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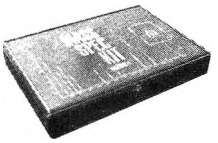

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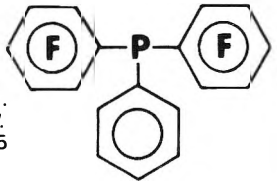

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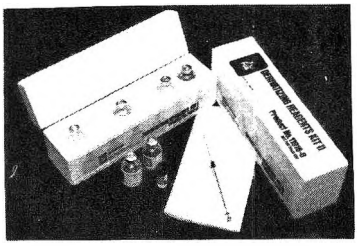

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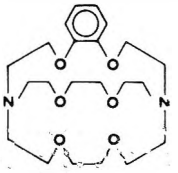

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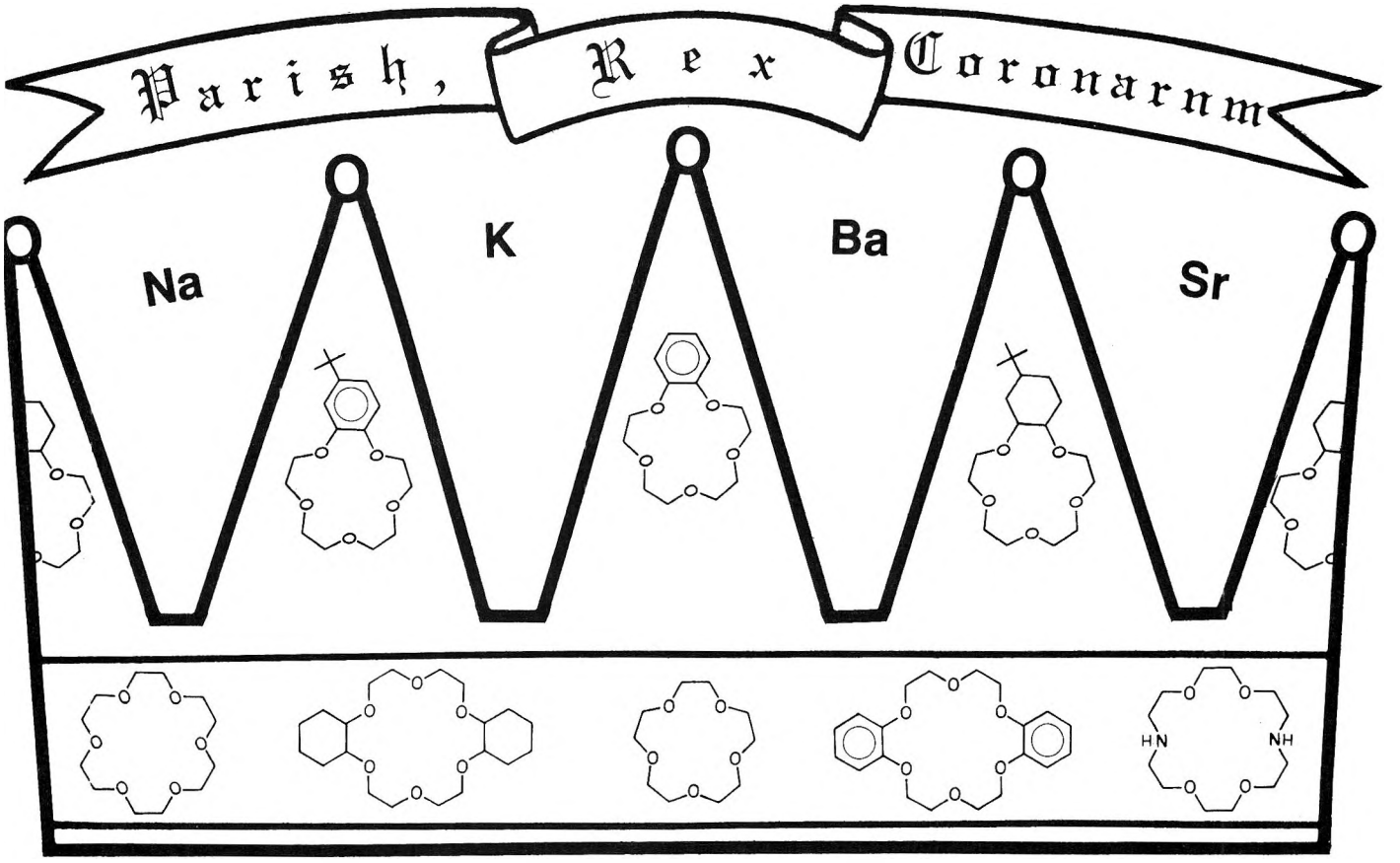

