 2729 (1963), for the dimerization of triphenylcyclopropene and subsequent dehydrogenation to hexaphenylbenzene.] It is not clear if tetraphenylbenzene is the product of unusual reactions of the 1,3-diketone or side reactions of the unstable cyclopropene.
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(12) Note: care must be taken to avoid solvent loss during the prolonged heating period under N_2 or substantial product loss will result. Substitution of 1,2-dimethoxyethane for THF as the solvent decreased the reaction time to 2 days with little or no effect on the yields.
(13) We thank Professor D. R. Arnold of the University of Western Ontario, Canada, for the gracious donation of an authentic sample of 3,3-dimethyl-1,2-diphenylcyclopropene.
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On the Epimerization of 6α-Bromopenicillanic Acid and the Preparation of 6β-Bromopenicillanic Acid

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The epimerization of penicillanic acid derivatives at C-6 (see **1**) has been of considerable interest for some years now, both to organic chemists and to biologists, since only compounds possessing the 6β configuration are biologically active as "penicillins". It has been demonstrated (these points have been recently reviewed by Stoodley[1]) that both the bulk of the 6 substituent and its electronic properties are important to this process, the former dictating the position of the equilibrium and the latter the rate of its achievement. The 6α epimer

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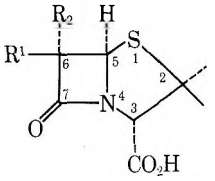
is apparently always the thermodynamically favored species, presumably because of unfavorable steric interactions of 6β substituents with the thiazolidine sulfur cis to them and with the 2β-methyl group. Indeed, in certain cases where very bulky 6 substituents are present, e.g., phthalimidopenicillin[2] and hetacillin,[3] the equilibrium amounts of 6β epimers are not detectable by the usual NMR methods, i.e., presumably ≤1%.

Another well-known case is that of the 6-halopenicillanic acids. The 6-bromo and 6-chloro compounds have been prepared by treatment of 6β-aminopenicillanic acid in the appropriate hydrogen halide solution with sodium nitrite and as prepared both have the 6α configuration, **1a**[5] and **1b**.[6] The former compound has also been obtained, again in the 6α configuration, by partial hydrogenation of 6,6-dibromopenicillanic acid, **1c**.[7]



1a, R_1 = H; R_2 = Br
b, R_1 = H; R_2 = Cl
c, R_1 = R_2 = Br
d, R_1 = Br; R_2 = H

Although certain derivatives have been reported,[8,9] all previous attempts to detect or isolate the parent 6β-halopenicillanic acids have failed.[7,10] Despite this all available data[1] would suggest that 6-halopenicillanic acids should epimerize with moderate ease and probably even in aqueous solution. This is apparently true. Clayton et al.[6] report that although **1a** is recovered unchanged on prolonged exposure to dilute sodium hydroxide, exchange of the 6α-hydrogen with solvent occurs. This suggests equilibration of **1a** with an undetectably (by NMR) small concentration of 6β-bromopenicillanic acid, **1d**.

We report here the preparation of **1d** (as a mixture with **1a**) and present evidence for the existence of a substantial (ca. 12%) amount of **1d** in equilibrium with **1a** in aqueous solution.

The NMR spectrum of a 30 mM solution of **1a** in 20 mM sodium pyrophosphate in H_2O at pH 9.1 (aliquots were freeze-dried and spectra taken in ^2H_2O) maintained at 30 °C changed slowly with time. The initial spectrum was as expected from those reported for **1b**[10] and for **1a** methyl ester:[7] τ (^2H_2O, p^{2}H ca. 9) 8.52 (3 H, s, CH_3), 8.42 (3 H, s, CH_3), 5.71 (1 H, s, 3-H), 4.90 (1 H, d, J = 1.5 Hz, 6-H), and 4.55 (1 H, d, J = 1.5 Hz, 5-H). The magnitude of the coupling constant here, 1.5 Hz, is characteristic of that for a trans configuration between vicinal hydrogens in the β-lactam ring of a penam system.[11] Under the above conditions the following new peaks appear uniformly with time in a first-order manner ($t_{1/2}$ ca. 12 h): τ 8.50 (3 H, s), 8.37 (3 H, s), 5.76 (1 H, s), and 4.44 and 4.39 (2 H, AB quartet, J = 3.7 Hz). Integration indicates that a final (10 half-lives) conversion of 12 ± 2% of **1a** to product has occurred. This product spectrum is readily interpretable as arising from the hitherto unknown **1d**. The coupling constant is as expected for cis β-lactam protons[11] and the chemical shift differences between these resonances and those of **1a** are analogous to those between α- and β-benzylpenicillin.[12] The spectrum is certainly not consistent with those of other likely possibilities, the rearrangement product, 6-bromo-2,3,4,5-tetrahydro-2,2-dimethyl-7-oxo-1,4-thiazepine-3-carboxylic acid,[13] the penicilloate hydrolysis product,[5] or 3,6-dicarboxy-2,2-dimethyl-2,3-dihydro-1,4-thiazine, the rearrangement product of the penicilloate.[5] Reactions producing these species would not likely stop at 12% reaction either, of course.

Incubation of either **1a** or the equilibrium mixture from above in ^2H_2O (p^{2}H ca. 9) for several days at 30 °C yielded spectra essentially identical to the final spectrum above except that the 6-H resonance of the starting material had disappeared and the 5-H resonance had collapsed to a single hydrogen singlet at τ 4.55 and that the AB quartet of the product had collapsed to a single hydrogen singlet at τ 4.40. These observations are consistent with exchange at the C-6 position of **1a** concomitant with epimerization yielding 6-^{2}H-**1d**.

Hydrogenation of **1c** over 10% Pd/C in phosphate buffer at pH 7.5 yielded a product mixture, after uptake of 1 equiv of hydrogen, whose NMR spectrum indicated the same components present as in the aqueous equilibration mixture of **1a**. Here also the content of the minor component, here proposed to be **1d**, was close to 10%. Hydrogenation of **1c** in dioxan over solid disodium hydrogen phosphate heptahydrate yielded the same mixture again but with 30% of the minor component. Elemental analysis of the *p*-bromophenacyl ester of the latter mixture (which still contained ca. 30% of the minor component by NMR) was identical, within the accepted limits to that of the ester of **1a**.

We believe that the above data show that we have prepared (but not yet separated from its 6-epimer **1a**) **1d** and that the latter does arise from epimerization of **1a** in aqueous solution to an equilibrium level of some 12%. Our attempts to separate the two epimers by several methods, including high pressure liquid chromatography, were not successful. In view of the available data[1] 12% does not seem to be an impossibly high equilibrium concentration of **1d**. It is of interest to note, for example, that Bose et al.[14] have shown that although *cis*-1,4-diphenyl-3-phthalimidoazetidin-2-one epimerizes completely to the trans β-lactam in the presence of base (as does the methyl ester of 6-phthalimidopenicillin[2]), the analogous bromo compound, *cis*-3-bromo-1,4-diphenylazetidin-2-one, equilibrates with 30% of the cis isomer remaining. We do not understand, at present, the failure of Clayton et al.[6] to observe **1d** in their spectra. We have carried out the epimerization under their reported conditions (NaOH or NaO^{2}H at pH 10–11) and have observed **1d** in quantities comparable to those under our conditions described above.

We are currently investigating the properties of **1d** and its analogues. In particular the epimeric mixtures of **1a** and **1d** are potent irreversible inhibitors of β-lactamases. Since pure **1a** has no effect on these enzymes, the inhibitor must be **1d**. Experiments with purified β-lactamases of *Bacillus cereus* and *Escherichia coli* suggest that **1d** is at least as effective as the naturally occurring inhibitor clavulanic acid.[15] Details of these inhibition studies are reported elsewhere.[16]

Experimental Section

Proton nuclear magnetic resonance spectra were run on the 270 MHz Brüker instrument at the Southern New England High Field NMR Facility at Yale University, New Haven, Conn. Internal standards were 2,2-dimethyl-2-silapentane 5-sulfonate in ^2H_2O and tetramethylsilane in $CDCl_3$.

6α-Bromopenicillanic Acid (1a). The *N,N'*-dibenzylethylenediamine salt of 6α-bromopenicillanic acid was prepared from 6β-aminopenicillanic acid (Aldrich Chemical Co.) by diazotization in the presence of sodium bromide[4] and recrystallized from methanol to a constant melting point, 159.5–160.5 °C (lit.[4] mp 159–160 °C). A solution of the sodium salt of this compound was obtained by stirring a suspension of the above amine salt in water with an excess of Dowex 50W-X8 resin in the sodium form. The solid sodium salt was obtained by freeze-drying this solution.

Hydrogenation of 6,6-dibromopenicillanic acid (1c) prepared from 6β-aminopenicillanic acid by diazotization in the presence of bromine[7].

(a) In Aqueous Solution. Routinely 0.5-g samples of 6,6-dibromopenicillanic acid dissolved in water (ca. 50 mL) containing 0.9 g (2.5 equiv) of disodium hydrogen phosphate heptahydrate and 0.1

g of 10% Pd/C were hydrogenated at room temperature and pressure until 1 equiv of hydrogen had been taken up (ca. 1 h) after which the rate of uptake slowed essentially to zero. The filtered solution was then freeze-dried to obtain the sodium salts of the products. To obtain the products free of phosphate, the reaction mixture was stirred at 0 °C under a layer of diethyl ether and the pH of the aqueous layer reduced to 1 by the addition of 1 M hydrochloric acid. The ether layer was separated, dried over magnesium sulfate, and evaporated to dryness. The resulting acid, an oil, could be used as such or converted into the sodium salt (add 1 equiv of aqueous sodium bicarbonate and freeze-dry) or the *N,N'*-dibenzylethylenediamine salt (oil dissolved in ether and 1 equiv of the amine added).

(b) In Dioxan. Samples of 6,6-dibromopenicillanic acid (0.5 g) dissolved in 50 mL of dioxane (freshly distilled from sodium) to which had been added 1.8 g of disodium hydrogen phosphate heptahydrate and 0.1 g of 10% Pd/C were hydrogenated at room temperature and pressure for 2 h. The filtered solution was evaporated to dryness under reduced pressure. The residue was extracted with ether and the solution dried and evaporated. The residual acidic oil could be converted to its sodium or *N,N'*-dibenzylethylenediamine salts as above.

Total isolated monobromopenicillanic acid yields were about 50% in each case.

The infrared spectra of the amine salt of **1a** and the amine salts from the hydrogenation mixtures were very similar. Their NMR spectra, which are discussed in detail above, indicate that the hydrogenation products were mixtures of **1a** and **1d** with the latter making up approximately 10% (aqueous hydrogenation) or 30% (dioxane hydrogenation) of the total. It is clear also from the NMR spectra that the amine salts from the hydrogenations contained small but variable quantities of excess amine and thus these salts were not suitable for chemical analysis. Consequently, sodium salts of pure **1a** and of the dioxan hydrogenation mixture were converted essentially quantitatively into *p*-bromophenacyl esters by the method of Bamberg and co-workers.[17] The **1a** ester (mp 93.5–94 °C) was purified by recrystallization from methanol and yielded the following spectral data: IR (KBr) 1775 (β-lactam C=O), 1740, 1700 cm^{-1}; NMR ($CDCl_3$) τ 8.32 (6 H, broad s, $(CH_3)_2$), 5.34 (1 H, s, 3-H), 5.19 (1 H, d, J = 1.5 Hz, 6-H), 4.63 (2 H, s, CH_2), 4.58 (1H, d, J = 1.5 Hz, 5-H), and 3.20, 2.09 (4 H, AB quartet, J = 8.5 Hz, Ar-H). Anal. Calcd for $C_{16}H_{15}Br_2NO_4S$: C, 40.28; H, 3.17; N, 2.94; Br, 33.49. Found: C, 40.35; H, 3.09; N, 3.28; Br, 33.20. The hydrogenation product esters, an oil, were purified as a mixture by elution from a silica column with benzene and yielded the following spectral data: IR (neat) 1775 (β-lactam C=O), 1750, 1700 cm^{-1}; NMR ($CDCl_3$), the peaks of the α-epimer as above and the following peaks integrating to ca. 30% of the total: τ 8.28 (6 H, s, $(CH_3)_2$), 5.37 (1 H, s, 3-H), and 4.71, 4.34 (2 H, AB quartet, J = 4.6 Hz, 5-H, 6-H). The remaining peaks of the β-epimer are superimposed on those of the α-epimer. Anal. Calcd for $C_{16}H_{15}Br_2NO_4S$: as above. Found: C, 40.25; H, 3.27; N, 3.11; Br, 33.60.

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Registry No.—**1a,** 24138-28-1; **1a** *p*-bromophenacyl ester, 66842-39-5; **1c,** 24158-88-1; **1d,** 26631-90-3; **1d** *p*-bromophenacyl ester, 66842-40-8.

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Reaction of α-Aryl-*N*-alkyl- and α,*N*-Diarylnitrones with Aroyl Chlorides. A New Synthesis of *N*-Alkyl-*O*-aroylhydroxylamines

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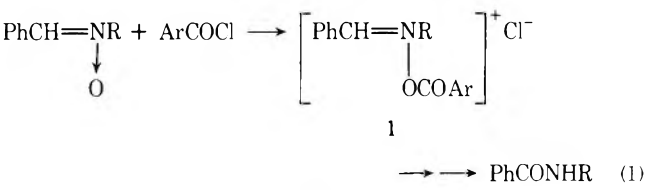
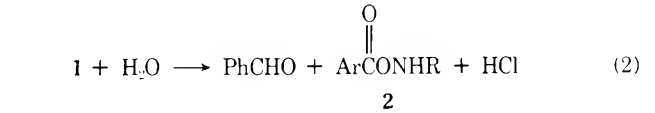
In 1890 Beckmann observed that acetyl chloride, benzoyl chloride, and acetic anhydride catalyzed the isomerization of α-phenyl-*N*-benzylnitrone to *N*-benzylbenzamide.[1] Since then many examples of the isomerization of nitrones into amides by acylating reagents have been reported.[2] Discussion continues on the mechanism of the rearrangement,[2-5] but all investigators agree that the first step of the reaction is a nucleophilic displacement by the nitrone oxygen on the electrophilic carbon of the acylating reagent. Thus, in the case of the isomerization of an α-phenyl-*N*-alkylnitrone by an aroyl chloride it is presumed that the aroyloxy(benzylidene)ammonium chloride **1** is formed initially (eq 1). With the exception of a few compounds obtained from the interaction of heterocyclic *N*-oxides with very electrophilic acyl halides,[6-8] compounds such as **1** have not been isolated.



(1)

We have augmented the evidence for the existence of **1** by treating α-phenyl-*N*-alkylnitrones and aroyl chlorides at ambient temperature in moist solvents (acetone, ether, and acetonitrile). The products, which apparently arise by the hydrolysis of **1**, are *N*-alkyl-*O*-aroylhydroxylamines (**2**) and aldehydes (eq 2).



(2)

The crude hydrochlorides **2**·HCl separated from the reaction mixture and were hydrolyzed to give the bases **2** (Table I). In those cases where **2** were oils ($PhCO_2NHMe$, $PhCO_2NH$-*t*-Bu, and 3,4-$Cl_2C_6H_3CO_2NH$-*t*-Bu) the corresponding hydrochlorides (**2**·HCl) were isolated and purified (Table I). *N*-Methyl-*O*-(*p*-nitrobenzoyl)hydroxylamine hydrochloride was also prepared in 58% yield when α-(*p*-nitrophenyl)-*N*-methylnitrone was substituted for α-phenyl-*N*-methylnitrone in the reaction with *p*-nitrobenzoyl chloride.

The proof of structure for **2** consists of NMR, IR, and mass spectroscopy. Unequivocal characterization was provided by utilizing a synthesis developed by Zinner[9] to prepare *N*-methyl- and *N*-*tert*-butyl-*O*-(*p*-nitrobenzoyl)hydroxylamine hydrochlorides and *N*-methyl- and *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochlorides. The spectral and physical properties of the *N*-alkyl-*O*-aroylhydroxylamine hydrochlorides made by our method and that of Zinner's were identical. The yields were comparable by the two methods in those in-

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Table I. The Reaction of α-Aryl-*N*-alkylnitrones with Aroyl Chlorides

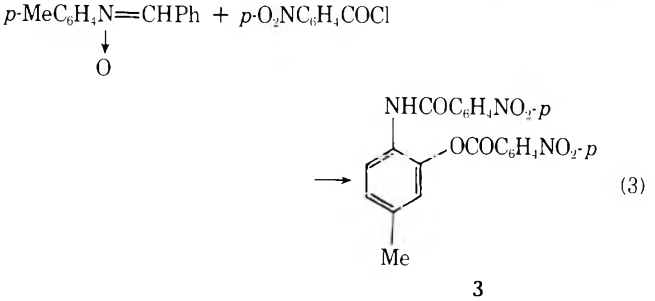
$$ArCH{=}N(O)R + Ar'COCl \xrightarrow{(Me)_2CO-H_2O} \underset{\mathbf{2}}{Ar'CO_2NHR} + HCl + ArCHO$$

			2			2·HCl		
Ar	R	Ar'[f]	% yield	mp, °C	registry no.	% yield	mp, °C	registry no.
Ph	Me[d]	Ph		oil	66809-88-9	67	131–134[a,b]	27130-46-7
Ph	Me	*p*-$O_2NC_6H_4$	63	107–110[a]	66809-82-3			
Ph	Me	*m*-$O_2NC_6H_4$	68	75–76[a]	66809-83-4			
Ph	Me	3,4-$Cl_2C_6H_3$	32	75–77[a]	66809-84-5			
Ph	*t*-Bu[e]	Ph		oil	51339-03-8	69	173–179[c]	66809-86-7
Ph	*t*-Bu	*p*-$O_2NC_6H_4$	60	69–71[a]	1746-98-1			
Ph	*t*-Bu	*m*-$O_2NC_6H_4$	44	57–60[a]	66809-85-6			
Ph	*t*-Bu	3,4-$Cl_2C_6H_3$		oil	66809-89-0	49	145–148[a]	66809-87-8

[a] Satisfactory analytical data for C, H, and N were reported. [b] Zinner[10] reported a melting point of 123–124 °C. [c] Zinner[9] reported a melting point of 178–180 °C. [d] Registry no.: 3376-23-6. [e] Registry no.: 3376-24-7. [f] Registry no.: PhCOCl, 98-88-4; *p*-$O_2NC_6H_4COCl$, 122-04-3; *m*-$O_2NC_6H_4COCl$, 121-90-4; 3,4-$Cl_2C_6H_3COCl$, 3024-72-4.

stances when the *N*-alkyl group was *tert*-butyl, but were dramatically lower by Zinner's method (e.g., 7–14%) when the *N*-alkyl group was methyl. The molecular ions for *N*-methyl-*O*-(*p*-nitrobenzoyl)- and *N*-methyl-*O*-(3,4-dichlorobenzoyl)hydroxylamines were determined and corresponded to the theoretical values. The NMR spectra taken in Me_2SO-d_6 for all the *N*-methyl-*O*-aroylated hydroxylamines and hydroxylamine hydrochlorides showed a single sharp absorption peak for the methyl group at δ 2.95–3.10, while the methyl groups of the *N*-*tert*-butyl-*O*-aroylated hydroxylamine hydrochlorides all absorbed at δ 1.30–1.40.

The reaction of α,*N*-diarylnitrones and aroyl chlorides in ether followed by the addition of water afforded *O*,*N*-diaroyl-*o*-aminophenols. For example, reaction of *p*-nitrobenzoyl chloride and α-phenyl-*N*-*p*-tolylnitrone gave a 74% yield of *N*-(*p*-nitrobenzoyl)-2-(*p*-nitrobenzoyloxy)-4-methylaniline (**3**) (eq 3). Similarly, reaction of α-phenyl-*N*-*p*-tolylnitrone



(3)

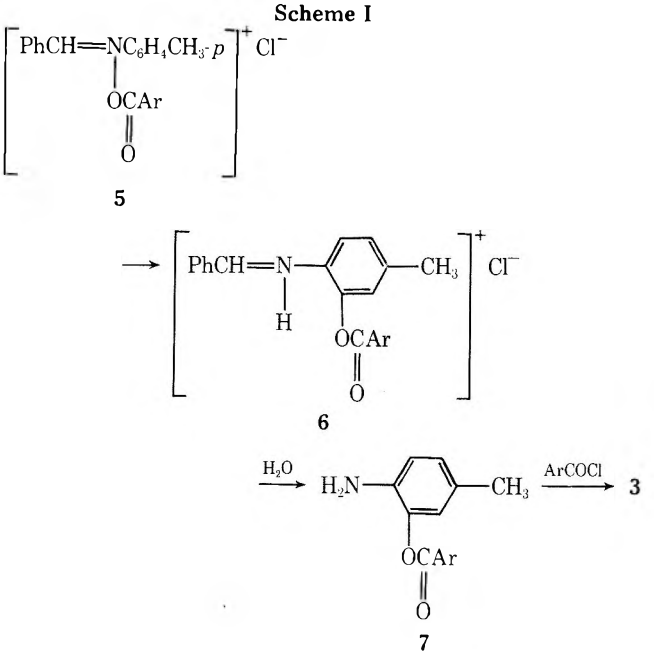
3

with *p*-chlorobenzoyl chloride formed *N*-(*p*-chlorobenzoyl)-2-(*p*-chlorobenzoyloxy)-4-methylaniline (**4**) in 53% yield. The identities of **3** and **4** were substantiated by alternate syntheses involving the reaction of 2-amino-5-methylphenol with *p*-nitrobenzoyl chloride and *p*-chlorobenzoyl chloride, respectively.