CROWN ETHERS

The crown ethers are probably some of the most fascinating compounds investigated in recent years. Their remarkable ability to form stable cation complexes, particularly with the alkali or alkaline earth cations, has led to some truly amazing chemistry.[1] Stability constants of selected cations with 18-crown-6 and 15-crown-5 at 25° in water are illustrated in table I.[2]

Table I

Ligand	$Log_{10}Ks$ for Cations									
	Na	Ks	Rb	Cs	NH_4	Ag	Sr	Ba	Pb	Tl
15 crown 5	0.70	0.74	0.62	0.8	1.71	0.94	1.95	1.71	1.85	1.23
18 crown 6	0.80	2.03	1.56	0.99	1.23	1.50	2.72	3.87	4.27	2.27

With the exception of the ammonium cation 18-crown-6 invariably forms more stable complexes than 15-crown-5. Benzo substitution on the crowns leads to more rigid structures with lower solubility and lower stability constants whereas Cyclohexo substitution generally gives increased solubility in nonpolar organics with stability constants about the same as the unsubstituted parent crown. Less polar nonaqueous solvents also give much higher stability constants than aqueous systems. Larger crown ring sizes show increased selectivity for the larger cations.

The crown ethers have shown great utility as catalysts for promoting reactions which would otherwise be impractical or impossible. A few of these reactions are illustrated below: [1]

$$CH_3(CH_2)_6CH_2OTs + KO_2 \xrightarrow{DMSO} CH_3(CH_2)_6CH_2OH \quad 75\%$$

$$CH_3(CH_2)_6CH_2Br + KF \longrightarrow CH_3(CH_2)_6CH_2F \quad 92\%$$

$$C_6H_5\text{-}CH_2\text{-}C_6H_5 \xrightarrow[benzene]{KMnO_4} C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}C_6H_5 \quad 100\%$$

The improved yields and enchanced reactivity are probably due to a combination of phenomena such as increased reagent solubility, liquid-liquid and solid-liquid phase-transfer, ligand separated ion activation, altered reagent geometry and altered conformation of the transition state or activated complex.

Potential applications exist in such exciting fields as selective decorporation of radioactive or toxic elements such as strontium, thallium and lead from living organisms[3]; models for studies of biological membranes and biological cation transport mechanisms[4]; trace metal carriers in nutrition experiments; construction of ion selective membrane electrodes[5]; studies of the solvated electron in the non-amine solutions[6]; solubilization of photosensitizing dye salts in synthetic applications[7]; solubilization of cationic and anionic dyes for tunable dye laser applications; selective concentration and separation of alkali, alkaline earth, rare earth, actinide, and lanthanide cations[8]; isotope separations; homogeneous base catalyzed polymerizations[9]; homogeneous hindered Lewis acid catalysts for polymerizations and oligimerizations; homogeneous transition metal and noble metal catalysts for oxidations, reductions and carbonylations; starting materials for novel types of drugs and pharmaceuticals[8]. Perhaps a crown ether is the answer to your research problem.

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NOTES

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DECEMBER 10, 1976

The Photochemistry of Acyclic Acetylenic Di-π-methane Systems. Syntheses of Substituted Isomeric Acetylenic Cyclopropanes[1a-c]

G. W. Griffin,* D. M. Chihal,[1d] J. Perreten, and N. S. Bhacca

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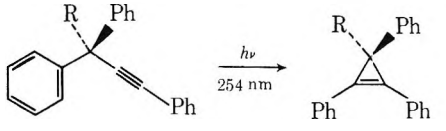
Received April 20, 1976

In this paper we describe the synthesis and photochemistry of *cis*- and *trans*-1,5-diphenyl-3-methyl-3-methoxy-1-penten-4-yne which were studied in order to assess and extend the synthetic utility and mechanistic understanding of the di-π-methane reaction. It is clear from this study that the traditional di-π-methane rearrangement involving migration of an sp^2 center to an sp^2 site may be extended to include migration of an sp bonded carbon atom to an sp^2 terminus. An intriguing aspect of the di-π-methane conversions observed is the efficiency with which the phenylacetylenic function participates as the migrating function even when a styryl moiety is available for interaction. This photoreaction provides a convenient synthesis for phenylacetylenic cyclopropanes capable of incorporating a diverse group of additional substituents. Triplet sensitized irradiation of the trans enyne substrate was utilized to obtain sufficient quantities of the cis isomer for study and is a process which competes with di-π-methane photocyclization at least in benzene. In no case where sensitizers were employed was cyclopropane formation observed which indicates that the chemically significant excited state in the formation of these di-π-methane photoproducts is singlet in character.

The di-π-methane rearrangement constitutes a basic class of photochemical transformations and extensive effort has been expended to define the scope, limitations, and synthetic utility of this interesting reaction.[2] Of late we have focused our attention on the effect of altering hybridization at various centers in both the migrating and stationary π moieties on the photochemical behavior of several di-π-methane substrates. To date examples incorporating an acetylenic sp atom at the terminus of the stationary moiety,[3] as well as an allenic group as the migrating component in the reactant,[4a-c] have been investigated in our laboratories.

Not unexpectedly, if one of the requisite pair of π bonds is incorporated in an aromatic nucleus, the di-π-methane rearrangement is restricted to migration of the aromatic ring from the sp^3 center to an acetylenic sp terminus with concomitant cyclopropene formation. For example, it was found that the direct photorearrangements of **1a** and **1b** afford the cyclopropenes **2a** and **2b** as primary photoproducts (eq 1).[3]

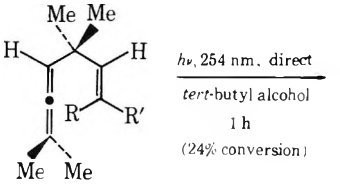


(1)

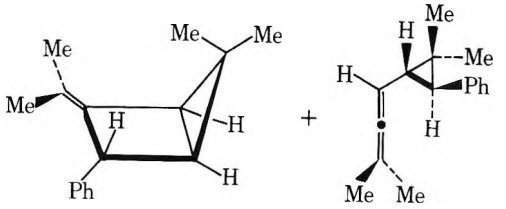
1a, R = Ph
b, R = OMe

2a, R = Ph
b, R = OMe

In parallel studies conducted concurrently with the present work we have observed that introduction of an sp hybrid center at a site within the potential migrating group may exert a pronounced effect upon the di-π-methane rearrangement. For example, with the isomeric allenes **3a** and **3b** as substrates it was possible to demonstrate that an allenic group is capable of altering the course of the reaction such that typical di-π-methane products are the minor photoproducts observed and [2 + 2] intramolecular cycloadditions dominate the reaction course.[4a-c] In this case the major photoproduct observed upon direct irradiation of the trans allene **3b** in *tert*-

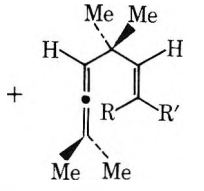


3a, R = Ph; R′ = H; Φ = 0.282
b, R = H; R′ = Ph; Φ = 0.384



4. Φ = 0.099
Φ = 0.183

5, Φ = 0.043
Φ = 0.106



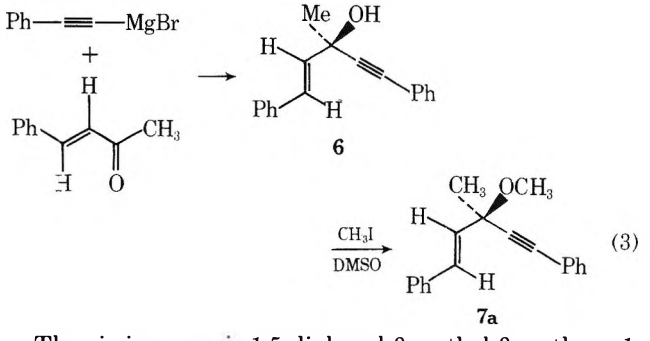
(2)