A reasonable mechanism to account for **3** and **4** is the formation and rearrangement of an aroyloxy(benzylidene)-ammonium chloride (**5**) into **6**, subsequent hydrolysis of **6** to **7**, and further aroylation of **7** (Scheme I). The rearrangement of **5** to **6** is quite similar to the reaction of *N*-arylnitrones with oxalyl chloride, in which a chloroglyoxalate group is introduced into the ortho position of the *N*-aryl ring.[11]

Another mechanistic possibility is the formation of *O*-(*p*-nitrobenzoyl)-*N*-*p*-tolylhydroxylamine (similar to the formation of **2**) which ionizes to the nitrenium ion *p*-$CH_3C_6H_4NH^+$ and a *p*-nitrobenzoate ion. Recombination of these ions gives **7** and further aroylation of **7** yields **3**. A precedent for this view is the ionization of *N*-alkyl-*N*-chloroanilines to *N*-alkyl-*N*-phenylnitrenium ions and a chloride

Scheme I



ion, which then forms *o*-chloro- and *p*-chloro-*N*-alkylanilines.[12]

Experimental Section

Synthesis of 2 and 2·HCl. The aroyl chloride (2 mmol) is added all at once to a well-stirred solution of the nitrone (2 mmol) in 6 mL of commercial acetone. Within several minutes the *N*-alkyl-*O*-aroylhydroxylamine hydrochloride (**2**·HCl) precipitates and is filtered, followed by washing with ether, whereupon more of the hydrochloride is collected from the filtrate. The **2**·HCl's were slurried with water for a few minutes and the crude **2** was filtered. *N*-Methyl-*O*-(*m*-nitrobenzoyl)- and *N*-*tert*-butyl-*O*-(*p*-nitrobenzoyl)hydroxylamines were recrystallized from cyclohexane, *N*-methyl-*O*-(*p*-nitrobenzoyl)-hydroxylamine was recrystallized from 95% ethanol, *N*-methyl-*O*-(3,4-dichlorobenzoyl)hydroxylamine was recrystallized from hexane, and *N*-*tert*-butyl-*O*-(*m*-nitrobenzoyl)hydroxylamine was recrystallized from petroleum ether (bp 63–65 °C).

Synthesis of 3. *p*-Nitrobenzoyl chloride (0.371 g, 2 mmol) was added to a solution of 0.211 g (1 mmol) of α-phenyl-*N*-*p*-tolylnitrone in 10 mL of dry ether. After 5 min some nitrone hydrochloride precipitated and was filtered. The filtrate was allowed to stand overnight and then treated with a few drops of water. The solvent was evaporated, the residue was slurried with a small quantity of cold methanol, and the crude **3** (0.30 g, 74%) was filtered. After recrystallization from ethanol **3** melted at 240–242 °C. Anal. Calcd for $C_{21}H_{15}N_3O_7$: C, 59.86; H, 3.59; N, 9.97. Found: C, 59.85; H, 3.73; N, 9.60.

Synthesis of 4. Compound **4** was prepared in a similar manner as **3** in 53% yield. It melted at 202–203 °C after recrystallization from

toluene. Anal. Calcd for $C_{21}H_{15}Cl_2NO_3$: C, 63.02; H, 3.78; N, 3.50. Found: C, 62.88; H, 4.20; N, 3.96.

Alternate Synthesis of 3. To a rapidly stirred mixture of 1.23 g (10 mmol) of 2-amino-5-methylphenol, 100 mL of benzene, and 21 mL of 1 N NaOH was added in portions 3.71 g (20 mmol) of *p*-nitrobenzoyl chloride. After 1.5 h the crude **3** was filtered, washed with water, and weighed (3.64 g, 87%). Recrystallization of **3** from ethanol gave crystals melting at 240–242 °C.

Alternate Synthesis of 4. By employing the same procedure described above for the synthesis of **3**, compound **4** was prepared in 95% yield by admixing 0.620 g (5 mmol) of 2-amino-5-methylphenol, 25 mL of benzene, 10 mL of 1 N NaOH, and 1.75 g (10 mmol) of *p*-chlorobenzoyl chloride. Recrystallization of **4** from toluene gave crystals that melted at 203–204 °C.

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Registry No.—**3**, 66809-90-3; **4**, 66809-91-4; α-phenyl-*N*-*p*-tolylnitrone, 19064-77-8; *p*-chlorobenzoyl chloride, 122-01-0; 2-amino-5-methylphenol, 2835-98-5.

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4,5-Dihydropyridazines: X-ray Structure of a Dimer

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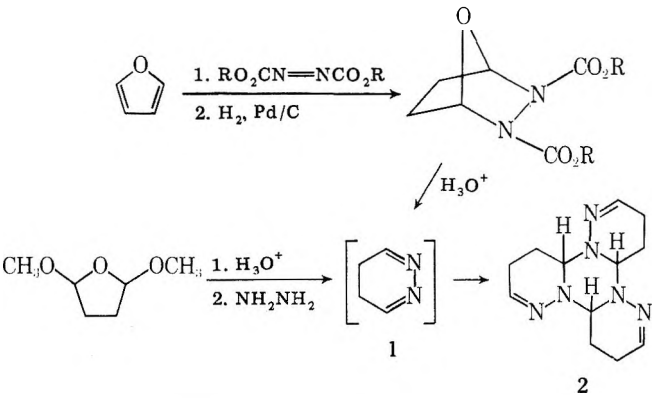
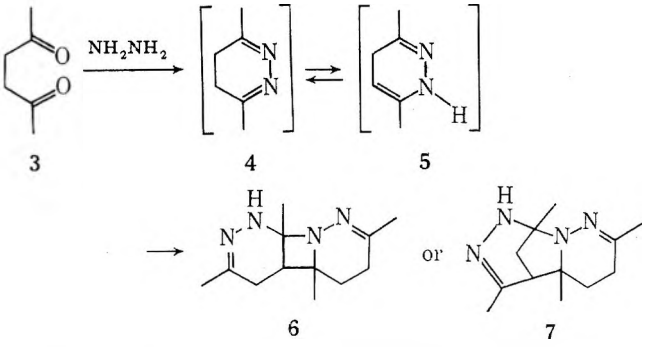
Our interest in 4,5-dihydropyridazines (**1**) as pseudodienes in Diels–Alder reactions prompted us to investigate the tautomerizations and self-condensations of this class of compounds.

Earlier[1] we reported the preparation and X-ray structure of a trimer (**2**) of 4,5-dihydropyridazine (**1**) obtained in ~5% overall yield from dialkyl azodicarboxylate and furan. We find that this trimer is more easily prepared by the aqueous hydrolysis of 2,5-dimethoxytetrahydrofuran, followed by addition of hydrazine to the hydrolysis mixture. Yields are 35–40% based on dimethoxytetrahydrofuran. Since the isolation of succinaldehyde from this hydrolysis is reported in 30% yield,[2] the conversion of aldehyde to trimer is reasonably good.



1 2

It is known that the condensation of hexane-2,5-dione (acetonylacetone (**3**)) with hydrazine affords a dimer of 3,6-dimethyl-4,5-dihydropyridazine[3,4] rather than the monomer or trimer. More recently, De Mayo, Stothers, and Usselman[4] reduced the possible structures of the dimer to **6** and **7**, giving



3 4 5 6 7

preference to **7** on the basis of ^{13}C NMR data. Initial attempts to take X-ray structural data of the dimer itself were unsuccessful due to the instability of the dimer. However, the N-acetylated derivative of the dimer, originally reported by De Mayo, Stothers, and Usselman[4] as being more stable, was successfully used in the structure determination. We have found, in support of the ^{13}C NMR work, that **7** is the correct structure.

Crystal Data. $C_{14}H_{22}N_4O$: monoclinic, $P2_1/c$, a = 12.145 (1) Å, b = 8.132 (1) Å, c = 15.536 (2) β = 110.44 (1)°, Z = 4, D_c = 1.21 g/cm^3, Cu = Kα, λ 1.54178 Å. Of the 1050 data collected with a G.E. XRD-490 computer controlled system by the stationary counter, stationary-crystal method 971 were considered statistically significant. Balanced Ross filters with Cu Kα radiation were used to measure all reflections to a 2θ maximum of 90°. The structure was solved by a multisolution $\Sigma 2$ sign expansion and ultimately refined (nonhydrogens) anisotropic, hydrogens with fixed isotropic temperature factor) to R_w = 0.038. The surprising feature is that all 22 hydrogen atoms are prominently displayed on the difference map. The hydrogens of the five methyl groups are rigidly constrained by the proximity of the other molecules and by steric requirements of the molecule itself and hence are readily apparent in the maps generated.

It is interesting to note the different reaction paths taken by 4,5-dihydropyridazine (**1**) and 3,6-dimethyl-4,5-dihydropyridazine (**4**) in their self-condensation reactions. While the steric requirements of the axial groups in the central ring are important in blocking trimerization of **4**, the basic difference is that trimerization occurs from a 4,5-dihydrotautomer (**1**)[5] and dimerization appears to occur through a key 1,4-dihydro tautomer (**5**).[4]

To test how monosubstitution at position 3 might affect these reactions we synthesized 3-*tert*-butyl-4,5-dihydropyridazine (**9**) by condensation of 4-oxo-5,5-dimethylhexanal (**8**) with hydrazine. If the reaction is worked up without allowing the temperature to rise above room temperature, the product obtained is a viscous oil having a complex NMR similar to that

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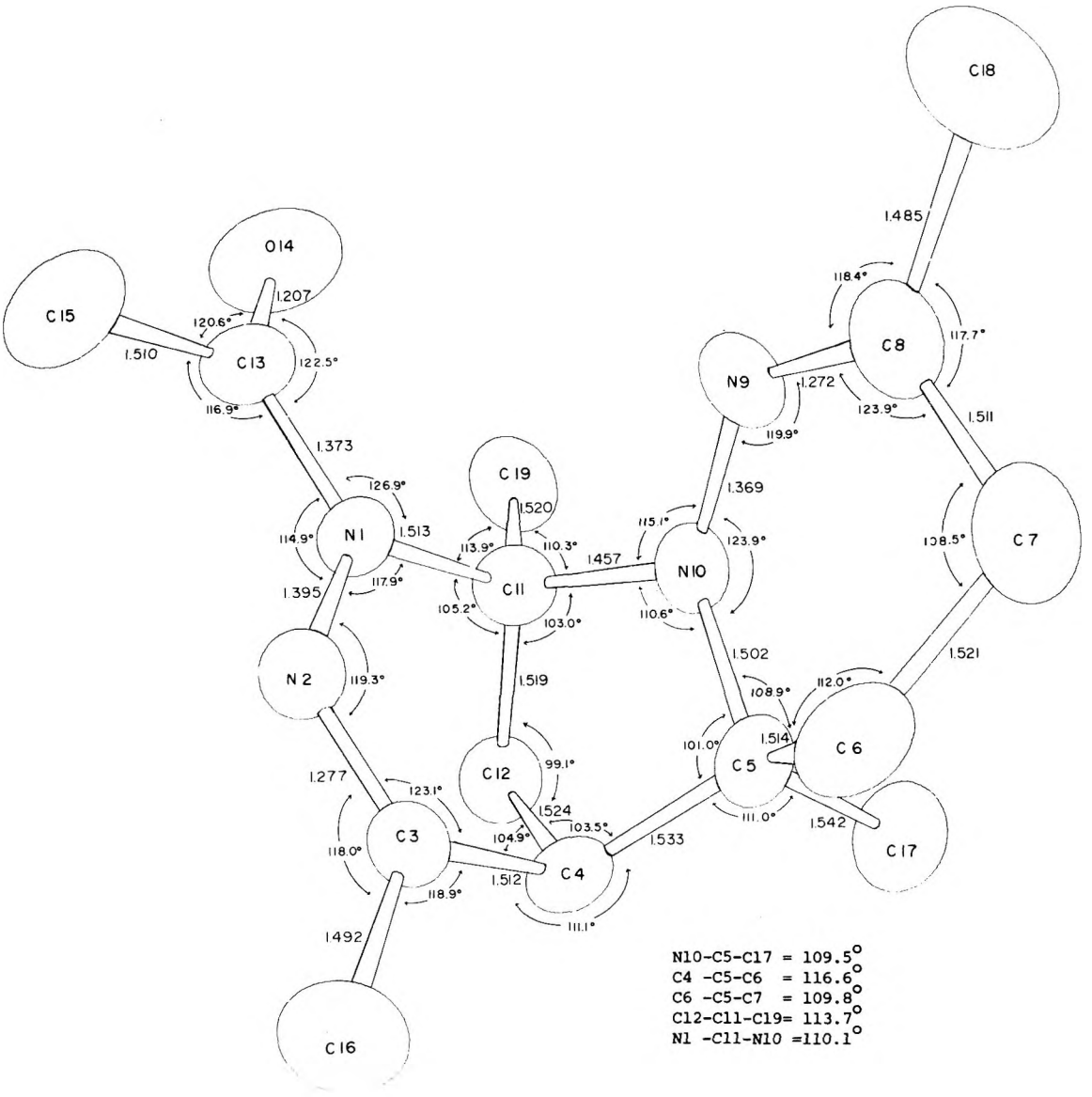
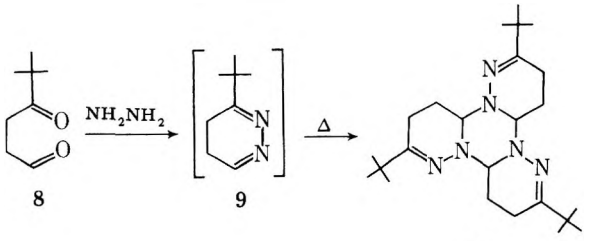


Figure 1.

of **7**. If heated in refluxing benzene prior to workup, a crystalline trimeric product (**10**) is obtained. If an attempt is made to distill the oil in vaccuo, some trimer (**10**) is produced along with substantial decomposition. This may indicate reversible formation of a dimer similar to **6** which goes back through the monomer **9** to trimer **10** upon heating.



8 **9** **10**

In anticipation that both dimerization and trimerization might be sterically precluded we synthesized 3,6-di-*tert*-butyl-4,5-dihydropyridazine (**11**) from the corresponding diketone and hydrazine. Indeed it was found to be monomeric although it quickly aromatizes in the presence of air.

In this work we have attempted to clarify the reaction paths available to 4,5-dihydropyridazines in their self-condensation reactions. If unsubstituted at the 6 or 3,6 positions they can trimerize via a 4,5-dihydro tautomer. If substituted in the 3 and 6 positions they may still dimerize via a 1,4-dihydro tautomer. The 3-substituted dihydropyridazines may well go by either route although we have only spectroscopic evidence for the dimerization at this time.

Experimental Section

Melting points were taken in open capillaries on a Mel-temp melting point apparatus. Infrared spectra were obtained on a Perkin-Elmer 283. NMR spectra were obtained on a Varian A60 and a Hitachi Perkin-Elmer R20B. Elemental analyses were carried out by Galbraith Analytical Laboratories.

Synthesis of the Trimer of 4,5-Dihydropyridazine (2). To 75 mL of H_2O was added 4 drops of concentrated HCl and 10 mL (77 mmol) of 2,5-dimethoxytetrahydrofuran. After stirring 4 h at 40–50 °C, the mixture was allowed to cool to room temperature. Hydrazine (3.2 mL, 100 mmol) was added and stirring continued for 1 h. The reaction mixture was then extracted with 4 × 25 mL of ether and the extract dried over $MgSO_4$. The solvent was removed in vaccuo yielding 2.23 g (36% yield) of **2**. Recrystallization from ether gave white crystals, mp 138–140 °C (lit.[1] mp 139–140 °C).

Synthesis of Dimer 7. The dimer was synthesized by the method of Overberger and Kesslin,[3] mp 49–51 °C (lit. mp 52–53 °C).

Synthesis of the *N*-Acetyl Derivative of 7. This derivative was prepared by the method of DeMayo, Stothers, and Usselman, mp 153–155 °C (lit.[4] 153–153.5 °C).

Synthesis of 4-Oxo-5,5-dimethyhexanal. The Grignard reagent of 2-(2-bromoethyl)-1,3-dioxane was prepared according to the method of Stowell[6] using 15 g (76.9 mmol) of 2-(2-bromoethyl)-1,3-dioxane and 5.61 g (230 mmol) of Mg in 50 mL of THF. This Grignard

was added dropwise by syringe to a slight excess (12 mL, 97.4 mmol) of trimethylacetyl chloride in 50 mL of the THF while maintaining a positive N_2 pressure. The reaction mixture was stirred 0.5 h after addition was complete and then 15 mL of water was added. The THF was removed in vaccuo and the product was extracted with a 3 × 75 mL portion of hexane. The hexane extract was washed with dilute HCl and dried over $MgSO_4$.

Concentration of the hexane and distillation gave 2-(3-oxo-4,4-dimethylpentyl)-1,3-dioxane (12.34 g, 61.7 mmol): bp 115–122 °C (7 mm); IR (neat) 2962, 2851, 1708, and 1149 cm^{-1}; NMR (CCl_4) δ 1.11 (s, 9 H), 1.2–2.2 (m, 4 H), 2.3–2.7 (m, 2 H), 3.4–4.3 (m, 4 H), and 4.45 (t, 1 H).

This compound was hydrolyzed to 8 as follows. In a 50-mL flask equipped with magnetic stirring was placed 40 mL of H_2O and 5.34 g of 2-(3-oxo-4,4-dimethylpentyl)-1,3-dioxane and 1 g of oxalic acid. A Dean-Stark trap modified to return the bottom layer was attached and filled with water. The mixture was refluxed for 3 h, steam distilling 8 into the trap. The product was taken up in 10 mL of ether, dried over $MgSO_4$, concentrated, and distilled in vacuo (bp 88 °C (12 mm)). The yield was 2.30 g (6.12 mmol, 61%): IR (neat) 2968, 2825 (shoulder), 2718, 1725, and 1707 cm^{-1}; NMR (CCl_4) δ 1.14 (s, 9 H), 2.50 (s, 4 H), and 9.80 (s, 1 H).

Synthesis of the Trimer of 3-*tert*-Butyl-4,5-dihydropyridazine (10). In a 100-mL flask equipped with N_2 atmosphere, condenser, and magnetic stirring was placed 50 mL of benzene and 3.01 g (21.2 mmol) of 4-oxo-5,5-dimethylhexanal. Hydrazine (97%, 2 mL, 63 mmol) was added dropwise. After stirring at reflux for 1 h a Dean-Stark trap was attached and the water azeotroped off over a 2-h period. The benzene was removed in vaccuo and the oil produced was crystallized by addition of 95% ethanol. A second crop of crystals was obtained by addition of water to the ethanol. The yield was 1.30 g (9.4 mmol, 44%): mp 123–125 °C; IR ($CHCl_3$) 2960, 1624, 1475, and 1362 cm^{-1}; NMR δ 1.09 (s, 9 H), 1.9–2.6 (m, 4 H), and 3.2–3.6 (m, 1 H). Mass spectrum showed a large parent ion at 414 ± 1.

Anal. Calcd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.36; H, 10.34; N, 20.14.

Acknowledgment. The authors thank the Army Research Office (J.W.T.) and the Warner Lambert Co. (L.M.T.) for partial support of this research.

Registry No.—**2**, 37819-05-9; **7**, 36046-77-2; **7** *N*-acetyl derivative, 36046-34-1; **8**, 66662-24-6; **10**, 66842-46-4; 2,5-dimethoxytetrahydrofuran, 696-59-3; hydrazine, 302-01-2; 2-(2-bromoethyl)-13-dioxane, 33884-43-4; trimethylacetyl chloride, 3282-30-2; 2-(3-oxo-4,4-dimethylpentyl)-1,3-dioxane, 66842-47-5; 4,5-dihydropyridazine, 56962-82-4.