3a, R = Ph; R′ = H; Φ = 0.095
b, R = H; R′ = Ph; Φ = 0.140

butyl alcohol is the bicyclo[2.1.0]pentane **4**. The anticipated trans allenic cyclopropane **5** as well as the alternate geometric isomer **3a** are formed as minor products through competing processes. The allenic cis di-π-methane substrate **3a** was found to undergo facile cis–trans isomerization with subsequent rearrangement of the trans isomer **3b** to **4** and **5** (eq 2). The bicyclo[2.1.0]pentane was shown to be formed in a triplet photochemical process while the cyclopropane **5** is generated in a singlet excited state reaction.[4]

In the present study we wish to describe the effect of introducing a phenylethynyl group which interposes sp hybrid centers at each terminus of the potential migrating group while maintaining an sp^2 hybrid center at the probable migratory receptor site. To our knowledge the isomeric alkynes employed, *trans*- and *cis*-1,5-diphenyl-3-methyl-3-methoxy-1-penten-4-yne (**7a, 7b**), represent the first such substrates incorporating sp hybrid carbon atoms in which the anticipated cyclopropane is formed efficiently upon direct irradiation.[1a-c,2] We also desired to assess and/or reaffirm certain stereochemical aspects of the potential di-π-methane rearrangements and the isomeric acetylenes **7a** and **7b** embody the prerequisite structural features. Although it may not be possible to rely upon quantum yield data obtained for these and other substrates employed in our laboratories and by other investigators to evaluate *true* migratory aptitudes of π-substituent groups from such quantum yield data due to variations in photophysical behavior which generally accompany structural modification, the information may provide "relative migratory efficiencies" which are sufficiently invariant to provide synthetically useful yardsticks.

Synthesis and Structure of the Isomeric Allylic Acetylenes 7. The synthesis of *trans*-1,5-diphenyl-3-methyl-3-methoxy-1-penten-4-yne (**7a**) was achieved in 60% overall yield by addition of phenylethynylmagnesium bromide to benzalacetone.[5] The resulting alcohol, *trans*-1,5-diphenyl-3-methyl-1-penten-4-yn-3-ol (**6**),[6] was subsequently O-methylated with methyl iodide in dimethyl sulfoxide to give the trans enyne **7a** in high purity. The overall reaction scheme is delineated in eq 3.



The cis isomer, *cis*-1,5-diphenyl-3-methyl-3-methoxy-1-penten-4-yne (**7b**), is obtained conveniently by acetophenone sensitized photoisomerization of the trans isomer **7a**. The photoequilibrated mixture consists of approximately equimolar amounts of **7a** and **7b**.[7] Isolation of pure samples of **7b** proved a complicated and tedious task since both enynes are relatively unstable to heat, acidic conditions, and oxygen, and tend to decompose upon elution during chromatographic separations unless the special precautions outlined in the Experimental Section are exercised during the chromatographic separation and subsequent purification by bulb-to-bulb distillation.

The gross skeletal structures of **7a** and **7b** were confirmed by combustion analysis, mass spectrometry, ^1H NMR, and infrared spectroscopy. The stereochemistry of the acetylenic ethers was deduced from observed spectral properties and mode of formation. A band appearing at 970 cm^{-1} characteristic of trans 1,2-disubstituted alkenes[8] is observed in the infrared spectrum of **7a** and is absent in the spectrum of **7b**. Furthermore, trans vicinal NMR coupling constants for vinyl protons in isomeric 1,2-disubstituted alkenes are generally larger than their cis counterparts.[9] Such is the case with **7a** and **7b** where coupling constants of 15.5 and 12.0 Hz, respectively, are observed. In addition, five of the ten aromatic protons of each isomer are deshielded as would be anticipated in view of the presence of an adjacent ethynyl substituent on the ring.[10] In contrast, the signals assigned to the corresponding aromatic protons of the olefinic counterparts are found at higher field, which provides additional evidence that **7a** and **7b** are in fact enynes. Characteristic signals for the vinyl and aromatic protons are also present.