Supplementary Material Available: Table I listing final refined coordinates and anisotropic temperature factors (isotropic for hydrogen atoms) (3 pages). Ordering information is given on any current masthead page.

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Kinetics of the Rearrangement of *N*-Nitroso(2-methylamino)acetonitrile in Basic Methanol by Differential Pulse Polarography

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Daeniker[2] had reported earlier that *N*-nitroso(2-methylamino)acetonitrile (I) undergoes an interesting rearrangement in basic methanol solution to yield α-isonitroso-*N*-methylaminoacetonitrile (II) (eq 1). During the course of electroanalytical studies on I and other *N*-nitrosamines we observed that the kinetics of this reaction could be studied by differential pulse polarography. A similar application of this technique had been used by us to study the anchimeric role of the nitroso group in the aqueous basic hydrolysis of I.[3] The current study lends support to the mechanism of rearrangement proposed by Daeniker and, in addition, outlines an isolation procedure for II that gives considerably improved yields.

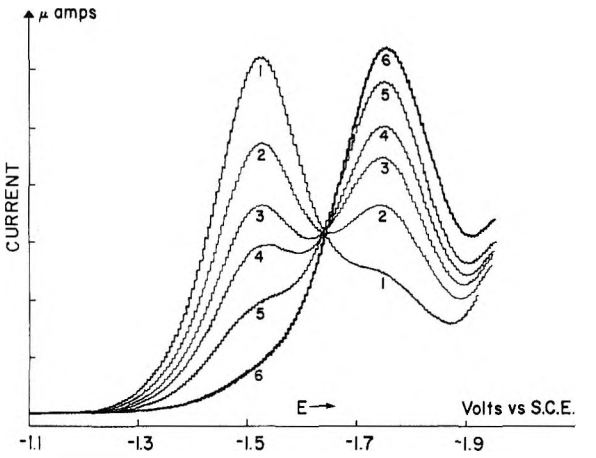

Figure 1. Differential pulse polarograms of rearrangement of *N*-nitroso-2(methylamino)acetonitrile in basic methanol solution: Supporting electrolyte 0.1 M Et_4NClO_4; temperature 22 °C; $[OH^-]$ = 0.006 M; scan rate 5 mV/s; drop time 1.0 s; pulse amplitude 50 mV (p-p); Hg flow rate 1.20 mg/s. Curve 1: 0 min. Curve 2: 6 min. Curve 3: ~12 min. Curve 4: ~20 min. Curve 5: ~32 min. Curve 6: ~105 min.

$$\underset{\underset{N=O}{|}}{CH_3NCH_2CN} \xrightarrow[\text{Base}]{ROH} \underset{\underset{NOH}{\|}}{CH_3NHCCN} \qquad (1)$$

I II

In neutral methanol, I displays a single, diffusion-controlled, differential pulse polarographic peak at −1.52 V vs. SCE. In the presence of methoxide ion, however, the expected peak is followed by a second peak (−1.74 V), an unusual result for a nitrosamine.[4] The heights of the two peaks vary in a regular fashion as a function of time. Typical results are shown in Figure 1; curves 1–6 were recorded on the same solution over a period of approximately 100 min. The species giving rise to the second peak is stable; once it is fully formed the peak height remains constant over a period of 12 h.

The most logical explanation for the observed polarographic results is that proposed by Daeniker (Scheme I). To insure that the reaction described by eq 1 is occurring in the polarographic cell and that II is the species giving rise to the second peak, the solution conditions used in the polarographic cell were repeated on a preparative scale. The physical and spectral data for the sublimed product isolated were identical

Scheme I

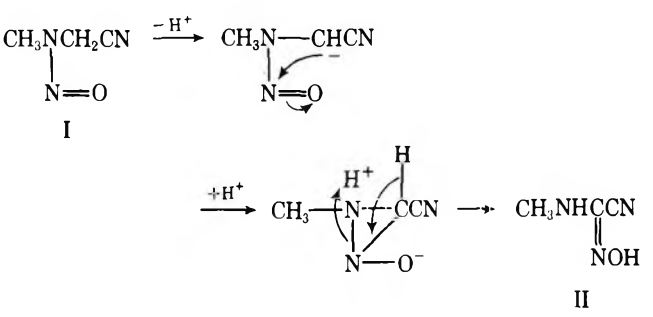

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Table I. Kinetic Data for the Rearrangement of *N*-Nitroso(2-methylamino)acetonitrile in Basic Methanol

t, °C	k, L mol^{-1} s^{-1}
1.0 ± 0.02	(5.96 ± 0.07) × 10^{-3}
11.0 ± 0.02	(1.41 ± 0.19) × 10^{-2}
23.0 ± 0.02	(3.32 ± 0.09) × 10^{-2}

$\Delta H^{\ddagger}$ = 12.0 ± 0.34 kcal mol^{-1} $\Delta S^{\ddagger}$ = −24.7 eu

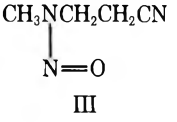
with those of α-isonitroso-*N*-methylaminoacetonitrile reported earlier.[2] A polarogram obtained after addition of the isolated crystals to the solution that yielded curve 6 (Figure 1) showed an increase in peak height without any shift in peak potential, strongly suggesting that the isolated product is the species giving rise to the peak at −1.74 V.

The kinetics of the reaction in eq 1 were determined by measuring the rate of decay of the peak current at −1.52 V, i.e., at the peak potential of species I. Kinetic studies were performed at 1.0, 11.0, and 23 °C.

The reaction was found to be second order (first order with respect to both I and base). The second-order rate constants and activation parameters were calculated in the usual fashion[6] and are given in Table I. The most significant value in the table is the large negative entropy of activation. A pathway that agrees with the kinetic observations is shown in Scheme I; a similar mechanism involving a three-membered ring was first suggested by Daeniker.[2]

The transformation of I to II is facilitated by the relatively high acidity of the methylene protons. The anion that forms is stabilized by the adjacent *N*-nitroso and nitrile groups. To check this conclusion, the next higher homologue of I, *N*-nitroso(3-methylamino)propionitrile (III), was examined polarographically under identical experimental conditions. Compound III gave single differential pulse polarographic peaks in *both* neutral and basic methanol solutions that remained unchanged over a period of 12 h.

The strong acidity of the methylene protons in I is further supported by NMR studies. At room temperature in D_2O, I incorporates two deuteriums instantaneously to yield I-D_2. No such incorporation occurs with III.



III

Experimental Section

α-Isonitroso-*N*-methylaminoacetonitrile (II) from *N*-Nitroso(2-methylamino)acetonitrile (I). Dry methanol (20 mL) was placed in a round-bottom flask fitted with a drying tube and a side arm for the passage of N_2 gas. Dry N_2 was bubbled through the solution for 10 min. A freshly cut piece of sodium metal (0.2 g) was then added and, after it had reacted, I (1.0 g) was added. The solution was allowed to remain at room temperature for 5 h in a nitrogen atmosphere and then evaporated to dryness under vacuum. The residue was dissolved in water (30.0 mL) and adjusted to pH 6.5 with hydrochloric acid. The solution was evaporated to dryness under vacuum and the residue was extracted with chloroform (300 mL). The chloroform solution was evaporated to dryness under vacuum and the residue was sublimed under vacuum yielding white needle-shaped crystals (0.5 g, 50%; mp 154–156 °C (lit.[2] mp 155–157 °C)): single spot on TLC; NMR (D_2O), $-CH_3$, δ 2.90 (s, 3 H); IR 2.93 (OH), 3.12 (NH), 4.42 (C≡N), 6.01 μm (C=N); UV_{max} in absolute ethanol 2550 Å. Anal. Calcd: C, 36.36; H, 5.05. Found: C, 36.39; H, 5.10.

Kinetics of I → II.[6] Methanol solutions of constant ionic strength containing tetrapentylammonium iodide as supporting electrolyte and base were prepared. A 10^{-2} M solution of I in methanol was used as stock solution. The cell was thermostated at 1, 11, and 23 °C using Forma Scientific Model 2095 refrigerated and heated bath and circulator. The decrease in peak current was monitored by recording successive polarograms at fixed time intervals. All the observations were made twice to check the reproducibility of the results. In all cases a plot of ln I_p vs. t was linear and independent of concentration of I, indicating the transformation to be first order with respect to I. The pseudo-first-order rate constants were calculated from the slope of ln I_p vs. t. Variation of the pseudo-first-order rate constants with concentration of base was linear at all temperatures, yielding a first-order reaction rate with respect to base. Second-order rate constants were calculated and are given in Table I. The activation parameters were calculated in the usual fashion.[6]

Spectra and Differential Pulse Polarography. NMR, UV, and IR spectra and differential pulse polarograms were obtained as previously described.[3]

Acknowledgments. This investigation was supported by DHEW Research Grants CA-18618 and 12227 from the National Cancer Institute and by the Samuel S. Fels Fund.

Registry No.—I, 3684-97-7; II, 66922-13-2; III, 60153-49-3.

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Stopped-Flow Study of Salt Effects on the Hydroxide and Borate Ion Catalyzed Hydrolysis of Covalent *p*-Tolylsulfonylmethyl Perchlorate in Aqueous Borax Buffer Solutions

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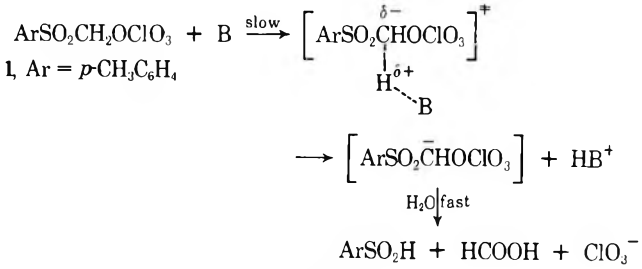
As part of a detailed study of environmental[1,2] and micellar effects[3] on the general base-catalyzed hydrolysis of covalent[4] arylsulfonylmethyl perchlorates, we have recently reported kinetic salt effects on the water-catalyzed process.[2] This pH-independent hydrolysis involves rate-determining proton transfer from the reactant to water via a dipolar transition state in which the negative charge at the α-sulfonyl carbon atom is highly dispersed.[1,5] The electrolyte effects were rationalized mainly by invoking the importance of electrostatic ion–water interactions in the joint cybotactic regions of the ions and the reactant and/or transition state. This theory



emerged as a result of the observation that the salt effects were predominantly governed by the charge type and density of the distinct ions.[2] Electrolyte-induced changes in water structure were assigned a secondary role. As an extension of these studies, we now report the effects of some neutral electrolytes on the rates of hydroxide and borate ion catalyzed hydrolysis in aqueous borax buffer solutions of constant ionic strength (I = 1.0 M). The main objective of this work was to see

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Table I. Second-Order Rate Constants for the Hydroxide and Borate Ion Catalyzed Hydrolysis 1 and 1-d_2 in Aqueous Borax Buffer Solutions at 25 ± 0.05 °C

compd	conditions	pH (±0.02)	$k_{OH} \times 10^4$, $M^{-1} s^{-1}$	k_{borate}, $M^{-1} s^{-1}$	k^H_{OH}/k^D_{OH}	$k^H_{borate}/k^D_{borate}$
1	A[a]	9.20	9.21	13.0		
1-d_2	A[a]	9.20	1.51	1.9	6.1	6.8
1	B[b]	8.88	10.1	10.1		
1-d_2	B[b]	8.88	1.94	1.4	5.2	7.2

[a] 1×10^{-1}, 2×10^{-2}, 2.5×10^{-2}, and 4×10^{-2} M borax solutions. [b] As under *a*, but now at constant ionic strength (I = 1.0 M $NaClO_4$).

Table II. Kinetic Salt Effects on the Hydroxide and Borate Ion Catalyzed Hydrolysis of 1-d_2 at 25 ± 0.05 °C

electrolyte	molarity	$k_{obsd} \times 10^2$, $M^{-1} s^{-1}$, for $c_{borate} \times 10^2$ M[a]				$k_{OH} \times 10^{-4}$, $M^{-1} s^{-1}$	k_{borate}, $M^{-1} s^{-1}$
		1	2	2.5	4		
$NaClO_4$[b]	0.5	17.6	20.4	21.8	25.8	1.94	1.4
NaBr[a]	0.5	18.4	22.6	23.8	30.2	1.94	2.0
NaCl[b]	0.5	19.5	23.1	27.1	35.4[f]	1.98	2.1
CsBr[c]	0.5	28.6	34.5	35.7	49.0	2.00	3.4
Me_4NBr[d]	0.5	35.4	43.6	44.3	57.2	2.08	3.6
n-Bu_4NBr[e]	0.5	48.8	68.7	75.7	104	1.90	9.0

[a] Borax concentration. NaCl added until I = 0.5 M. [b] pH 8.88. [c] pH 9.01. [d] pH 9.14. [e] pH 9.22. [f] $c_{borax} = 5 \times 10^{-2}$ M.

whether the simple theory advanced for the neutral hydrolysis[2] could also provide a framework for understanding salt effects in these buffer systems.

Results and Discussion

It has been demonstrated that at low stoichiometric tetraborate concentrations (as employed in the present study) and at pH >2 dissociation into boric and (mono)borate ion is essentially complete:[6,7]

$$B_4O_7^{2-} + 7H_2O \rightleftharpoons 2B(OH)_3 + 2B(OH)_4^-$$

Thus, pseudo-first-order rate constants (k_{obsd}) for hydrolysis of 1 and its dideuterated analogue (p-$CH_3C_6H_4SO_2CD_2OClO_3$ (1-d_2)) in borax buffers of pH ca. 9.0 will be composed of contributions due to hydroxide ion, borate ion, and water catalysis (eq 1) but the anion-induced deprotonation will dominate the "water" reaction[1,2] by many orders of magnitude (k_{obsd} (H_2O) = 6.05×10^{-4} s^{-1}, k_{borate} ca. 10 $M^{-1} s^{-1}$, k_{OH} ca. 10^5 $M^{-1} s^{-1}$ at 25 °C).

$$k_{obsd} = k_{OH}c_{OH} + k_{borate}c_{borate} + k_{H_2O}c_{H_2O} \qquad (1)$$

Second-order rate constants k_{borate} and k_{OH} for hydrolysis of 1 and 1-d_2 in borax buffers both at constant and at differing ionic strength (I) were obtained by the stopped-flow technique and are listed in Table I. The large primary kinetic deuterium isotope effects clearly substantiate rate-determining deprotonation of the substrates by the general base and definitely rule out a salt-induced mechanistic change toward an S_N2 type process. In view of the fast reaction of 1 with hydroxide ion, salt effects were largely determined for hydrolysis of 1-d_2. Results are displayed graphically in Figure 1. The k_{obsd} values pertain to buffer solutions of constant ionic strength 1 M in which the concentration of the neutral electrolyte under study (c_{salt}) was varied between 0 and 0.5 M at constant I_{borate} + I_{NaCl} = 0.5 M (see Experimental Section). For the $NaClO_4$, NaBr, and CsBr solutions the pH (8.88) was constant within experimental error and identical to that in the absence of the salt. However, for the tetraalkylammonium salts there was a slight increase in pH (pH 8.8–9.2) with increasing c_{salt} which will be partly responsible for the rate acceleration observed for these electrolytes. Nevertheless, the *order* of the kinetic salt effect (n-Bu_4NBr > Me_4NBr > CsBr > NaBr > $NaClO_4$) is similar to that observed for the water-catalyzed reaction.[2] In order to separate salt effects operating on k_{OH} and k_{borate}, k_{obsd} values have been measured at constant c_{salt} = 0.5 M in the presence of varying concentrations of borax and NaCl (for these two salts the sum of their ionic strengths was maintained at 0.5 M leading to a total ionic strength of 1.0 M). Kinetic data are summarized in Table II and plotted in Figure 2. First of all, we note that in all moderately concentrated salt solutions there exists a linear dependence of rate on the borax concentration.[8] Second, the data show that there are only substantial kinetic salt effects on k_{borate} whereas k_{OH} is hardly affected by the nature of the electrolyte. The salt effects on k_{borate} follow the sequence $NaClO_4$ < NaBr < NaCl < CsBr ~ Me_4NBr < n-Bu_4 NBr. It appears that borate anion catalysis is accelerated by increasing charge density on the anion and by decreasing charge density on the cation. Therefore it is likely that the salt effects are not just determined by the availability of water molecules for hydration of the reactants and the transition state.[9] If structure 2 represents a likely model[10] for the transition state for proton transfer from covalent arylsulfonylmethyl perchlorates to the borate anion, it is reasonable to suppose that the hydrogen bond donor capabilities of the O-H_a and O-H_b bonds in 2 are enhanced

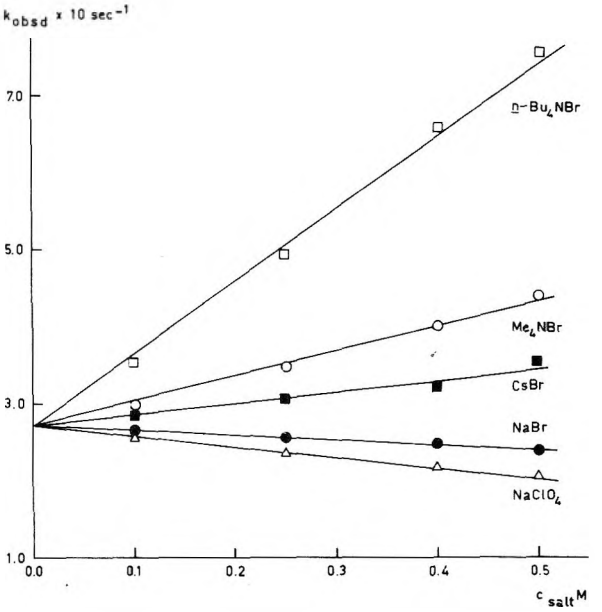


Figure 1. Plots of k_{obsd} vs. concentration of salt for hydrolysis of 1-d_2 in aqueous borax buffers of total ionic strength 1 M (see text).

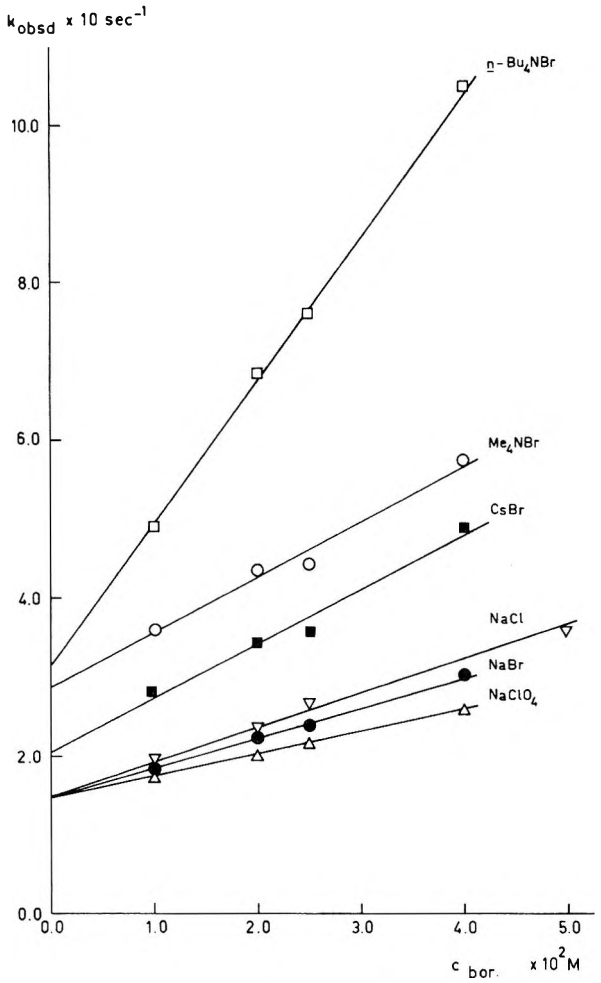
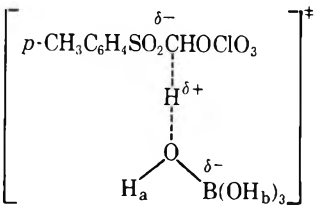


Figure 2. Plots of k_{obsd} vs. borax concentration at total ionic strength 1 M for hydrolysis of 1-d_2 in the presence of 0.5 M $NaClO_4$, NaBr, NaCl, CsBr, Me_4NBr, and n-Bu_4NBr (see text).

as compared with those of the OH bonds in the $B(OH)_4^-$ anion. Now the order of the salt effects is consistent with the model advanced previously,[2] which suggests that polarized and strongly oriented water molecules in type I cospheres[11] of anions of appreciable charge density will stabilize[12] transition states such as 2 through hydrogen bonding to H_a and H_b. Since the negative charge developed at the α-sulfonyl



2

carbon atom in 2 is strongly dispersed,[1] there will be no or only little transition state stabilization by interaction with water molecules of enhanced hydrogen bonding donor capability in the hydration sheaths surrounding cations of high charge density. This rationale then leads to the prediction, which is in agreement with experiment, that the greatest positive salt effects will be observed for electrolytes composed of cations of low charge density and hydration enthalpy ($Na^+ < Cs^+ < Me_4N^+ < n$-$Bu_4N^+$) and anions of high charge density and hydration enthalpy ($ClO_4^- < Br^- < Cl^-$). In conclusion, we note that the present results reveal a striking similarity between the order of kinetic salt effects on a molecule–ion reaction (i.e., 1-d_2 with borate ion) and on a molecule–molecule reaction (i.e., 1 with water). This is not a priori anticipated in terms of simple electrostatic theories for salt effects in aqueous media.[13] The present data and those obtained earlier[2] consistently suggest that kinetic salt effects on the hydrolysis of the arylsulfonylmethyl perchlorates at moderate or even higher electrolyte concentration predominantly reveal effects due to extensive hydration sphere overlap.[14,15] These effects appear to be determined by the strength of directional ion–water interactions and by the magnitude of charge separation and delocalization which accompanies the transfer of the reactants into the transition state.[15]

Experimental Section

Materials. p-Tolylsulfonylmethyl perchlorate (1) and its deuterated analogue (1-d_2) were prepared as described previously, taking into account the appropriate safety precautions.[2,5] The salts used in all experiments were of the highest quality available (usually from Merck or Fluka) and were used as such with the exception of n-Bu_4NBr, which was recrystallized twice from ethyl acetate and dried at 45 °C in vacuo over P_2O_5 for 20 h. The water was demineralized and distilled twice in an all all-quartz distillation unit.

Buffer solutions of low borax concentration (≤0.05 M) were of constant ionic strength, I = 1.0 M, and were made up by weight. These solutions were prepared as follows. Up to I = 0.5 M, NaCl was employed as the electrolyte. The final ionic strength was adjusted by adding calculated amounts of NaCl and the electrolyte under study. Thus, the salt effects reported in this paper pertain to variation between 0 and 0.5 M salt at a total ionic strength of 1.0 M.

Kinetic Measurements. The kinetic measurements were carried out using an Aminco-Morrow stopped-flow apparatus, connected to a data acquisition storage and retrieval system (DASAR). The two reagent solutions were injected in equal quantities. Temperature control was within ±0.1 °C. The change in absorbance at 230 nm was recorded on a W & W recorder (type 3012) to allow the calculation of the pseudo-first-order rate constants (k_{obsd}). These k_{obsd} values were reproducible to within 2%. The estimated accuracy of k_{OH} and k_{borate} listed in Table I is ±6 and ±10%, respectively. The pH measurements were carried out by means of a Findip pH meter, type 555A, using a glass and calomel electrode at 25 °C. The pH values are accurate to within ±0.02.

Acknowledgment. We thank the Netherlands Foundation for Chemical Research (SON) for support in the purchase of the stopped-flow apparatus.

Registry No.—1, 14894-56,5; 1-d_2, 66922-37-0.

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(8) This linearity with buffer concentration in salt solutions of high ionic strength is by no means a general rule: E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **97**, 6221 (1975).
(9) Compare: (a) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **90**, 5965 (1968); (b) D. G. Oakenfull, *Aust. J. Chem.*, **24**, 2547 (1971).
(10) In view of the rather high kinetic acidity of **1** and 1-d_2, it is not a priori excluded that one or more intervening water molecules are present between the organic reactant and the anionic base in the transition state. This will not affect our rationalization for the order of the kinetic salt effects.
(11) For a detailed discussion of ion hydration, see: H. L. Friedman and C. V. Krishnan in "Water, Comprehensive Treatise", Vol. 3, F. Franks, Ed., Plenum Press, New York, N.Y., 1972, p 1.
(12) It is tentatively suggested that the insensitiviness of k_{OH} to electrolyte effect reflects the more favorable free energy of hydration of OH^- as compared with $B(OH)_4^-$ making it less susceptible to interaction with hydration spheres of other ions present in solution and to changes in charge distribution as a result of these interactions.
(13) E. S. Amis and J. F. Hinton, "Solvent Effects on Chemical Phenomena", Vol. 1, Academic Press, New York, N.Y., 1959, Chapter 5.
(14) In another type of approach M. C. R. Symons (*J. Chem. Res.*, in press) has recently rationalized the electrolyte effects on the water-induced deprotonation in terms of an equilibrium between completely hydrogen bonded

water molecules and water molecules containing "free" OH groups and "free" lone pairs. However, this theory cannot easily be applied to the anion induced process reported here.
(15) Kinetic salt effects have been earlier ascribed to water polarization as a result of specific interactions with cations or anions: (a) A. R. Olson and L. K. J. Tong, *J. Am. Chem. Soc.*, **66**, 1555 (1944); (b) D. B. Dennison, G. A. Gettys, D. G. Kubler, and D. Shepard, *J. Org. Chem.*, **41**, 2344 (1976).
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Regiospecific α-Tropolone Synthesis. A Selective Preparation of the Isomeric Thujaplicins

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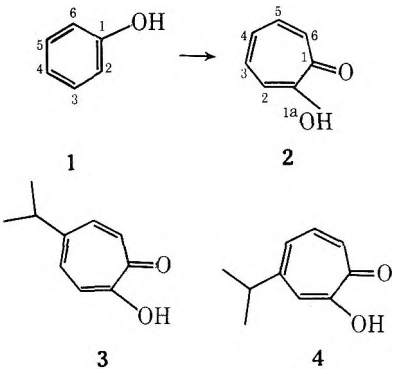
Received February 14, 1978

The seven-membered, aromatic α-tropolone ring **2** occurs naturally in three biosynthetically distinct classes:[1,2] in the essential oils of *Cupressae* (e.g., α-thujaplicin), in mold metabolites of the *Penicillium* family (e.g., stipitatonic acid) and in the *Colchicum* alkaloids (e.g., colchicine). The unique character of these seven-membered carbocycles has attracted considerable synthetic, biogenetic, and theoretical attention[3] since the structure elucidation of the first natural α-tropolone, stipitatonic acid by Dewar, in 1945. However, general synthetic entry into the α-tropolone system has been limited for the most part to the exhaustive oxidation of α-ketocycloheptanones[3] or the $[_\pi 2_s + _\pi 2_a]$ cycloaddition of dihaloketenes with cyclopentadienes followed by rearrangement.[3,4]

As a general approach to natural α-tropolone systems, we desired synthetic access to the α-tropolone ring via site-specific single-carbon expansion of the corresponding suitably substituted phenol (e.g., **1** → **2**). This approach allows the utilization of well-defined phenolic chemistry in establishing the requisite substitution pattern or functionality on the ultimately generated α-tropolone ring and minimizes subsequent chemical manipulation in the presence of the α-tropolone system. We wish to report the realization of this general synthetic objective as illustrated by regiospecific syntheses of the isomeric thujaplicins γ-3 and β-4.



1 **2**

3 **4**

Our synthetic scheme called for the regiospecific establishment of a dihydroaromatic silyl ether. The recent development of lithium/ammonia reduction of O-silylated phenols affords excellent regiopredictability and facile synthetic entry into such systems.[7] For the synthesis of γ-thujaplicin **3** (Scheme I), dissolving metal reduction of triethylsilyl (4-isopropylphenyl) ether **5** afforded the dihydroaromatic silyl ether **6**. Subsequent sodium trichloroacetate mediated dichlorocyclopropanation and methanolic aqueous hydrochloric acid hydrolysis[9,10] afforded the stable bicyclic dichlorocyclopropanol **7**. The regiospecificity of dichlorocyclopropanation is well established to proceed via attack on the most nucleophilic olefin in cases not overshadowed by steric considerations. The stability of such unsaturated bicyclic α,α-dichlorocyclopropanols appears to be unique and **7** is thus a representative of a novel class of functionalized cyclopropane.[11,12] *syn*-Hydroxyl directed peracid epoxidation afforded the epoxide **8** which

Table I. Physical Data for Isolated Intermediates in γ-Thujaplicin Synthesis

	registry no.	bp, °C/mm or Mp, °C	IR, cm^{-1}	NMR ($CDCl_3/Me_4Si$), δ	MS (*m/e*) rel abundance, %
5	66967-06-4	155–165/0.1	1580 (w) 1250 (s) 740 (s)	0.48–1.05 (brm, 15 H) 1.13 (d, *J* = 6.5 Hz, 6 H) 2.75 (q, *J* = 6.5 Hz, 1 H) 7.75 (d, *J* = 10 Hz, 2 H) 8.05 (d, *J* = 10 Hz, 2 H)	250 (81) 235 (73) 195 (95) 121 (100)
6	66967-07-5	Kugelrohr 150/0.1	1610 (med) 1250 (stg)	1.05–0.50 (m, 21 H) 2.30 (b, qt, *J* = 7.0 Hz, 1 H) 2.65 (s, 2 H) 4.85 (s, 1 H) 5.35 (s, 2 H)	
7[a]	66967-08-6	white spindles 71.0–73.5	3425 (stg) 850 (stg)	0.97 (d, *J* = 7.0 Hz, 6 H) 1.82 (d, d, *J* = 7.5, 1.5 Hz, 1 H) 1.90–2.50 (m, 3 H) 2.64 (d, d, *J* = 6.5, 4.5 Hz, 2 H) 2.95 (brs, OH, 1 H) 5.30 (brs, 1 H)	220 (16) 185 (89) 167 (33) 97 (100
8[a,17]	66967-09-7	white blocks 75–77	3420 (stg) 1040 (stg) 830 (stg)	0.94 (d, d, *J* = 6.5 Hz, 6 H) 1.50 (qt, *J* = 6.5 Hz, 1 H) 1.62 (d, d, *J* = 9.0, 2.0 Hz, 1 H) 1.83 (d, d, *J* = 16.0, 2.0 Hz, 1 H) 2.31 (d, d, *J* = 16.0, 9.0 Hz, 1 H) 2.5 (d, *J* = 2.0 Hz, 2 H) 2.79 (t, *J* = 2.0 Hz, 1 H)	236 (4.2) 201 (65) 193 (96) 175 (88) 157 (100)
9[a]	66967-10-0	light oil	1622 (stg) 1599 (stg) 940 (stg)	1.20 (d, *J* = 8.0 Hz, 6 H) 2.80 (qt, *J* = 8.0 Hz, 1 H) 6.74 (d, *J* = 10.5 Hz, 1 H) 7.12 (s, 2 H) 7.65 (d, *J* = 10.5 Hz, 1 H)	182 (79) 139 (100) 109 (32) 103 (59)

[a] Satisfactory elemental analysis was obtained (C, H ±0.3%).

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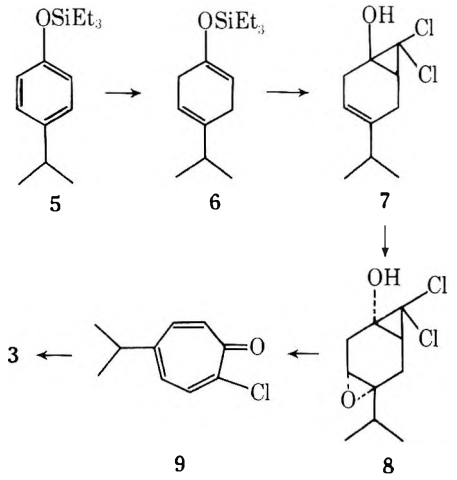
Table II. Physical Data for Isolated Intemediates in δ-Thujaplicin Synthesis

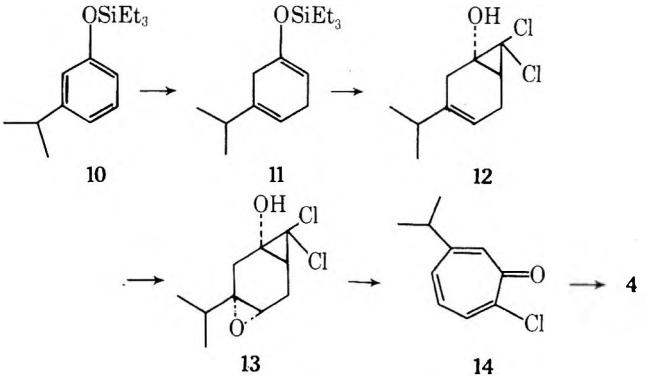
	registry no.	bp, °C/mm	IR, cm^{-1}	NMR ($CDCl_3/Me_4Si$), δ	MS (m/e) rel abundance, %
10	66967-11-1	150–162/0.1	1580 (w med) 1260 (stg) 750 (stg)	0.60–1.10 (m, 15 H) 0.60–1.10 (d, J = 7.0 Hz, 6 H) 2.82 (q, J = 7.0 Hz, 1 H) 6.50–6.82 (m, 3 H) 7.08 (t, J = 9.0 Hz, 1 H)	
11	66967-12-2	Kugelrohr 150°/0.1 mm	1650 (med) 1250 (stg) 730 (stg)	1.16–1.78 (m, 21 H) 2.92 (t, J = 7.0 Hz, 1 H) 5.48 (br, s, 1 H) 6.00 (br, s, 1 H)	
12[a]	66967-13-3	154/0.1 colorless oil	3350 (stg) 1020 (stg)	0.97 (d, J = 7.0 Hz, 6 H) 1.80 (d, d, J = 7.5, 1.5 Hz, 1 H) 1.96–2.40 (m, 3 H) 2.50–2.70 (m, 2 H) 3.20 (b, s, **OH**, 1 H) 5.20 (s, 1 H)	220 (25) 185 (96) 167 (35) 97 (100)
13	66967-14-4	colorless oil	3325 (brd, stg) 1280 (stg) 770 (stg)	0.93 (br, t, J = 8.0 Hz, 6 H) 1.45 (q, J = 8.0 Hz, 1 H) 1.55 (br, d, J = 9.0 Hz, 1 H) 1.85 (d, t, J = 16.0, 2.5 Hz, 1 H) 2.24 (d, J = 15.5 Hz, 1 H) 2.45 (d, J = 15.5 Hz, 1 H) 2.50 (d, d, d, J = 2.0, 9.5, 16.0 Hz, 1 H) 2.83 (br, s, 1 H) 3.50 (br, s, **OH**, 1 H)	236 (5.5) 201 (58) 193 (100) 175 (85) 157 (100)
14[a]	66967-15-5	light oil	1595 (stg) 1630 (stg) 900 (stg)	1.18 (d, J = 8.0 Hz 6 H) 2.72 (q, J = 8.0 Hz, 1 H) 6.50–6.80 (m, 2 H) 6.96 (d, d, J = 8.5, 1.10 Hz, 1 H) 7.48 (d, d, J = 6.0, 9.5 Hz, 1 H)	182 (59) 139 (100) 109 (45) 103 (65)

[a] Satisfactory elemental analysis was obtained (C, H ±0.3%).

Scheme I



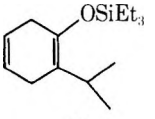
Scheme II



upon treatment in refluxing benzene with a trace of p-toluenesulfonic acid catalyst gave the α-chlorotropone **9**. Conversion of the α-chlorotopone **9** to γ-thujaplicin **3** by treatment with aqueous phosphoric acid in acetic acid at reflux[13] completed the synthesis.

In a similar fashion, triethylsilyl 3-isopropylphenyl ether **10** (Scheme II) could be reduced to dienylsilyl ether **11** then dichlorocyclopropanated and hydrolyzed to give the dichloronorcarenol **12**. Subsequent conversion of norcarenol **12** to epoxide **13** and acid-catalyzed ring expansion afforded the α-chlorotropone **14**. Again completion of the synthesis could be effected by strong acid treatment of α-chlorotropone **14** to generate β-thujaplicin **4**. Proceeding along identical lines, phenol **1** could be converted into α-tropolone **2**.

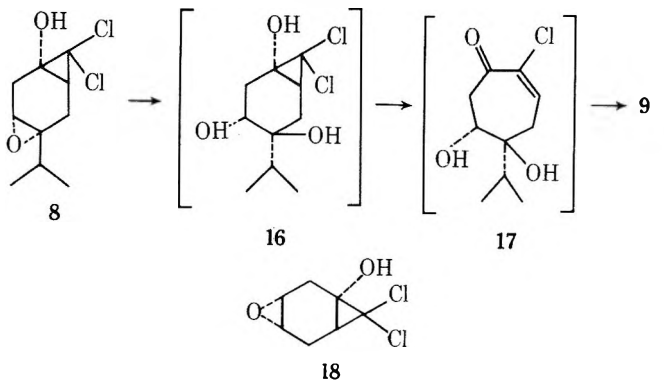
This phenol to α-tropolone conversion is direct in its synthetic manipulation, efficient in its yield, and reasonably general in synthetic applicability. The principle difficulty encountered in the scheme is the effective and regiospecific dichlorocyclopropanation of hindered enol silyl ethers. Although enhanced nucleoplilicity of the enol silyl ether unsaturation ensures highly regioselective (>95%) olefin reactivity in the α-tropolone and β- and γ-thujaplicin syntheses, the dichlorocyclopropanation of cyclohexadienyl silyl ether **15**, an intermediate in proposed α-thujaplicin preparation, proceeded in unserviceably low yield (~12%). Apparently, steric hindrance to olefin access inhibits enol silyl ether reactivity.



15

The high yield rearrangement of the norcaranol oxide system (**8** and **13**) directly to the α-chlorotropone (**9** and **14**) represents an interesting synthetic transformation. The process is acid catalyzed and corresponds to an overall ring

Scheme III



expansion–bisdehydration of the resultant α-chloroenone system. In the γ-thujaplicin sequence, both the epoxide **8** (refluxing toluene, $t_{1/2} \gg 24$ h) and the parent olefin **7** (refluxing toluene or *n*-butyl alcohol–water, $t_{1/2} \gg 24$ h) possess excellent thermal stability. In addition, the parent norcarenol **7** is stable to the acidic conditions required for epoxide **8** rearrangement. Thus, the suggested mechanism for this ring expanding transformation (e.g., **8** → **9**) is acid catalyzed *epoxide opening* to generate the bicyclic triol **16**, followed by facile ring enlargement to the α-chloroenone diol **17** (Scheme III). Subsequent acid mediated bisdehydration produces the α-chlorotropone **9**. The rate-determing step must be epoxide opening, since no intermediates chould be detected (TLC) in the conversion of **8** to **9**.

This postulated rate-determining oxirane opening requires rapid (or spontaneous) ring expansion of the saturated 7,7-dichloronorcaran-1-ol structure **16** (to **17**), which is generated upon release of the C-3–C-4 constraint on the norcaranol system. The rapid rearrangement of saturated 7,7-dichloronorcaranol systems relative to their $\Delta^{3,4}$-unsaturated counterparts has been observed.[11] Furthermore, the observation that trisubstituted norcaranol oxide **8** rearranges at a rate faster than the corresponding disubstituted norcaranol oxide **18** (competitively in the same reaction media) is consistent with rate-determining electrophilic epoxide opening. Such an oxirane substitution–reactivity pattern is a consequence of enhanced stability of the transition state incipient carbocation for the alkyl substituted oxirane **8** relative to the unsubstituted analogue **18**.

In addition, the regiospecific conversion of the α-chlorotropone structures generated via this route to specific 2-substituted troponoids has considerable synthetic potential. For example, regiospecific displacement of the α-chloro substituent by methoxide under known conditions would generate specific *O*-methyltropolones.[14] Alternate schemes for tropolone *O*-methylation proceeding via the parent α-tropolone generally yield *O*-methyltropolone isomers as a consequence of facile α-tropolone tautomerization. Thus, diazomethane methylation of *O*-demethylcolchicine affords both colchicine and isocolchicine.[15] In principle, regiospecific α-chlorotropone generation and subsequent nucleophilic introduction of methoxide could circumvent such isomer formation.

Experimental Section

General. Melting points were taken with a Thomas-Hoover apparatus using open capillaries and are uncorrected. Proton magnetic resonance spectra were recorded at 100 MHz with a Jeol JNM-MH-100 spectrometer employing tetramethylsilane as an internal standard. Low resolution mass spectra were obtained by direct insertion with an LKB 9000 spectrometer at 70 eV. The parent ion and the most intense peaks (2–4) are reported. Infrared spectra were obtained on a Perkin-Elmer 727 infrared spectrometer. Elemental analyses were preformed by Galbraith Laboratories, Inc., Knoxville, Tenn. For all column chromatography, E. Merck (type 60) silica gel and short column techniques were utilized and for TLC analysis, E. Merck Silica Gel 60, F-254 precoated (0.25 mm) plates were employed. Magnesium sulfate was used as the drying agent throughout and all experimental procedures were performed under an atmosphere of dry nitrogen.