Photochemical Investigations. Direct irradiation of *trans*-1,5-diphenyl-3-methyl-3-methoxy-1-penten-4-yne (**7a**) in *tert*-butyl alcohol at 254 nm for 30 min affords two main photoproducts, *r*-1-methoxy-1-methyl-*t*-2-phenyl-*c*-3-phenylethynylcyclopropane (**8**) and *r*-1-methoxy-1-methyl-*c*-2-phenyl-*t*-3-phenylethynylcyclopropane (**9**), in a 2:1 ratio, respectively (eq 4).[11] Quantum yield experiments employing potassium ferrioxalate actinometry were performed on **7a** in *tert*-butyl alcohol at 254 nm and gave quantum yields (average

Scheme I

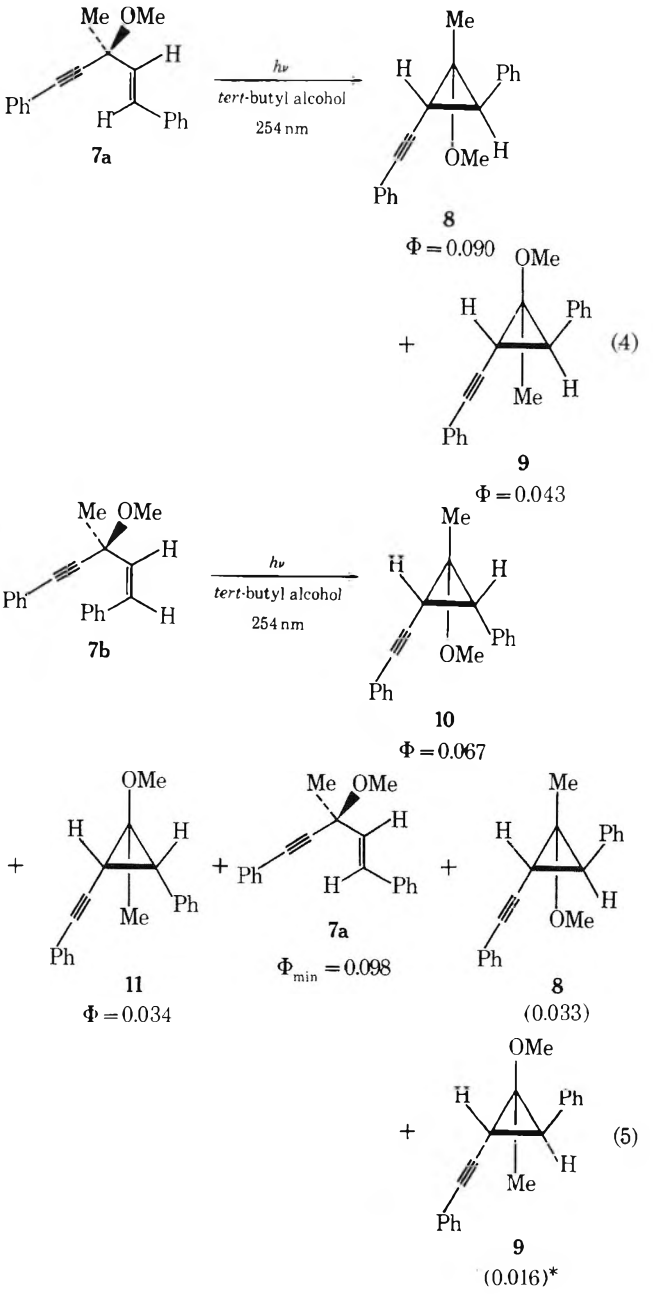
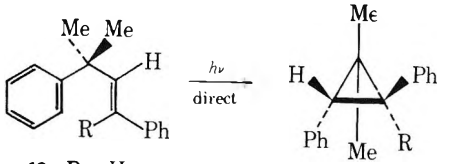


Table I. Results of Direct Irradiations of 7a and 7b[a,b]

Compd irradiated	Solvent	Concn, mol/l.	Time, h	% conversion	% composition 7a	7b	8	9	10	11
7a	*tert*-Butyl alcohol	0.045	0.5	9.0	91.0	0.0	6.1	2.9	0.0	0.0
7a	Benzene	0.038	0.5	35.6	64.4	3.5	18.8	9.6	3.8	Trace
7b	*tert*-Butyl alcohol	0.041	0.5	18.5	6.9	81.5	2.6	1.2	5.2	2.6
7b	Benzene	0.040	0.5	32.7	21.6	67.3	3.4	1.6	3.6	2.4
7b	Acetonitrile	0.037	0.5	41.3	20.6	58.7	5.8	2.6	6.9	5.4

[a] Direct irradiations were conducted at 254 nm. [b] Product ratios were determined by NMR.