Physical data for the intermediate compounds described in the experimental procedures are presented in Table I (γ-thujaplicin synthesis) and Table II (β-thujaplicin synthesis).

General Triethylsilyl Phenyl Ether Synthesis.[8] The requisite phenol (50.0 mmol) was dissolved in anhydrous dimethyl formamide (40 mL) to which imidazole (8.50 g, 125.0 mmol) and triethylchlorosilane (9.00 g, 0.06 mmol) were subsequently added. The solution was heated at reflux, maintained for 3 h, allowed to cool (~1 h), then poured into pentane (150 mL) and extracted with cold 1 N aqueous sodium bicarbonate, water, and brine. The organic layer was dried and the solvent removed in vacuo affording the triethylsilyl phenyl ether (48.0 mmol, 96%) sufficiently pure (~95%, VPC) to employ in the reduction step without purification. If the triethylsilyl phenyl ether is to be stored for extended periods (~4 months) distillation is suggested. In addition, phenols reluctant to undergo *O*-silylation (e.g., 2-isopropylphenol) require extended periods at reflux (~12 h) and distillation prior to use.

Isopropyl-7,7-dichloronorcar-3-en-1-ols 10 and 15. (a) Dissolving Metal Reduction of Triethylsilyl Isopropylphenyl Ethers. The method of Donaldson and Fuchs[8] can be employed without modification. However, our initial studies utilized an alternate procedure which might prove useful in larger scale (>20 mmol) phenyl silyl ether reduction and which produces comparable yields when undertaken with triethylsilyl phenyl ethers. This modified procedure is described here.

Isopropylphenyl triethylsilyl ether **5** or **10** (2.50 g, 10.0 mmol) was introduced (in 10 mL of anhydrous THF) via syringe to a −33 °C solution of anhydrous THF (55 mL), *tert*-butyl alcohol (10 mL), and ammonia (120 mL) containing lithium wire (70.0 mmol), The reaction mixture was maintained at reflux for 35 min, then cooled to −78 °C, quenched with ammonium chloride (4.0 g), and then hexane (150 mL) was introduced carefully. With rapid stirring and gentle warming the bulk of the ammonia is allowed to evaporate over the course of ¾ h. Subsequent partitioning of the mixture between hexane (150 mL) and saturated ammonium chloride solution (200 mL) followed by drying the organic layer and solvent removal afforded the crude dihydroaromatic enol ethers **6** (2.226 g, ~90% reduced) and **11** (2.090 g, ~90% reduced). The sole impurity was unreduced (and noninterfering) starting material and the crude product was consequently utilized without further purification.

(b) Dihydroaromatic Triethylsilyl Enol Ether Cyclopropanation. The crude dihydroaromatic silyl ether **6** or **11** (~9.0 mmol) was dissolved in freshly distilled tetrachloroethylene (10 mL) and anhydrous dimethoxyethane (10 mL), to which anhydrous sodium trichloroacetate (2.100 g, 11.25 mmol) was introduced, and the suspension was refluxed for 1.5 h. The solution was then cooled, poured into pentane (150 mL), and washed rapidly with water then brine and the organic layer was dried. Solvent removal in vacuo afforded the crude silyloxy norcarene compounds which were immediately subjected to silyl ether hydrolysis.

(c) Methanolic Aqueous Hydrochloric Acid Hydrolysis. The crude product silyloxy norcarene was dissolved in a solution of methanol (150 mL) and 10% (by volume) aqueous hydrochloric acid (50 mL) then stirred at room temperature overnight. The mixture was partitioned between ether (300 mL) and water (200 mL); the ethereal layer was washed once with water then brine and dried. Chromatography (4% ethyl acetate/pentane) afforded dichloronorcarenols **7** (1.433 g, 65% based on starting ether **5**) and **12** (1.270 g, 58%).

7,7-Dichloronorcaron-1-ol Oxides 8 and 13. The precursor norcarenol **7** (or **12**) (0.880 g, 4.00 mmol) was dissolved in anhydrous methylene chloride (75 mL) and *m*-chloroperbenzoic acid (1.550 g, 7.6 mmol) was added and the mixture stirred at room temperature. After 2 h, excess peracid was destroyed by stirring with aqueous thiosulfate solution. The resultant solution was partitioned between ether and water and the ethereal layer was washed once with water then brine and subsequently dried. Solvent removal in vacuo followed by chromatography (10% ethyl acetate/pentane) afforded the epoxides **8** (0.861 g, 91%), **17**, and **13** (0.897 g, 95%).

2-Chloro-5(or 6)-isopropyltropone 12 (or 17). The precursor norcarane oxide **11** (or **16**) (0.306 g, 1.29 mmol) was dissolved in benzene (70 mL) containing *p*-toluenesulfonic acid (~25 mg) and refluxed for 2.5 h. The reaction mixture was then cooled and partioned between ether and 3% aqueous sodium bicarbonate. The ethereal layer was washed with brine and dried and the solvent removed in vacuo affording the crude α-chlorotropone. Chromatography (12% ethyl acetate/pentane) gave the isomeric isopropylchlorotropones as col-

orless oils **12** (0.213 g, 91%) and **17** (0.195 g, 78%).

Thujaplicin. The requisite α-chlorotropone **9** or **14** (0.207 g, 1.11 mmol) was dissolved in glatial acetic acid (10 mL) containing aqueous phosphoric acid (44%; 8 ml) and heated at reflux for 15 h.[13] The reaction mixture was then cooled and poured into water (40 mL) and the solution pH adjusted to pH 4–5 with aqueous sodium hydroxide. The aqueous phase was extracted with methylene chloride (5 × 20 mL) then the combined organics dried and the solvent removed in vacuo. Chromatographic filtration (Silica Gel; ether (50%)/pentane) afforded γ-thujaplicin (**3**) [mp 75–77 °C (lit.[16] mp 82 °C)] (0.142 g, 78%) and β-thujaplicin (**4**) [mp 44–46 °C (lit.[16] mp 50–52 °C)] (0.150 g, 83%).

Acknowledgment. The author is grateful for the financial assistance of the Vanderbilt University Natural Science Committee.

Registry No.—**16**, 66967-16-6; **17**' 66967-17-7; 4-isopropylphenol, 99-89-8; 3-isopropylphenol, 618-45-1; triethylchlorosilane, 994-30-9.

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(3) For a review covering troponoid synthesis and chemistry see: F. Pietra, *Chem. Rev.*, **73**, 293 (1973).
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(6) (a) S. Tobinaga, E. Kootani, and F. Miyazaki, *J. Chem. Soc., Chem. Commun.*, 300 (1974); (b) W. V. E. Doering and F. L. Detert, *J. Am. Chem. Soc.*, **73**, 876 (1951).
(7) The work of Donaldson and Fuchs[8] was published concurrent with our own investigation in this area. Only minor differences need be noted. To retain continuity with our earlier work on the dichlorocyclopropanation of trialkylsilyl enol ethers,[9] our studies employed triethylsilyl phenyl ethers, instead of *tert*-butyldimethylsilyl phenyl ethers. As noted by Donaldson and Fuchs,[8] trimethylsilyl phenyl ethers are too labile under the dissolving metal conditions to be useful. However, triethylsilyl phenyl ethers are at least as stable as the corresponding *tert*-butyldimethylsilyl phenyl ethers to the reaction conditions.
(8) R. E. Donaldson and P. L. Fuchs, *J. Org. Chem.*, **52**, 2032 (1977).
(9) G. Stork and T. L. Macdonald, *J. Am. Chem. Soc.*, **97**, 1264 (1975).
(10) J. M. Conia, P. Amico, and C. Blanco, *Synthesis*, 196 (1976).
(11) T. L. Macdonald, *J. Org. Chem.*, in press.
(12) Birch and Keeton[5b] have isolated two related dichlorocyclopropanols. To the best of our knowledge, these compounds represent the only previously isolated α,α-dichlorocyclopropanols.
(13) For example, see: T. Nozoe, T. Asao, E. Takahasi, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **39**, 1310 (1966).
(14) (a) M. Cavazza, R. Cabrino, and F. Pietra, *Synthesis*, 298 (1977); (b) R. Cabrino, M. Cavazza, and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 721 (1976).
(15) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **40**, 193 (1957).
(16) T. Nozoe, *Fortschr. Chem. Org. Naturst.*, **13**, 232 (1956).
(17) ^{13}C NMR data were obtained for this compound. The author would like to acknowledge the assistance of Kevin Darst. Chemical shifts (in ppm downfield from Me_4Si) 17.74, 18.42, 18.65, 28.44, 31.70, 34.92, 58.55, 58.83, 61.85, 68.30.

Synthesis of (3*S*,4*S*)-4-Amino-3-hydroxy-6-methylheptanoic Acid Derivatives. Analysis of Diastereomeric Purity

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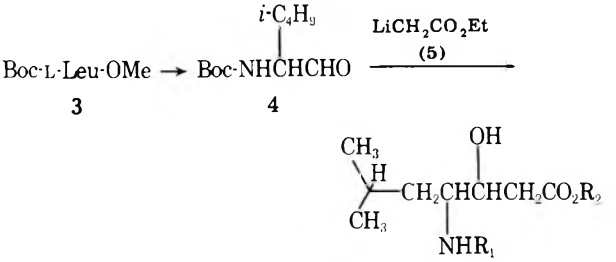
Pepstatin, isovaleryl-L-valyl-L-valyl-(3*S*,4*S*)-statyl-L-alanyl-(3*S*,4*S*)-statine (**1**),[1] is a low molecular weight inhibitor of acid proteases, e.g., pepsin, renin, and cathepsin D.[2] Pepstatin contains the novel amino acid statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid (**2a**). Kinetic studies have shown that the (3*S*)-hydroxyl group in the statine residue in position 3 of pepstatin is necessary for tight-binding-inhibition of pepsin.[3,4] Synthetic statine is needed to further study the kinetic and biological properties of pepstatin and the importance of the (3*S*)-hydroxyl group of statine requires that its stereochemistry be rigorously established. However, while several syntheses of statine **2** have been reported,[5-8] the preparation of (3*S*,4*S*)-statine free of contamination from the (3*R*,4*S*) diastereomer is not readily achieved. We report here a convenient, high-yield synthesis of (3*S*,4*S*)-statine via a route that allows for separation of diastereomers and for determination of optical purity.

Scheme I



2a, $R_1 = R_2 = H$ (3*S*,4*S*)
b, $R_1 = R_2 = H$ (3*R*,4*S*)
5a, R_1 = Boc; $R_2 = C_2H_5$ (3*S*,4*S*)
b, R_1 = Boc; $R_2 = C_2H_5$ (3*R*,4*S*)
6a, R_1 = Boc; $R_2 = H$ (3*S*,4*S*)
b, R_1 = Boc; $R_2 = H$ (3*R*,4*S*)

Results and Discussion

The preparation of statine derivatives is outlined in Scheme I. Boc-L-leucine methyl ester (**3**) was reduced with diisobutylaluminum hydride in toluene at −78 °C for 6 min. Excess hydride was destroyed with methanol,[9] and the reaction worked up using Rochelle salt[10] to solubilize the complex. Aldehyde **4** was isolated in 85% yield. Addition of lithium ethyl acetate (**5**) at −78 °C to **4** according to a modification of the procedure of Steulmann and Klostermeyer[7] gave an 80% yield of the ester **5a,b** as a mixture of diastereomers (60% (3*S*,4*S*); 40% (3*R*,4*S*)). Diastereomers **5a** and **5b** can be separated by standard column chromatography over silica gel. A better and faster separation is achieved by using commercially prepared columns (Lobar) (3.7 × 44 cm) which can provide 1–2 g of pure **5a** from 2–4 g of the mixture in only a few hours. The overall yield of pure Boc-(3*S*,4*S*)-statine ethyl ester **5a** from ester **3** is 38–40%. Saponification of ester **5a** gives acid **6a** (86%) which, in turn, is readily converted to free statine **2a** by mild acid hydrolysis with trifluoroacetic acid.

Both Boc acids **6a** and **6b** can be crystallized from diethyl ether–petroleum ether (30–60 °C) mixtures. It was possible to isolate the less soluble **6b** by fractional crystallization of the mixture of diastereomers but further concentration of the mother liquor gave **6a** in only 80% optical purity. We were unable to crystallize either **6a** or **6b** from isopropyl alcohol.[7]

A convenient method for establishing the optical purity of the various statine diastereomers has been needed. Diastereomers **2a** and **2b** do not easily separate when subjected to standard amino acid analysis and other ion exchange conditions[8] although separation can be achieved at high temperatures.[6] We have found that the esters **5a** and **5b** are easily separated by gas-liquid chromatography (GC) on an OV-225 column. A mass spectrum of the material eluting from the GC column shows that the diastereomers are chromatographing as the intact Boc esters **5a** and **5b** and have not been degraded

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Table I. Properties of Statine and Derivatives

	registry no.	^{1}H NMR, δ C-2	C-3	C-4	C-5,6	C-7,8	$[\alpha]^{24}_D$, deg	mp, °C
2a[a]	49642-07-1	2.43[c] 2.57	4.0 m	3.30 m	1.45 m	0.96 d (J = 6 Hz)	−20 (c 1, H_2O)	201–202[d]
2b[a]	49642-13-9	2.40[c] 2.43	4.2 m	3.4 m	1.45 m	0.93 d (J = 5 Hz) 1.01 d (J = 6 Hz)	−18 (c 1, H_2O)	202–203[d]
5a[b]	67010-43-9	2.49[c] 2.52	4.0 m	3.6 m	1.45 m	0.92 d (J = 6 Hz)	−37.9 (c 0.84, CH_3OH)	oil
5b[b]	67010-44-0	2.45[c] 2.49	4.0 m	3.6 m	1.45 m	0.90 d (J = 5 Hz) 0.92 d (J = 6 Hz)	−23.2 (c 0.94, CH_3OH)	oil
6a[b]	58521-49-6	2.52[c] 2.57	3.98 m	3.65 m	1.45 m	0.92 d (J = 6 Hz)	−39.6 (c 0.31, CH_3OH)	117–118
6b[b]	66967-01-9	2.48[c] 2.53	3.98 m	3.65 m	1.45 m	0.90 d (J = 5 Hz) 0.91 d (J = 6 Hz)	−27.6 (c 0.31, CH_3OH)	135–136

[a] Taken in D_2O with DSS added as internal reference. [b] Taken in $CDCl_3$ with internal Me_4Si as standard. [c] AB portion of ABX pattern. [d] Data taken from ref 5, 6, and 8.

to either cyclic carbamates or dehydro amino acids. Using the GC method to analyze the diastereomeric purity of **5a** and **5b** it has been possible to prepare the optically pure (>99%) statine derivatives listed in Table I.

The data in the table show that the optical rotation of derivatives **2a**, **2b**, **5a**, and **5b** is not a sensitive test for optical purity. However, the nuclear magnetic resonance (NMR) spectra of these diastereomers can be used to assign configuration and to estimate optical purity. In general the C-2 protons appear as an AB portion of an ABX pattern. The chemical shift of one of these protons resonates farther downfield in **2a** and **5a** than in **2b** and **5b**. This method is not as sensitive as the GC method for measuring optical purity and is probably accurate to only ±10%. In contrast to the above, the optical purity of the Boc acids **6a** and **6b** can be accurately established by optical rotation and melting point (Table I). The rotations reported in the table were obtained on analytically pure derivatives shown to be single diastereomers by GC. To be certain that no epimerization of the 3-hydroxyl group had occurred during saponification of **5a** and **5b**, the Boc acids **6a** and **6b** were converted to methyl esters by reaction with diazomethane. Each sample was analyzed by GC and shown to be homogeneous (retention times: (3*S*,4*S*) methyl ester, 10.0 min; (3*R*,4*S*) methyl ester, 11.4 min).

Steulmann and Klostermeyer described the first synthesis of (3*S*,4*S*)-Boc-Sta **6a** and reported that fractional crystallization from isopropyl alcohol gave pure **6a** ($[\alpha]^{20}_D$ −27.8°; mp 95 °C).[7] However, we observe both a more negative rotation and a higher melting point for **6a** (Table I). These differences could result from different experimental procedures or could indicate that the Boc-Sta **6a** reported by Steulmann and Klostermeyer contains only 77% of the (3*S*,4*S*) diastereomer. We found that a synthetic mixture of **6a** and **6b**, which contained 77% of the (3*S*,4*S*) diastereomer by GC, gave a rotation of −28° and melted over the temperature range 97–102 °C. These results suggest that their fractional crystallization procedure may not provide an optically pure sample of **6a**.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. The ^{1}H NMR spectra were recorded on a Bruker HX-90E-pulse Fourier transform NMR spectrometer interfaced with a Nicolet 1080 computer and disk unit. Optical rotations were measured at the sodium D line using a Perkin-Elmer 241 polarimeter. Mass spectra were determined on a Finnigan Model 1015 mass spectrometer. Microanalyses were performed by Galbraith Laboratory, Knoxville, Tenn.

Gas chromatography was carried out on a Nuclear Chicago Selectra System 5000 gas chromatograph using glass columns (4 ft × 5 mm) packed with 1% OV-225 on gas Chromosorb Q (110–120 mesh) at 165 °C. The injection temperature was 255 °C and the flow rate was 35 mL/min.

Thin-layer chromatography (TLC) was performed on silica gel G plates using 20% ethyl acetate in benzene as eluant [R_f (1)].

Preparative HPLC was carried out using a Lobar Lichroprep Si 60 column, obtained from E. Merck, Darmstadt, Germany, eluting with 20% ethyl acetate in hexane or benzene.

Boc-L-leucinal (4). To a stirred solution of Boc-L-leucine methyl ester 3 (4.0 g, 16.3 mmol) in dry toluene (70 mL) was added a hexane solution of diisobutylaluminum hydride (40.8 mmol) at −78 °C under a nitrogen atmosphere. After 6 min, the reaction was quenched with methanol (4 mL)[9] and Rochelle salt solution[10] was added immediately. The mixture was allowed to warm to 25 °C and ether (100 mL) was added. The etheral layer was separated and combined with ether extracts of the aqueous layer. The combined layers were dried ($MgSO_4$) and concentrated under reduced pressure.

The crude product (oil) was passed through a short pad of silica gel, eluting with 4% ethyl acetate in benzene to remove the alcohol side product. The weight of Boc-leucinal obtained was about 2.98 g (85%): R_f(1) = 0.47; ^{1}H NMR ($CDCl_3$) δ 9.57 (s, 1 H), 5.28 (1 H), 4.15 (1 H), 1.15–2.0 (m, 12 H, with singlet at δ 1.47), 0.96 (d, 6 H, J = 6 Hz). This product was used without further purification.[11]

(3*RS*,4*S*)-*N*-Boc-4-amino-3-hydroxy-6-methylheptanoic Acid Ethyl Ester (5). To 5 mL of dry tetrahydrofuran cooled in dry ice–CCl_4 was added diisopropylamine (15 mmol) under a nitrogen atmosphere, followed by a solution of *n*-butyllithium in hexane (15 mmol). After 1 h the bath temperature was lowered to −78 °C and dry ethyl acetate (15 mmol) was added via syringe and stirred for 15 min. Boc-leucinal **4** (2.15 g, 10 mmol) in 10 mL of tetrahydrofuran was added and the reaction mixture was stirred for 5 min before 1 N HCl was added. The flask was warmed to room temperature and the reaction mixture acidified with cold 1 N HCl to pH 2–3, then extracted with ethyl acetate three times. The organic layer was washed with saturated NaCl and dried ($MgSO_4$). Evaporation under reduced pressure gave an oil which after silica gel column chromatography gave 2.42 g of Boc-Sta-OEt (80%) as a mixture of diasteromers (**5a,b**).

Chromatography of mixture **5a,b** on silica gel eluting with a gradient of 10% ethyl acetate in benzene to 50% ethyl acetate in benzene separated **5a** [R_f(1), 0.21] from **5b** [R_f(1), 0.17].

(3*S*,4*S*)-*N*-Boc-4-amino-3-hydroxy-6-methylheptanoic acid ethyl ester (5a) was isolated in 38–40% yield as an oil: GC retention time, 11.3 min; mass spectrum *m/e*, 303 (0.5), 230 (8.3), 202 (6.1), 187 (14), 186 (32), 158 (10), 140 (5.7), 131 (14.9), 130 (84), 129 (6.2), 117 (13), 86 (100), and 57 (95). See Table I for other physical constants.

(3*R*,4*S*)-*N*-Boc-4-amino-3-hydroxy-6-methyl heptanoic acid ethyl ester (5b): GC retention time, 13.5 min; mass spectrum *m/e*, 303 (0.3), 230 (8.3), 202 (4.1), 187 (14), 186 (32), 158 (10), 140 (5.7), 131 (15), 130 (83), 129 (4.2), 86 (100), 57 (95). See Table I for other physical constants.

(3*S*,4*S*)-*N*-Boc-4-amino-3-hydroxy-6-methylheptanoic Acid (6a). A solution of ester **5a** (548 mg, 1.8 mmol) in aqueous dioxane was maintained at pH 10 for 30 min. The solution was acidified (pH 2.5) with cold 1 N hydrochloric acid and the aqueous layer washed with ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated to give 428 mg (86%) of acid **6a**. See Table I for physical constants. Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.08; N, 5.09. Found: C, 56.66; H, 9.32; N, 5.05.

(3*R*,4*S*)-*N*-Boc-4-amino-3-hydroxy-6-methyl Heptanoic Acid (6b). This compound was prepared from ester **5b** using the procedure for **6a** and was isolated in 90% yield. See Table I for physical constants. Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.08; N, 5.09. Found: C, 56.68, H, 9.28; N, 5.11.

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Registry No.—3, 63096-02-6; 4, 58521-45-2.

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(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 983.
(11) Passage through silica gel must be rapid since the Boc-aldehyde **4** racemizes (about 5% per h) on contact with silica gel. See: A. Ito, R. Takahashi, and Y. Baba, *Chem. Pharm. Bull. Jpn.*, **23**, 3081 (1975), for the synthesis of (*Z*)-L-leucinal and its racemization on silica gel.

Communications

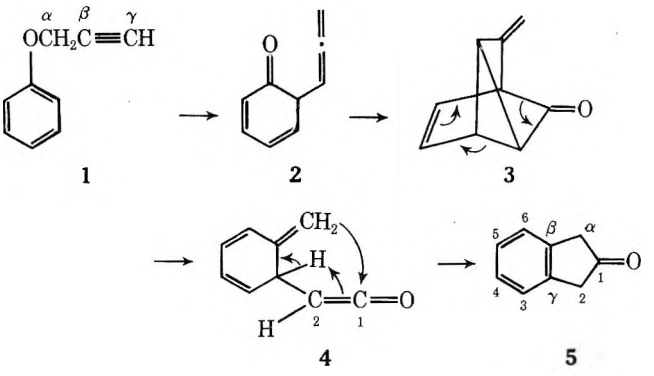
On the Mechanism of Flash Vacuum Pyrolysis of Phenyl Propargyl Ether. Intramolecular Deuterium Kinetic Isotope Effect on Claisen Rearrangement[1]

Summary: We wish to report the first intramolecular deuterium kinetic isotope effect observed in the Claisen type rearrangement of 2-deuteriophenyl propargyl ether (**8**), which is interpreted in terms of a nonsynchronous mechanism.

Sir: It has been reported by Trahanovsky and Mullen[2] that flash vacuum pyrolysis (FVP) of phenyl propargyl ether (**1**) gives rise to benzocyclobutene and 2-indanone (**5**). Based on their mechanistic studies, they proposed[2] the mechanism shown in Scheme I for the formation of **5**. Kinetic studies on the thermal rearrangement of **1** indicated that the step **1** to **2** is rate determining.[3] Furthermore, rearrangement of **1** to **2** has been classified as a [3,3] sigmatropic process.[3] Very recently, Dewar[4] has presented results of MINDO calculations on some pericyclic reactions and has concluded that two-bond ractions are never synchronous, with the exception of a number of ene reactions, but are two-stage or two-step processes which involve unsymmetrical transition states. Furthermore, it has been indicated that the Cope rearrangement of 1,5-hexadienes, a [3,3] sigmatropic process according to Woodward–Hoffmann rules,[5] is not a pericyclic reaction but follows a different mechanism which involves reaction intermediates.[4]

The study of secondary deuterium kinetic isotope effects provides a useful method to estimate the degree of force constant changes at the isotopic position between the ground and transition states,[6] and consequently is a powerful tool in determining the degree of bond cleavage–bond formation that occurs at the transition states of two-bond reactions.

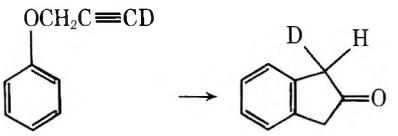
Scheme I



1 2 3 4 5

It is the purpose of this work to further test the mechanism outlined in Scheme I, and to determine the relative timing of bond cleavage–bond formation at the transition state for the rearrangement of **1** to **2**.

The mechanism suggested for the FVP of **1** implies, among other things, transfer of the acetylenic hydrogen (γ hydrogen) of the reactant, during the rearrangement, to a position which ends up as nonaromatic in the product 2-indanone (**5**, Scheme I). Therefore, by substituting the acetylenic hydrogen in **1** by deuterium, subsequent FVP of the resulting deuterated ether should produce an indanone with all deuterium bonded to the nonaromatic position. Thus, phenyl γ-deuteriopropargyl ether (**6**) was synthesized by five successive exchanges of the γ hydrogen in **1**[7] using D_2O/NaOD in dried diethyl ether. The NMR analysis of **6** revealed that 87% of deuterium is incorporated in the desired position. The FVP[7] of **6** was carried out



6 7

at 460 °C and 0.02 Torr. The NMR spectrum of the 2-indanone (**5**) in CCl_4 displays peaks at δ 7.15 (singlet, aromatic H's) and 3.25 (singlet, nonaromatic H's) and with an integration ratio of 1.00:1.00. The NMR spectrum of the deuterated 2-indanone derived from **6** gave an aromatic protons/nonaromatic protons ratio of 1.30:1.00, consistent with the prediction and the structure given by **7**. Thus, our observation further substantiates the mechanism proposed[2] for the FVP of **1** (Scheme I).

The problem of gaining an insight into the structure of the transition state for the rearrangement of **1** to **2** could be carried out by examining the magnitude of the intramolecular deuterium kinetic isotope effect involved in the FVP of 2-deuteriophenyl propargyl ether (**8**). Considering Scheme II, if bond formation is taking place at the rate-determining step, then due to the rehybridization change (sp^2 to sp^3) of the ortho C–H and C–D bonds an inverse isotope effect would be expected in the FVP of **8**. If on the other hand, bond formation is occurring in a subsequent fast step, then k_H would be equal to k_D. The FVP of **8** should give rise to dienones **9** and **10**, which subsequently lead to products **11** and **7**, respectively. The proportion of **9** and **10** would depend on the magnitude of the k_H/k_D involved, and would be reflected in the ratio of **11** to **7** as determined by NMR analysis. Synthesis of **8** was accomplished from the reaction of 2-deuteriophenol[9] with

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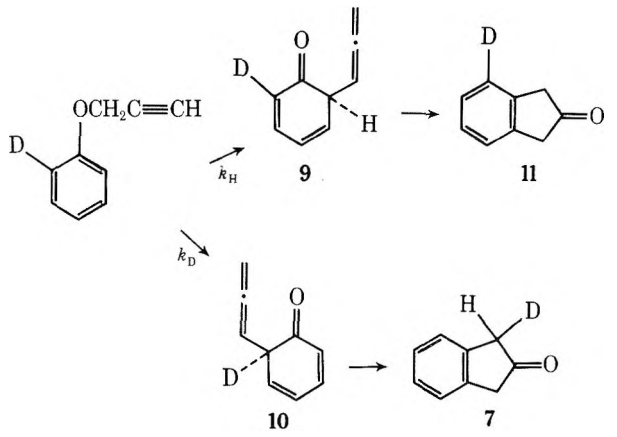
Scheme II



propargyl bromide following the same procedure used for 1.[7] The NMR analysis of 8 revealed 85% deuteration at the desired position. Flash vacuum pyrolysis of 8 was carried out under the same experimental conditions employed for 6. The NMR spectrum of the deuterated 2-indanones derived from 8 gave an integration ratio, obtained from at least ten integrations of aromatic/nonaromatic protons, corresponding to an intramolecular deuterium kinetic isotope effect of $k_H/k_D = 1.00 \pm 0.01$. Such a value of k_H/k_D indicates that the ortho C–H and C–D bonds in 8 are undergoing negligible or no force constant changes in going into the rate-determining transition state. Thus the observed k_H/k_D could be best accommodated by assuming that at the rate-determining transition state the oxygen–propargylic carbon (α carbon) bond in 1 is stretched in advance of any significant bond formation between the terminal acetylenic carbon (γ carbon) and the reacting ortho position. Therefore, the Claisen type rearrangement of 1 could be classified as a nonsynchronous process in accordance with Dewar's conclusion.[4]

Attempts to determine the magnitude of the intramolecular k_H/k_D in the Claisen rearrangement of allyl 2-deuteriophenyl ether, at 200–220 °C in a sealed ampule, leads to some discrepancy in the magnitude of the k_H/k_D. This is due to deuterium exchange[13] caused by the resulting phenol under such experimental conditions.

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(8) The apparatus consists of a chair-like tube made of Vycor glass (i.d. 2.2 cm, length 80 cm). The horizontal part is wrapped first with an asbestos tap, then a heating wire made of nickel–chromium, and finally a second asbestos tap giving a heating zone of about 33 cm. Temperature control was carried out by means of a variac. Inside temperature was measured by means of a thermocouple.
(9) 2-Deuteriophenol was prepared from the cleavage[10] of 2-deuterioanisole by ethylmagnesium bromide. 2-Deuterioanisole was prepared from the treatment of the Grignard complex of 2-bromoanisole[11] with deuterium oxide.
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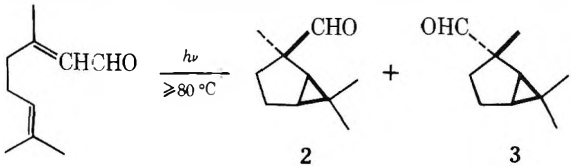
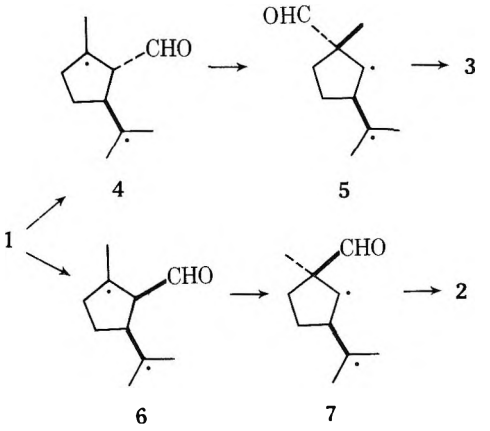
Triplet-Sensitized Photochemical Rearrangement of Geranonitrile at Elevated Temperature

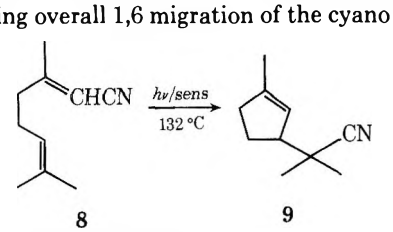
Summary: Photolysis of geranonitrile (8) at 132 °C furnishes 9 in a rearrangement that is not observed at 30 or 80 °C. This novel transformation can be rationalized through 1,3 shift of the cyano group in a biradical intermediate as shown in Scheme II.

Sir: We recently reported the novel photochemical rearrangement of citral (1) at 80–190 °C to form bicyclic aldehydes 2 and 3, products not seen at 30 °C;[1] we noted that these reactions could be accounted for by way of the biradical mechanism of Scheme I, but that other pathways, including concerted $[_\pi 2_s + _\pi 2_s + _\sigma 2_a]$ processes, were possible. In exploring this matter further we have examined the photochemical behavior of the closely related geranonitrile (8) at elevated temperature. We describe here the temperature-dependent photochemical isomerization of 8 to 9 in a process that may be mechanistically related to isomerization of citral to 2 and 3, but that provides an example of a new type of rearrangement requiring overall 1,6 migration of the cyano group.



Scheme I





In agreement with earlier observations we found that the triplet-sensitized photolysis of 8 in acetone as solvent at 30 °C gave as the only volatile products a ~4:1 mixture of the [2 + 2] cycloadducts 10 and 11.[2] We obtained similar results with propiophenone as sensitizer in either benzene or chlorobenzene at 30 °C and in benzene at reflux (80 °C). However, at 132

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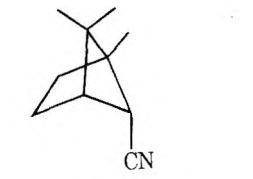

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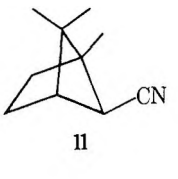

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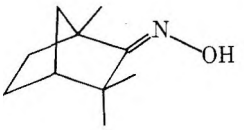

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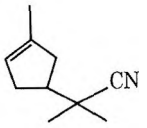
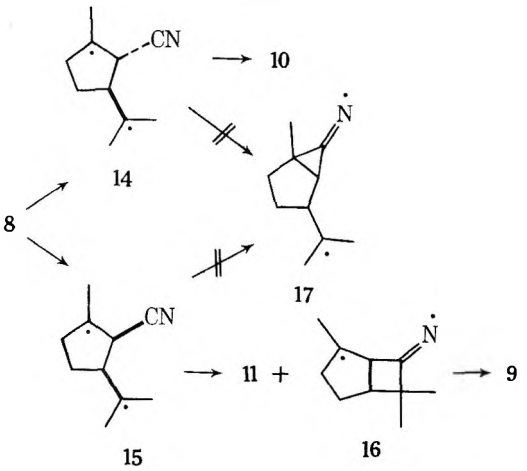


13

°C in refluxing chlorobenzene the propiophenone-sensitized irradiation of 8 furnished a volatile product consisting of **9** (60%), **10** (30%), and **11** (10%). All photolyses in which chlorobenzene was solvent were carried out with solid sodium bicarbonate added to the reaction mixture to prevent the possible accumulation of hydrogen chloride. In all experiments interconversion of the cis and trans isomers of geranonitrile (8) was rapid relative to other reactions, and a considerable amount of polymer was formed. The volatile products were isolated and purified by preparative vapor-phase chromatography, and **9** was tentatively identified on the basis of its spectroscopic properties[3] and the mechanistic considerations discussed below. This assignment was confirmed by comparison of the new photoproduct with an authentic sample of **9** prepared by the known acid-catalyzed Beckmann fragmentation of α-fenchone oxime (**12**).[4]

A stepwise mechanism for formation of **9, 10,** and **11** from 8 is shown in Scheme II. This involves interaction of the double bonds of 8 to furnish biradicals **14** and **15,** parallel to the suggested formation of 4 and 6 in Scheme I.[5] Closure of **15** to the bicyclic iminium species **16** and subsequent cleavage of the cyclobutane ring in the opposite sense could then furnish **9**. Presumably this cyclization and rearrangement would not be possible in **14** because of the trans stereochemistry of the substituents. The postulated formation of **16** has reasonable precedent in intermediates discussed by other investigators for several 1,4 transfers of a cyano group in radical reactions.[6,7] In one of these earlier cases a labeling study has shown this transfer specifically to be an intramolecular rearrangement.[7] We are unaware, however, of any previous report of the *1,3* transfer of a cyano group in a free-radical process. If the mechanisms of Schemes I and II are valid, irradiation of 1 and 8 leads to analogous biradicals, but in the case of 1 the observed rearrangements entail a 1,2 migration of the formyl group, while in 8 the cyano group undergoes only a 1,3 shift.

Scheme II



One possible factor contributing to the observed specificity of rearrangement of the nitrile may be that a 1,2 shift in **14** or **15** would require an intermediate (see **17**) with an sp^2-hybridized carbon atom in a strained three-membered ring. A similar intermediate in the rearrangement of 4 to **5,** and of **6** to **7,** would have only sp^3 carbons in the cyclopropane ring.

The present work then provides a second novel type of photochemical rearrangement that can compete with [2 + 2] cycloaddition at elevated temperature, and that can be rationalized through a biradical intermediate of the sort generally implicated[8] in such cycloadditions. We are continuing our search for additional examples of such processes.[9]

References and Notes

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(3) Spectroscopic data for 9 and **13** in CCl_4 follow. For **9:** IR 3048 (m), 2977 (s), 2940 (s), 2875 (s), 2850 (s), 2240 (m), 1655 (m), 1467 (s), 1451 (s), 1435 (s), 1382 (s), 1374 (m), 1367 (s), 977 (m) cm^{-1}; NMR (60 MHz) δ 5.24 (m, 1 H), 2.72 (br m, 1 h), 2.57–1.88 (m, 4 H), 1.78 (m, 3 H), 1.28 (s, 6 H). For **13:** IR 3045 (m), 2975 (s), 2930 (s), 2840 (s), 2235 (m), 1658 (w), 1468 (s), 1432 (s), 1380 (s), 1372 (m), 1362 (s), 1010 (m) cm^{-1}; NMR (60 MHz) δ 5.22 (m, 1 H), 2.30 (br s, 5 H), 1.72 (br s, 3 H), 1.33 (s, 6 H).
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(9) This investigation was supported by the National Science Foundation through Grant CHE74-21436. We thank Dr. W. I. Taylor, International Flavors and Fragrances, Inc., for a generous gift of geranonitrile.

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Poitediol, a New Nonisoprenoid Sesquiterpene Diol from the Marine Alga *Laurencia poitei*

Summary: A new sesquiterpenoid diol, poitediol (1), has been isolated from ethanol extracts of the red seaweed *Laurencia poitei* (Lamouroux) Howe. The structure of poitediol, as determined by X-ray crystallography, is composed of an unprecedented and nonisoprenoid bicyclo[6.3.0]undecane skeleton.

Sir: Red seaweeds of the genus *Laurencia* are known to produce regular terpenoids which contain halogens.[1] Brominated compounds are more commonly observed, but many chlorinated examples are known. Structurally these compounds appear to be the products of a bromonium ion induced cyclization of acyclic precursors.[2] We wish to report here the structure of an unusual *Laurencia* metabolite, poitediol (1), which contains neither the expected halogen substituents nor regular sesquiterpenoid structure characteristic of metabolites from this source. Recent investigations indicate that halogen solvolysis and concomitant rearrangement may be the

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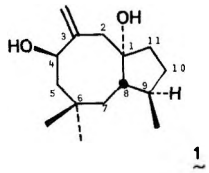

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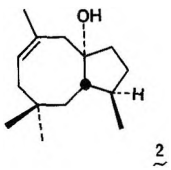

2

mechanistic pathway for the production of these nonisoprenoid metabolites.[3]

Standard column chromatography of the $CHCl_3$–ethanol extract of *L. poitei* (Lamouroux) Howe,[4] followed by extensive LC on μ-Porasil, gave poitediol (**1**) and dactylol (**2**), in addition to several other nonhalogenated sesquiterpenoids. Details of isolation and purification are included as Supplementary Material. Dactylol (**2**) has been recently isolated from the digestive glands of the herbivorous marine opisthobranch mollusc *Aplysia dactylomela*.[5] In view of the isolation of dactylol from this seaweed source, it seems likely that Aplysia concentrates this metabolite while grazing on *L. Poitei* or a related *Laurencia* species.

Poitediol (**1**), $[\alpha]_D$ −62.6° (*c* 4.3, $CHCl_3$), isolated finally as a very low melting solid, mp ~40 °C, showed only an $M^+ - H_2O$ fragment in its mass spectrum, but could be assigned the molecular composition $C_{15}H_{26}O_2$ by elemental analysis. Acetylation (Ac_2O/py at 25 °C) gave a monoacetate which still contained hydroxyl absorptions (3450 cm^{-1}) in its infrared spectrum, indicating that **1** is a diol composed of one secondary and one tertiary hydroxyl function. The ^1H NMR spectrum of **1** ($CDCl_3$) showed bands at δ 5.18 (d, J = 2 Hz) and 5.05 (d, J = 2 Hz) which were attributed to an *exo*-methylene constellation. A four-line pattern at δ 4.21 (J = 12, 4 Hz), which shifted to δ 5.50 in the corresponding acetate, was assignable as the secondary alcohol methine proton. Another feature of the spectrum was a two-proton singlet at δ 2.32, which was observed as an AB double doublet in the spectrum of the acetate. Three methyl bands were also observed, two of which were singlets at δ 0.94 and 0.86 and one of which was an overlapping doublet at δ 0.95. The region δ 1.2–2.1 showed complex bands which integrated for ten additional protons.