of four runs) for 8 and 9 of 0.090 and 0.043, respectively.[12] The quantum yield values determined for the photoproducts obtained from **7a** upon direct irradiation in *tert*-butyl alcohol are tabulated in Scheme I. The quantum yield for the rearrangement of an external reference, namely 1,1,3-triphenyl-3,3-dimethyl-1-propene (**12b**),[13a] was determined under conditions identical with those employed with **3a, 3b, 7a,** and **7b** in order to ensure that the quantum yield measurements on **8, 9, 10,** and **11** are consistent with those values reported by Zimmerman and co-workers for other di-π-methane systems. Our values determined for 1,1,3-triphenyl-3,3-dimethyl-1-propene (**12b**) compare favorably with that obtained by Zimmerman (Φ = 0.036) (eq 6).[13b]



(6)

12a, R = H
b, R = Ph

13a, $\Phi = 0.42$[13b]
b, $\Phi = 0.0356$[13a]

Direct irradiation of the alternate geometric isomer **7b,** namely *cis*-1,5-diphenyl-3-methyl-3-methoxy-1-penten-4-yne, under essentially identical conditions gives *r*-1-methoxy-1-methyl-*c*-2-phenyl-c-3-phenylethynylcyclopropane (**10**) and *r*-1-methoxy-1-methyl-*t*-2-phenyl-*t*-3-phenylethynylcyclopropane (**11**) in a 2:1 ratio, respectively; however, in contrast to the irradiation of the trans enyne **7a,** lesser amounts of **7a, 8,** and **9** are observed as photoproducts of **7b** (eq 5). That photoisomerization of **7b** to **7a** is a competing process in this case is evident from the product distribution as well as quantum yield data. Subsequent rearrangement of the trans isomer **7a** accounts for the presence of the trans cyclopropanes **8** and **9** among the photoproducts obtained from **7b.** No corresponding photoisomerization of **7a** to **7b** in *tert*-butyl alcohol is detectable, although such is not the case in benzene where competing cis–trans photoequilibration is observed. Quantum yield measurements performed by methods identical with those used with **7a** were conducted on **7b.**[12] The averages of four repetitive quantum yield determinations for the formation of **10, 11,** and **7a** are 0.067, 0.034, and 0.098, respectively. Reliable quantum yield data were not obtained on **8** and **9** since these are secondary photoproducts. The value cited for **7a** represents a minimum value since it is undoubtedly depleted as formed to give **8** and **9.** The values based on direct formation from **7b** were monitored and are cited for reference purposes only to provide some idea of the magnitude of partitioning between **7b** and **7a** in the event that the photoreaction is perhaps used synthetically and a knowledge of by-product formation becomes significant. For convenience a complete summary of the photoproducts obtained from **7b** in *tert*-butyl alcohol in addition to the photochemistry described for this isomer are depicted in Scheme I (eq 4 and 5) along with the aforementioned quantum yield data. The product distribution results obtained on direct photolyses of **7a** and **7b** in *tert*-butyl alcohol and other solvents are summarized in Table I.

Only trans–cis photoisomerization was found to occur upon irradiation of **7a** at 350 nm for 12 h in the presence of the sensitizer acetophenone. This photoequilibration leads to an essentially equimolar mixture of **7a** and **7b.** The equilibrium mixture may be approached by irradiating **7b** under similar conditions. Although the triplet energy of acetone is substantially higher than that of acetophenone and that photoisomerization occurs with the latter sensitizer, the equilibration is incomplete even after 20 h at which time **7a** predominates by a factor of 3:1. This difference in sensitizer efficiency is reasonably attributed to the differential absorption coefficients of the two ketones at 350 nm. Of primary significance is the fact that in no case where sensitizers were employed was cyclopropane formation observed from either **7a** or **7b** which indicates that the chemically significant excited state in the formation of these di-π-methane photoproducts, namely **8, 9, 10,** and **11,** is singlet in character.