The structure of poitediol was rigorously established by X-ray crystallography. Crystals of poitediol belong to the chiral, monoclinic space group $P2_1$ with a = 9.412 (6), b = 17.489 (8), c = 9.721 (3) Å, and β = 114.69 (4)°. A calculated and measured density of 1.09 g/cm^3 (Z = 4) indicated that *two molecules of* $C_{15}H_{26}O_2$ *formed the asymmetric unit.* All diffraction maxima with $2\theta \leq 114.1°$ were collected on a fully automated four-circle diffractometer using graphite-monochromated Cu Kα (1.5418 Å) radiation. Data were corrected for Lorentz, polarization, and background effects and only 1290 (63%) of the 2046 reflections surveyed were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$).

The angular dependence of the reflections was eliminated as they were converted to normalized structure factors.[6] Some difficulty was experienced in finding a reasonable set of phases. Presumably this difficulty had its genesis in the poor diffracting power of the crystal, which severely limited the high angle data. A magic integer approach[7] was employed successfully. A total of 100 starting sets, each composed of 54 normalized structure factors, was expanded into phases for the 250 largest normalized structure factors. A weighted E synthesis of the best set showed 21 chemically reasonable atoms. The remaining nonhydrogen atoms were located on the subsequent F_o synthesis.[8] Full-matrix least-squares refinements with anisotropic temperature factors for carbon and oxygen and isotropic hydrogens have converged to a final, unweighted crystallographic residual of 0.05 for the observed reflections.

Figure 1 is a computer-generated perspective drawing of one of the two crystallographically independent molecules of poitediol. The two conformations were identical within experimental error and the metrical details in the following discussion are averages. Poitediol is an unusual sesquiterpene with a trans-fused bicyclo[6.3.0]undecane. The five-membered ring is in the envelope conformation with C(8) as the flap (0.615 Å removed from the plane of atoms C(1), C(11), C(10), and C(9)). The eight-membered ring does not assume any simple conformation. This may be a result of the hydrogen bonding observed in the crystal and characterized by the following short intermolecular contacts: O(17)–O(17′) (2.905 Å), O(17)–O(16′) (2.960 Å), and O(16)–O(16′) (3.010 Å). The torsional angles can be found in the Supplementary Material along with other crystallographic details. The X-ray experiment defines only the relative configuration of the molecule, which is 1*S**,4*R**,8*S**,9*R**. Molecular distances and angles are generally in agreement with accepted values.[9]

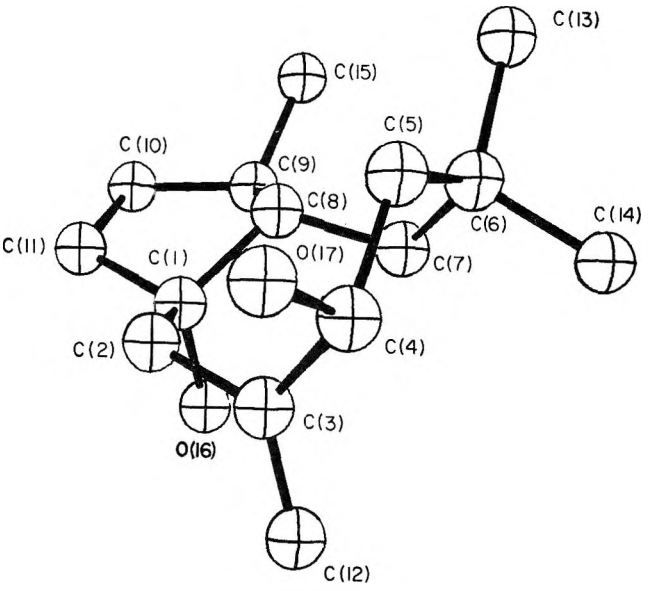

Figure 1. A computer-generated perspective drawing of one molecule from the crystal structure of poitediol.

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Supplementary Material Available: Experimental details on extraction of *Laurencia poitei*, isolation and characterization of poitediol, crystallographic information, and Tables I–III giving fractional coordinates and temperature factors, bond distances, and bond angles (10 pages). Ordering information is given on any current masthead page.

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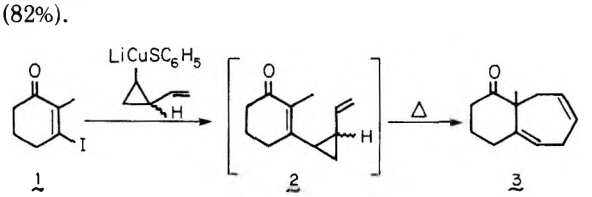
Stereoselective Preparation of Lithium Phenylthio[2,2-dimethyl-*cis*-(and -*trans*-)-3-vinylcyclopropyl]cuprates and Their Reaction with β-Iodocyclohexenones. Cope Rearrangement of 3-(2,2-Dimethyl-3-vinylcyclopropyl)-2-cyclohexen-1-ones

Summary: Lithium phenylthio[2,2-dimethyl-*cis*-(and -*trans*-)-3-vinylcyclopropyl]cuprates were prepared in a highly stereoselective fashion and were allowed to react with 3-iodo-2-cyclohexen-1-one and 3-iodo-2-methyl-2-cyclohexen-1-one. The Cope rearrangement of the resultant products [β-(2,2-dimethyl-3-vinylcyclopropyl)cyclohexenones] was investigated.

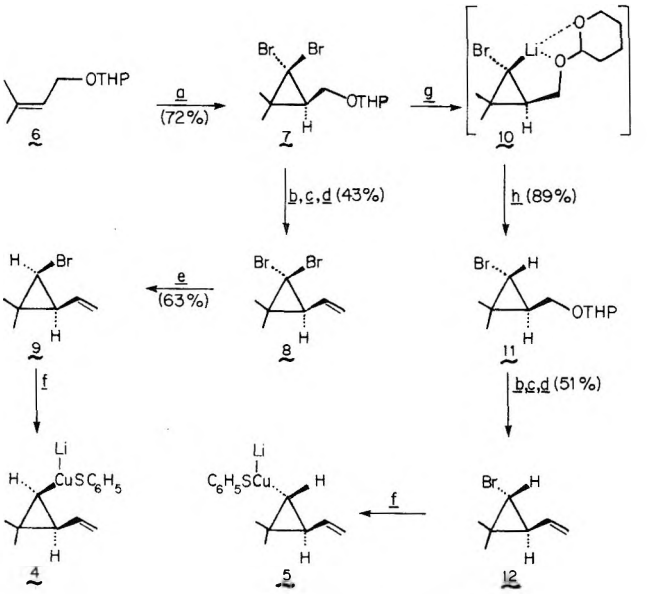
Sir: Reports concerning the results of recent studies in this[1] and other[2,3] laboratories have indicated that the Cope rearrangement of β-(2-vinylcyclopropyl)-α,β-unsaturated ketones could be a reaction of considerable synthetic utility. Our work[1] involved the preparation of the required substrates by reaction of β-iodo enones with suitable cyclopropylcuprate reagents. For example, treatment of 3-iodo-2-methyl-2-cyclohexen-1-one (**1**) with lithium phenylthio(2-vinylcyclopropyl)cuprate (mixture of epimers), followed by thermal rearrangement of the initially formed products **2**, afforded the bicyclic dienone **3** (82%).



1 **2** **3**

In order to study the effect of structural variations on the Cope rearrangement step, and to produce rearrangement products which could serve as suitable synthetic precursors in projected natural product syntheses, we have extended this type of work to include the use of highly functionalized cyclopropylcuprate reagents. We report herein (a) the *stereoselective* preparation of lithium phenylthio[2,2-dimethyl-*cis*-(and -*trans*-)-3-vinylcyclopropyl]cuprates (**4** and **5**, respectively), (b) the reaction of these reagents with the β-iodo enones **1** and **13** to give the corresponding β-(2,2-dimethyl-3-vinylcyclopropyl)cyclohexenones, and (c) the thermal rearrangement of the latter compounds. In connection with the last item, we have found that the Cope rearrangement of 2-methyl-3-(2,2-dimethyl-*cis*-3-vinylcyclopropyl)-2-cyclohexen-1-one (**17**) is a remarkably sluggish reaction, particularly when compared with the facile rearrangement of structurally very similar compounds (e.g., **2**, **14**).

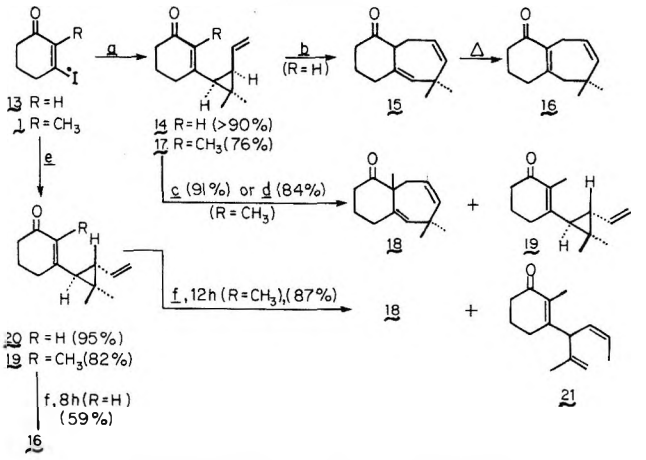
Scheme I



6 7 10 9 8 11 4 5 12

[a] $CHBr_3$, NaOH–H_2O, $C_6H_5CH_2N^+Et_3Cl^-$. [b] HCl–H_2O–MeOH, room temp. [c] $C_5H_5NCrO_3HCl$, CH_2Cl_2. [d] $(C_6H_5)_3P{=}CH_2$, THF, room temp. [e] Zn, HOAc, room temp. [f] *t*-BuLi (2 equiv), 10:1 Et_2O–THF, −90 °C; C_6H_5SCu, −20 °C. [g] *n*-BuLi, Et_2O, −90 °C. [h] CH_3OH, Et_2O.

Scheme II



[a] **4** (1.5 equiv), Et_2O–THF, room temp. [b] See text. [c] Refluxing o-dichlorobenzene, 3 h. [d] Refluxing *o*-xylene, 48 h. [e] **5** (1.5 equiv), Et_2O–THF, room temp. [f] o-Dichlorobenzene, sealed tube, 220 °C.

The starting material for the synthesis of the two cuprate reagents **4** and **5** was the tetrahydropyranyl ether of 3-methyl-2-buten-1-ol (**6**)[4] and the reactions involved are summarized in Scheme I. Of particular note in these syntheses was the high stereoselectivity associated with each of the transformations **8** → **9**[5] and **7** → **11**.[6] In the former conversion, it was presumably steric factors which were primarily responsible for the preferential reductive removal of the less hindered bromine atom (cis to CH_3 and H, trans to CH_3 and $CH{=}CH_2$). On the other hand, the exchange reaction (step g) employed in the conversion of **7** into **11** was expected to involve the bromine atom which was cis to the CH_2OTHP moiety. Protonation of the stabilized intermediate (cf. **10**) thus formed would afford **11**.

The ^1H NMR spectra of the two epimeric compounds **9** and **12** fully corroborated the stereochemical assignments. In **9** the proton adjacent to the bromine atom appeared as a doublet (δ 3.02) with a coupling constant of 8 Hz, while the corresponding proton in **12** gave rise to a doublet (δ 2.78) with J =

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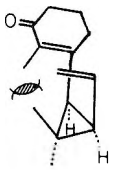
4 Hz. Since it is well known[7] that coupling constants associated with *cis*-vicinal protons on cyclopropane systems are larger than those related to trans protons, the stereochemical assignments appeared to be secure.

In spite of the fact that the copper-bearing carbon atom of the cis cuprate **4** appears to be quite hindered, this reagent reacted smoothly with the iodo enones **13**[8] and **1**[8] to afford the substitution products **14** and **17**, respectively (see Scheme II). Although the former product **14** could be isolated in nearly pure form if reaction workup was carried out at or below room temperature, this compound rearranged slowly (to **15**) upon standing. When a solution of **14** in hexane (bp 69 °C) was refluxed for ~4 h, **15** could be obtained in nearly quantitative yield. If either **14** or **15** was briefly heated (110 °C, neat) and then distilled under reduced pressure, the conjugated ketone **16** was obtained in >90% yield.

In marked contrast to **14**, the structurally similar compound **17** was extraordinarily resistant to Cope rearrangement. In fact, it was found that in this case, there was a competition between rearrangement and "simple" epimerization. For example, when a solution of **17** in *o*-dichlorobenzene (bp 179 °C) was refluxed for 3 h, there was obtained, in high yield, a mixture of two products **18** and **19** (ratio 0.8:1, respectively). In refluxing o-xylene (bp 144 °C), ~48 h was required for complete disappearance of **17**, and the two products **18** and **19** were obtained in a ratio of 2.7:1. Under both sets of conditions, the trans isomer **19** was stable.

The Cope rearrangement of *cis*-divinylcyclopropane systems has been proposed[9] to proceed via a boatlike transition state in which the vinyl groups are folded back over the three-membered ring. Molecular models clearly show that if such a geometric arrangement is to be achieved in the case of **17**, there is introduced a severe steric interaction between the vinyl methyl group and the *cis*-methyl group on the cyclopropane ring (cf. **17a**). This type of interaction is not involved in the rearrangement of **2** and **14** and it is thus possible to rationalize, in a qualitative way, the striking difference in reactivity of **17** vs. **2** and **14**.[10]



17a

Treatment of the iodo enones **13** and **1** with the trans cuprate reagent **5** gave excellent yields of the substitution products **20** and **19**, respectively. Cope rearrangement of the former under conditions outlined in Scheme II afforded the annelation product **16** as the only isolable product (59% yield). Similar treatment of **19**, however, resulted mainly in a homo-[1,5]-sigmatropic hydrogen shift[11] to afford the trienone **21**. In this case, the annelation product **18** was formed in only minor amounts (ratio of **18**/**21** = 1:4).

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(4) All compounds reported herein exhibited spectral data in full accord with the assigned structures. New compounds gave satisfactory elemental analysis and/or molecular weight determinations (high-resolution mass spectrometry).
(5) The product obtained from the Zn–HOAc reduction of **8** contained **9** and **12** in a ratio of approximately 20:1, respectively. Reduction of **8** with tri-*n*-butyltin hydride gave **9** and **12** in a ratio of about 3.7:1.
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New Methods and Reagents in Organic Synthesis. 3.[1] Diethyl Phosphorocyanidate: A New Reagent for C-Acylation

Summary: Diethyl phosphorocyanidate [DEPC, $(EtO)_2P(O)CN$], in combination with triethylamine, has been proved a new efficient reagent for the direct C-acylation of active methylene compounds with carboxylic acids.

Sir: Recent publications from our laboratory have revealed that diethyl phosphorocyanidate [DEPC, $(EtO)_2P(O)CN$], in combination with triethylamine, may be used for (i) N-acylation (peptide bond formation),[2-5] (ii) S-acylation (thiol ester formation),[6] and (iii) O-acylation (esterification)[3] (eq 1–3).

$$RCO_2H \xrightarrow[Et_3N]{(EtO)_2P(O)CN} \begin{cases} \xrightarrow{R'NHR''} RCONR'R'' & (1) \\ \xrightarrow{R'SH} RCOSR' & (2) \\ \xrightarrow{R'OH} RCO_2R' & (3) \end{cases}$$

We now wish to report that DEPC, together with triethylamine, may be efficiently used for the direct C-acylation of active methylene compounds with carboxylic acids as follows (eq 4).

$$RCO_2H + CH_2\begin{<}{X}{Y} \xrightarrow[Et_3N]{(EtO)_2P(O)CN} RCOCH\begin{<}{X}{Y} \qquad (4)$$

X and/or Y: electron-withdrawing group

In the usual base-catalyzed C-acylation of active methylene compounds,[7] carboxylic acids should first be converted to their activated derivatives such as acyl chlorides, acyl cyanides,[8,9] acyl azides,[10,11] mixed anhydrides,[12] carboxylic esters, and so on. Very few methods are concerned with the C-acylation by the direct use of carboxylic acids without prior isolation of active intermediates. Using DEPC in the presence of triethylamine, however, the direct C-acylation[13] of active methylene compounds with carboxylic acids easily occurs in a single operation under exceptionally mild conditions.

The preferred procedure is as follows. To a mixture of the carboxylic acid (1.2 equiv) and the active methylene compound (1 equiv) in dimethylformamide is added DEPC (1.2 equiv), followed by the addition of triethylamine (3.2 equiv). The mixture is stirred with ice cooling for 2 h, and then at room temperature for 20 h. After evaporation of the solvent, the residue is dissolved in benzene–ethyl acetate (1:1) and worked up with acid (10% aqueous H_2SO_4) and alkali (5% aqueous $NaHCO_3$). The crude product is purified by silica gel column chromatography and/or recrystallization. When the acylated product is an oil, it is characterized as its copper salt.

The reactions are best carried out in dimethylformamide solution, though hexane, toluene, diethyl ether, or tetrahydrofuran may be used. We preferably used triethylamine as a base, but *N,N,N',N'*-tetramethylethylenediamine, 1,5-

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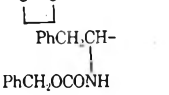
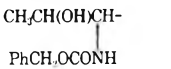
Table I

$RCO_2H + CH_2(X)(Y) \xrightarrow[\text{in DMF}]{(EtO)_2P(O)CN,\ Et_3N^a} RCOCH(X)(Y)$

R	X	Y	yield,[b] %	mp,[c] °C
Ph	CN	CO_2Et	93.4 (83)[d]	39.5–40[d]
Ph	NO_2	H	85.5 (73)[e]	106–108[e]
Ph	CN	CN	92.8 (88)[f] (87)[g]	129[f]
Ph	CO_2Et	CO_2Et	96.8[h] (68–75)[i]	(183–184)[j]
Ph	NC	Tos	80.7 (65)[k]	139–141[k]
$Ph(CH_2)_2$	CN	CO_2Et	98.4	(209–211)
n-C_5H_{11}	CN	CO_2Et	97.2	(101–102)
$CH_3CO(CH_2)_2$	CN	CO_2Et	93.4	(168–170)
$CH_3CO(CH_2)_2$	CN	CO_2Bu^t	quant	(163–164)
	CO_2Et	CO_2Et	58.1[l]	(134–136)
	CN	CO_2Et	87.8	146–148[m]
	CN	CO_2Et	63.8	128–130[n]

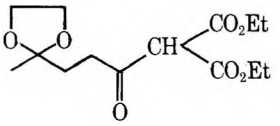
[a] Unless otherwise stated, the reactions were carried out as described in the text. [b] Yields by the reported procedures are in parentheses. [c] Melting points of copper salts are in parentheses. [d] Benzoyl cyanide was used: lit.[8] mp 41 °C. [e] Benzoyl cyanide was used: lit.[8] mp 105–106 °C. [f] Benzoyl cyanide was used: lit.[8] mp 129–130 °C. [g] Benzazide was used.[10] [h] Sodium hydride was used in place of triethylamine. [i] The mixed anhydride from benzoic acid and ethyl chlorocarbonate was used.[12] [j] Lit. mp 182 °C: D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957). [k] Benzoyl chloride was used. The isolated product was 5-phenyl-4-tosyloxazole. Lit. mp 142–143 °C: A. M. van Leusen, B. F. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, 2369 (1972). [l] Sodium hydride (2 equiv) and 1,5-diazabicyclo[5.4.0]undec-5-ene (2 equiv) were used in place of triethylamine. [m] $[\alpha]^{23}_D$ +37.1° (*c* 0.9, benzene). [n] $[\alpha]^{23}_D$ +38.2° (*c* 0.99, chloroform).

diazabicyclo[5.4.0]undec-5-ene, sodium hydride, or potassium carbonate can be used with similar efficiency. Three equivalents of the base are indispensable, because 2 equiv are used for the activation of both the carboxylic acid and the active methylene compound and 1 equiv for the salt formation of the acylated product.

The scope of the new C-acylation procedure is shown in Table I.[14] Benzoic acid efficiently coupled with various active methylene compounds, e.g., ethyl cyanoacetate, nitromethane, malononitrile, diethyl malonate, and tosylmethyl isocyanide. In the case of benzoylation of diethyl malonate, the use of sodium hydride in place of triethylamine gave a better result. Compared with the known method using activated forms of benzoic acid, the present method is more convenient to perform and gives benzoylated products in much higher yields under mild reaction conditions, as shown in Table I.