Structure of the Photoproducts. The set of acetylenic methoxycyclopropanes **8, 9, 10,** and **11,** which like their precursor pair **7a** and **7b** are highly unstable, were isolated using procedures similar to those employed in the isolation of the latter. The structures of **8, 9, 10,** and **11** were established using 100-MHz NMR, ir, and appropriate NOE spectral data. Combustion analytical and mass spectrometric data confirm that the cyclopropanes are isomeric with the precursor acetylenes **7a** and **7b.** An infrared absorption band in the region of 2250 cm^{-1} in each product attests to the fact that the acetylenic moiety is retained. Additional support for the retention of the acetylenic group is apparent from the NMR spectrum of the cyclopropanes. The chemical shift observed for five aromatic protons in each of the isomeric cyclopropanes provides additional evidence that the phenylethynyl moiety is preserved.[10] In addition, the chemical shift for the remaining five aromatic protons is normal. Furthermore, it is evident from the disappearance of the two olefinic proton doublets and the emergence of the AB doublet of doublets in the NMR spectra of the photoproducts that the photoreaction involves conversion of **7a** and **7b** to isomeric cyclopropanes at the expense of the styryl group rather than the phenylethynyl group. Differentation of the cis and trans isomeric cyclopropanes was achieved on the basis of the magnitude of vicinal spin-spin interactions of the cyclopropyl protons. Since J_{cis}(6.5–12.0 Hz) is larger than J_{trans}(3.5–8.5 Hz) in such systems the magnitude of the vicinal proton coupling in **10** (11.0 Hz) and **11** (9.5 Hz) attests to their cis geometry.[14,15] Correspondingly, trans configurations were assigned to **8** and **9** on the basis of the vicinal coupling observed for both isomers (6.5 Hz).

Our conclusions regarding the stereochemistry of **8, 9, 10,** and **11** are based on the long-range anisotropic shielding and deshielding effects induced by the phenyl ring, the acetylenic bond, the oxygen of the methoxy group, and the methyl substituent. The results of this self-consistent correlation are depicted graphically in Figure 1 with the relevant peaks

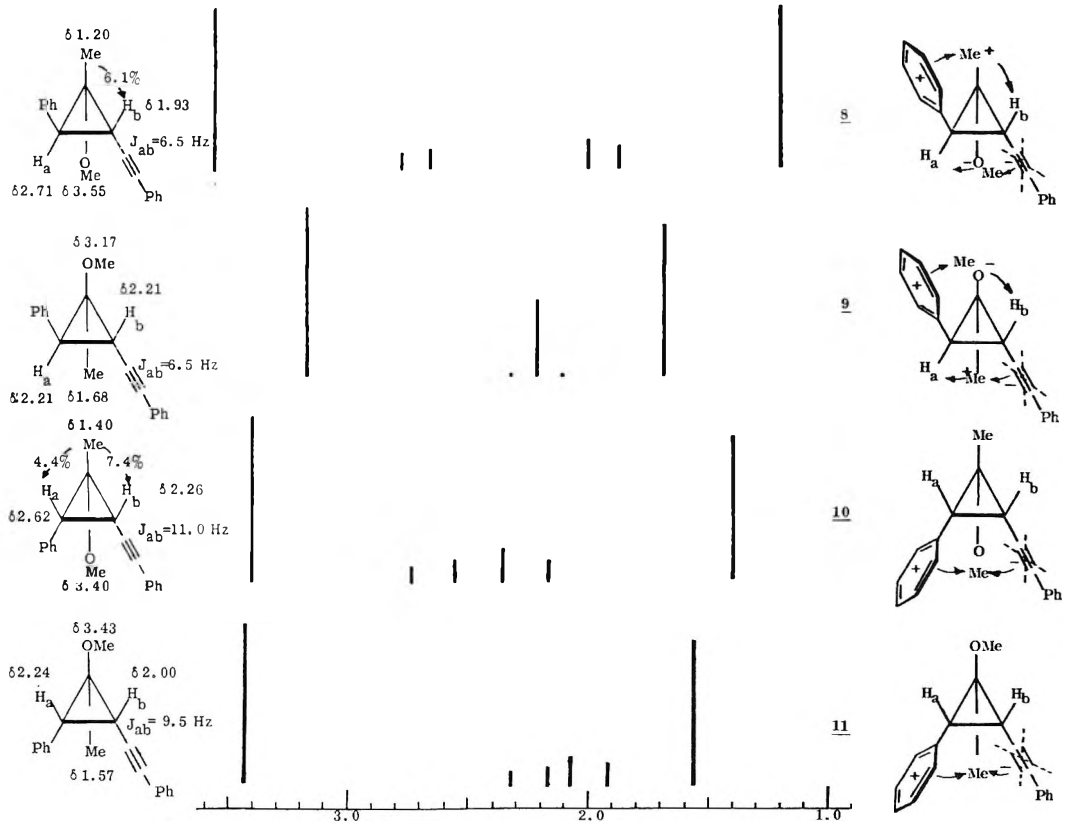


Figure 1.