3-Phenylpropionic acid and hexanoic acid caused no trouble to couple with ethyl cyanoacetate. Levulinic acid which contains γ-keto function smoothly reacted with cyanoacetates to give the corresponding C-acylated products in excellent yields. The ethylene ketal derivative of levulinic acid also coupled with diethyl malonate to yield the C-acylated product **1**, which was easily converted to the 1,4-diketone[15] **2** by the successive treatment with (i) allyl iodide in the presence of tetra-*n*-butylammonium hydroxide,[16] (ii) sodium chloride in hot wet dimethyl sulfoxide,[17] and (iii) methanolic hydrogen chloride.

Another interesting example of the C-acylation is the coupling of ethyl cyanoacetate with two N-protected derivatives



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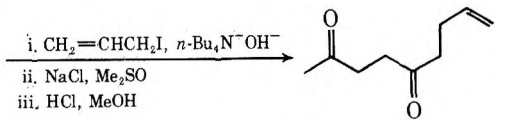

2

of α-amino acids, i.e., *N*-benzyloxycarbonyl-L-phenylalanine and -L-threonine, since the optical activities of the starting acids were retained in the products.

This direct C-acylation procedure in a single operation using DEPC appears to be quite general, may be used for many substrates containing various functions, and offers advantages over many existing methods.

Acknowledgment. We wish to thank Emeritus Professor S. Yamada and Professor K. Koga of University of Tokyo for their interests and discussions.

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(2) S. Yamada, Y. Kasai, and T. Shioiri, *Tetrahedron Lett.*, 1595 (1973).
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(8) A. Dornow and H. Grabhofer, *Chem. Ber.*, **91**, 1824 (1958).
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(11) Cf: S. Sugasawa and H. Tomisawa, *Chem. Pharm. Bull.*, **3**, 32 (1955).
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(13) The real activated species of the C-acylation will be acyl phosphates and/or acyl cyanides. See ref 3.
(14) All new compounds were fully characterized by NMR and IR spectral means and elemental composition. Known compounds were identified by comparing their physical data (melting points, IR and NMR spectra) with reported ones.
(15) For the recent 1,4-diketone synthesis, see T. L. Ho, *Synth. Commun.*, **7**, 351 (1977), and references cited therein.
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(17) A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 957 (1973).

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Thallium in Organic Synthesis. 52. Oxidations of 3-(Alkoxyaryl)propionic Acids by Thallium(III) Trifluoroacetate: Synthesis of Dihydrocoumarins, Spirocyclohexadienone Lactones, and *p*-Benzoquinones[1,2]

Summary: Dihydrocoumarins, spirocyclohexadienone lactones, and *p*-benzoquinones are formed via intramolecular capture of radical cation intermediates generated from 3-(alkoxyaryl)propionic acids by oxidation with TTFA.

Sir: The products obtained from the reactions of aromatic compounds with thallium(III) trifluoroacetate (TTFA) depend on the oxidation potentials of the aromatic substrates. Arylthallium bis(trifluoro)acetates, the products of overall

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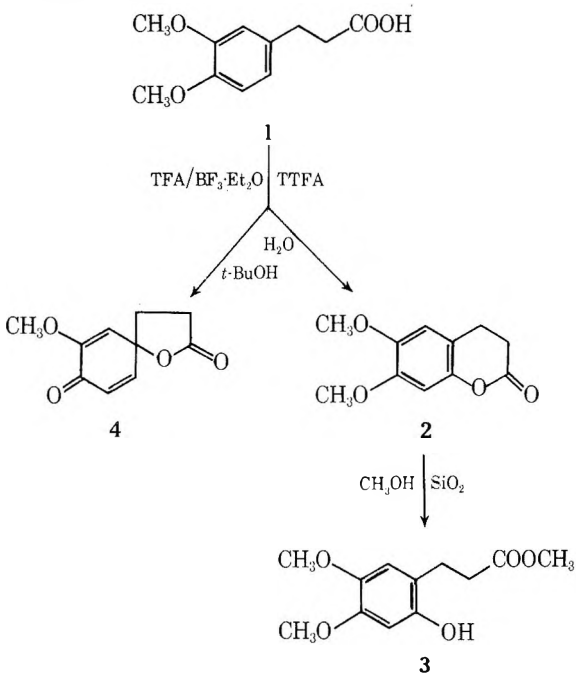
electrophilic aromatic thallation, are obtained from aromatic compounds with relatively high oxidation potentials (benzene, alkylbenzenes, halobenzenes, etc.), while biaryls, the products of overall dehydrodimerization, are obtained from aromatic compounds with lower oxidation potentials (polyalkoxybenzenes, naphthalenes, etc.). Mechanistically, biaryl formation is believed to involve electron transfer from the aromatic substrate to Tl(III), reaction of the resulting aryl radical cation with another molecule of the aromatic compound, and oxidative aromatization of the intermediate thus produced.[3]

The synthetic potential of nucleophilic aromatic substitution via radical cation intermediates is a topic of considerable current interest,[4] and we have recently demonstrated the utility of TTFA-induced *intra*molecular oxidative coupling of aromatic substrates to biaryls via radical cations for the synthesis of aporphine[5] and homoaporphine alkaloids.[6] We now demonstrate that radical cations can be trapped intramolecularly by a suitably positioned carboxyl group, and that this reaction has synthetic utility for the preparation of dihydrocoumarins, spirocyclohexadienone lactones, and *p*-benzoquinones.[7]

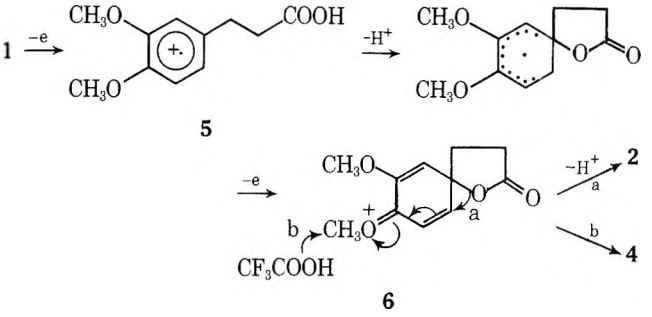
Reaction of 3-(3,4-dimethoxyphenyl)propionic acid (1) (1 mmol) with 1 equiv of TTFA in TFA (30 mL) containing boron trifluoride etherate (1 mL) was instantaneous at 0 °C. The reaction mixture was therefore quenched *immediately*[12] with water (50 mL); chloroform extraction followed by chromatography of the crude product on silica using chloroform–methanol (9:1) as eluent gave methyl 3-(2-hydroxy-4,5-dimethoxyphenyl)propionate (**3**) in 20% yield. Standard control experiments established that formation of the methyl



ester in the above sequence of operations occurred during chromatography. Quenching of the oxidation medium with methanol led directly to the ester **3**, while the use of *tert*-butyl alcohol gave a 3:1 mixture (57% yield) of the dihydrocoumarin **2** and the spirocyclohexadienone lactone **4**.[13,14]

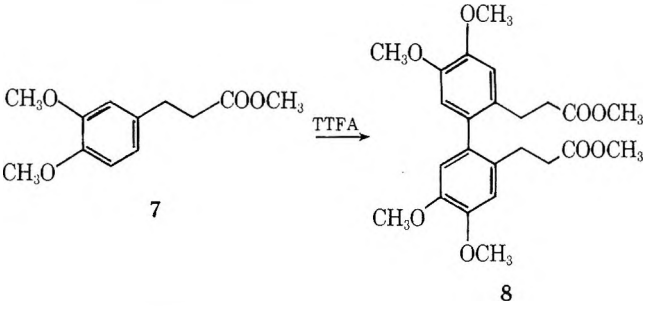
We suggest that formation of products **2**–**4** in these reactions is most easily explained on the basis of the ECE mechanism[15] outlined in Scheme I. Thus, one-electron oxidation of **1** by TTFA gives the radical cation **5**, intramolecular reaction of which with the carboxyl group gives **6**;[16] dienone–phenol type rearrangement of **6** leads to the dihydrocoumarin **2** (path a), which is either obtained as such on quenching of the reaction mixture with *tert*-butyl alcohol or is converted to the ester **3** when chloroform–methanol/silica is used. For-

Scheme I

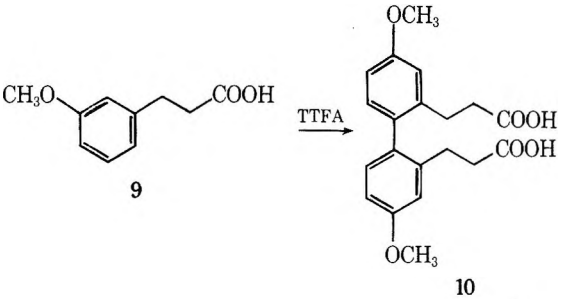


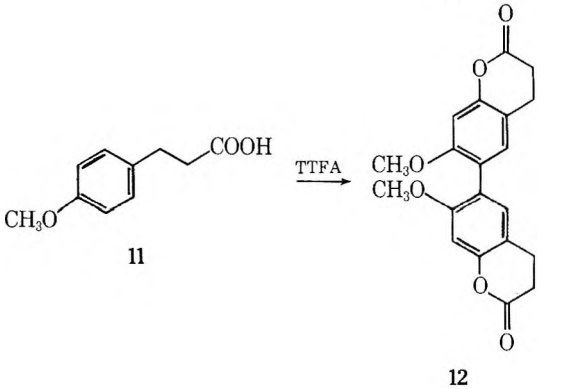
mation of the spirocyclohexadienone lactone **4** presumably arises via nucleophilic attack at the $CH_3O^+=$ methyl group by TFA (path b).

Evidence in support of the mechanism outlined in Scheme I comes from the following observations. (1) Oxidation of the methyl ester **7** with TTFA gave the biaryl **8** in 58% yield. In-



tramolecular trapping of the radical cation is clearly impossible in this case, and hence intermolecular coupling occurs. (2) Oxidation of 3-(3-methoxyphenyl)propionic acid (**9**) did not give any products of the type **2**–**4**, but only the biaryl **10** (56%). In this instance there is no mesomeric stabilization of

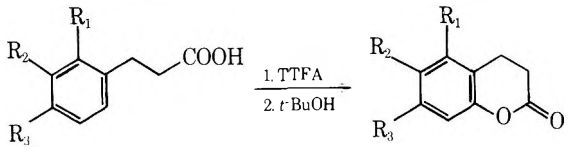




the reactive intermediates by the methoxy group, and intermolecular coupling is again the preferred pathway. (3) Oxidation of 3-(4-methoxyphenyl)propionic acid (**11**), on the other hand, resulted both in dihydrocoumarin formation and in biaryl coupling to give **12** in 24% yield.

The fate of the radical cations generated from 3-(3-alkoxyaryl)propionic acids thus appears to depend on the position

of the alkoxy substituent(s) relative to the carboxyethyl group. Substrates without a *p*-alkoxy group undergo oxidative dimerization to biaryls, whereas those with a *p*-alkoxy group[17] give dihydrocoumarins and lesser amounts of spirocyclohexadienone lactones.[18] In agreement with these conclusions, oxidation of the acids **13** with TTFA followed by quenching with *tert*-butyl alcohol gave the dihydrocoumarins **14**.

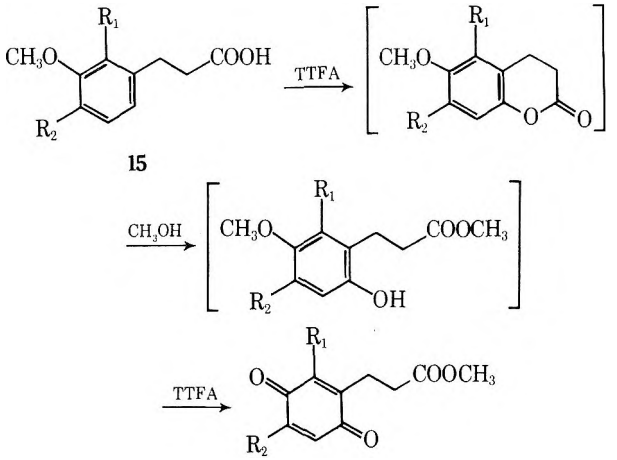


13 **14**

a, $R_1 = H$; $R_2 = R_3 = OCH_3$, 21%
b, $R_1 = R_2 = R_3 = OCH_3$, 53%

Moreover, use of methanol to quench the reaction mixture resulted in acid-catalyzed esterification and formation of a methyl 3-(2-hydroxyaryl)propionate; consequently, given that there is an alkoxy group para to the newly introduced hydroxy group and that excess TTFA is available, it is possible to effect a second, different type of oxidation.[19] Thus, treatment of the acids **15** with 2 equiv of TTFA and quenching of the reaction mixture with methanol gave the *p*-benzoquinones **16** directly (Scheme II).

Scheme II



15

16

a, $R_1 = H$; $R_2 = OCH_3$, 73%
b, $R_1 = R_2 = OCH_3$, 61%

These results clearly demonstrate that aromatic radical cations can be trapped intramolecularly by a suitably situated carboxyl group. They illustrate, moreover, that a substantial degree of control is possible over the nature of the products obtained from such intramolecular trapping reactions by variation in substrate structure, amount of oxidant employed, and the isolation procedure used. Further studies are in progress to extend and exploit these novel oxidations.

References and Notes

(1) For the previous paper in this series, see A. McKillop, D. W. Young, M. Edwards, R. P. Hug, and E. C. Taylor, *J. Org. Chem.*, in press.
(2) We are indebted to the National Science Foundation (Grant No. CHE76-16506) and to Eli Lilly & Co. for financial support of this work.
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(4) See, e.g., M. E. Kurz and G. W. Hage, *J. Org. Chem.*, **42**, 4080 (1977) and references cited therein.
(5) E. C. Taylor, J. G. Andrade, and A. McKillop, *J. Chem. Soc., Chem. Commun.*, 538 (1977).
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(7) Phenolic oxidative coupling of *p*-hydroxyarylpropionic acids to spirodienone lactones (and hence to dihydrocoumarins by rearrangement) is known,[8-11] but the only reported example of a nonphenolic oxidative coupling of this type appears to be that of Scott,[11] who employed NBS in $NaOAc/CH_3CN$ solution and obtained dibrominated products by a pathway which almost certainly does not involve radical cation intermediates.
(8) G. L. Schmir, L. A. Cohen, and B. Witkop, *J. Am. Chem. Soc.*, **81**, 2228 (1959).
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(10) H. Grisebach and W. D. Ollis, *Experientia*, **17**, 4 (1961).
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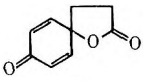
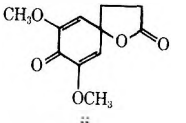
(12) It is essential that the reaction mixture be quenched immediately following completion of mixing of the reagents; otherwise complete oxidation to tarry materials occurs.
(13) Satisfactory microanalytical and spectroscopic data were obtained for all new compounds.
(14) Rearrangement of spirocylohexadienone lactones derived from *p*-hydroxyarylpropionic acids requires heating with mineral acid, often under extremely vigorous conditions. By contrast, rearrangement of **6** to **2** (see Scheme I) under our conditions occurs almost instantaneously at room temperature.
(15) J. H. P. Utley in "Essays in Chemistry", Vol. 6, J. N. Bradley, R. D. Gillard, and R. F. Hudson, Eds., Academic Press, London, 1977, p 83.
(16) It is possible that the low yield oxidative coupling of *p*-hydroxyphenylpropionic acid to the spirocyclohexadienone lactone i with peracetic acid, lead



i

tetraacetate in methanol, or by electrolysis occurs via a radical cation intermediate, but this mechanistic pathway has apparently not been considered previously for this conversion [J. S. Davies, C. H. Hassall, and J. A. Schofield, *J. Chem. Soc.*, 3126 (1964)].
(17) Oxidation of 3-(2-methoxyphenyl)propionic acid failed to give any products of the type **2–4**; starting material was recovered (~50%), and the material balance was comprised of dark-colored, resinous matter.
(18) 3-(3,4,5-Trimethoxyphenyl)propionic acid was converted almost exclusively to the spirodienone ii (37%). Trace amounts of 2,6-dimethoxy-*p*-benzo-



ii

quinone were also obtained, but no dihydrocoumarin was isolated, presumably since dienone–phenol rearrangement is considerably slower than dealkylation (cf. path b, Scheme I). Facile and selective demethylation of the 2-methoxy group of 1,2,3-trimethoxyarenes has been observed previously with both acid [A. Brossi, J. van Burick, and S. Teitel, *Helv. Chim. Acta*, **51**, 1965 (1968); A. Brossi and S. Teitel, *Org. Prep. Proced.*, **1**, 171 (1969)] and TTFA [A. S. Kende and P. S. Rutledge, *Synth. Commun.*, **8**, 245 (1978)].
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(20) On leave of absence from the University of Orange Free State, Bloemfontein, South Africa; financial assistance from the CSIR, Pretoria, is gratefully acknowledged.

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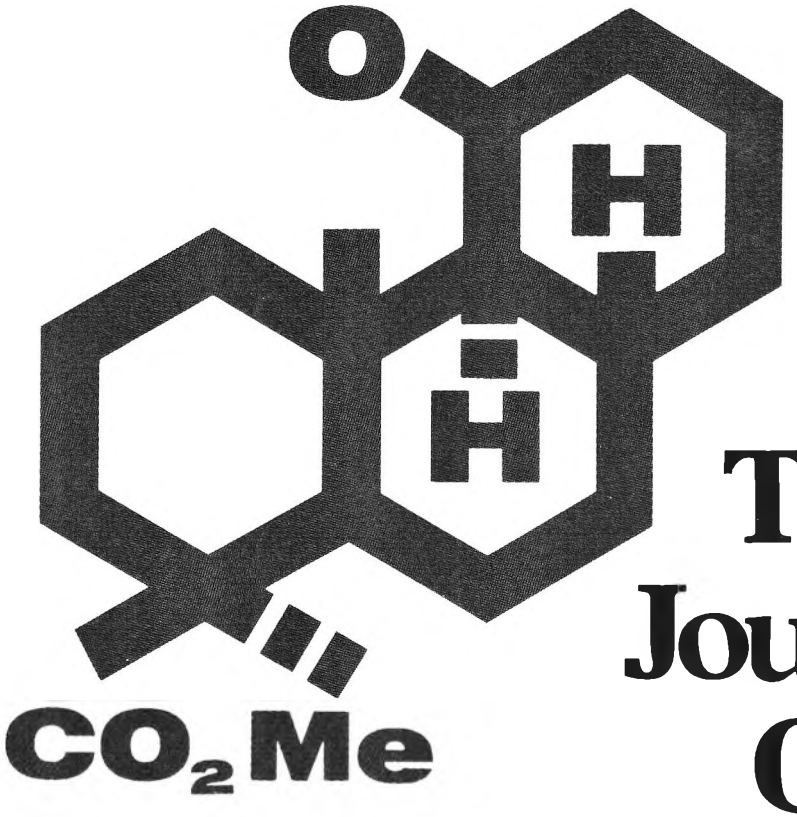

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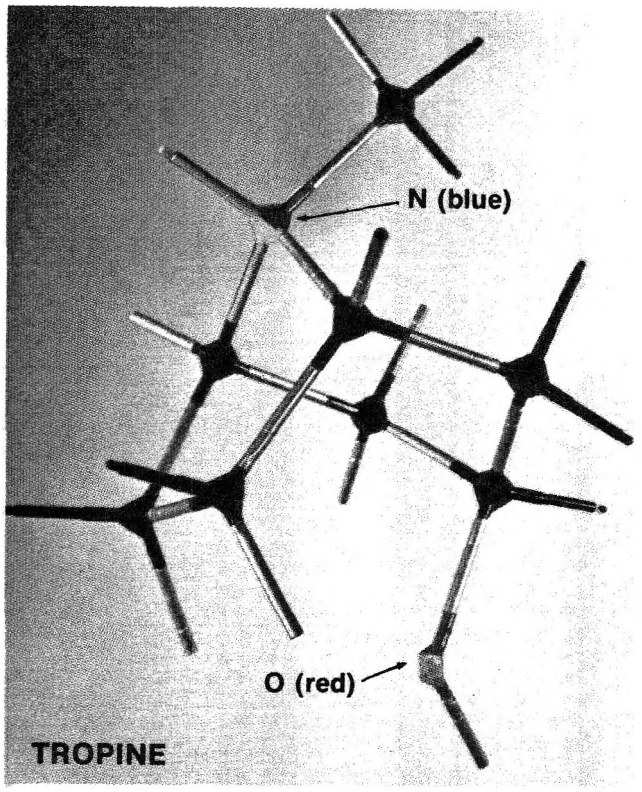

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(3) L.F. Fieser, *ibid.*, **42**, 408 (1965).
(4) L.F. Fieser, "Chemistry in Three Dimensions," Aldrich Catalog Number Z10,160-5.

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