plotted to assist the reader in analyzing those spectra where minor impurities are present since they were obtained at a time when we had not achieved sample purification levels ultimately required and reached for combustion analysis on these highly unstable compounds. The respective structures presented alongside the NMR traces are labeled to indicate the significant interaction responsible for the anisotropic shifts employed in the analysis as well as NOE results to be discussed later. The NMR signals for the corresponding protons of the four cyclopropanes may be compared readily by reference to Figure 1. The methoxy signal in **8** is deshielded (δ 3.55) by the acetylenic bond. The shifts observed for the methoxy signals of **10** and **11** do not vary greatly from the values observed for those groups in the precursor substrates. In **10** the deshielding effect of the acetylenic bond on the methoxy protons is compensated by the shielding experienced due to the phenyl ring giving rise to a signal at δ 3.40. The methoxy group in the cyclopropane **11** is trans to both the acetylenic bond and phenyl ring and thus is not significantly affected by either and the NMR signal appears at δ 3.43. The methyl groups of the cyclopropanes **8, 9, 10,** and **11** are affected in a manner corresponding to that observed for the methoxy substituents. A shielding effect is exerted on the methyl group of **8** by the aryl substituent and the NMR signal appears at δ 1.20; however, the opposite is true in the case of the methyl substituent of **9** which is deshielded (δ 1.68) by the acetylenic bond. The NMR signals of the methyl groups of **10** and **11** as might be expected, are found within these two extremes at δ 1.40 and 1.57, respectively. In the di-π-methane product, **10,** the methyl group is relatively unaffected by the substituents on the cyclopropane ring since it too is trans to these substituents. It is interesting that these anisotropic effects tend to cancel each other in the case of the cyclopropane **11.** The effect of the methyl and methoxy groups on the cyclopropyl protons H_a and H_b can be seen in the trans di-π-methane products, **8** and **9.** Here it is found that H_a of the cyclopropane **8** is shifted to lower field by the methoxy group, while H_b is displaced to higher field by the methyl group which results in a differential shift of the cyclopropyl proton signals of 0.78 ppm. Interestingly H_a of the other trans di-π-methane product, **9,** is shifted to higher field by the methyl group while H_b is shifted to lower field by the methoxy group creating a near superposition of the two NMR signals at δ 2.21. The anistropic solvent effect of benzene-d_6 was required to resolve these peaks.

The appropriate nuclear Overhauser experiments were performed on the cyclopropanes to verify the NMR spectral assignments. Upon radio-frequency irradiation of the methyl group of **8** there is an NOE of 6.1% observed for H_b, while no such effect is apparent for H_a, which confirms the proposed stereochemistry of the trans cyclopropanes, **8** and **9.** Similarly, radio-frequency irradiation of the methyl group of **10** gives an NOE of 4.4% on H_a and 7.4% on H_b, as expected if the proposed stereochemistry of the cis cyclopropanes, **10** and **11,** is correct.[15]

Results and Discussion

The acetylenic di-π-methane substrates *trans-* and *cis-*1,5-diphenyl-3-methyl-3-methoxy-1-penten-4-yne (**7a** and **7b,** respectively) incorporate both styryl and phenylethynyl groups. The primary objective in this study was to assess the migratory potential of a phenylethynyl moiety in the di-π-methane rearrangement and the possible utility of such a process for the synthesis of substituted acetylenic cyclopropanes. In addition we wished to evaluate the effect of C-1 olefinic stereochemistry on the reaction course; however, during the preparation of our initial publication in this area,[1a,b] the results of an independent investigation of the stereochemical consequences which occur at C-1 in the di-π-methane rearrangement of a diene were reported.[16]

An intriguing aspect of the di-π-methane conversions observed for **7a** and **7b** is the efficiency with which the phenylacetylenic function participates as the migrating moiety in the rearrangement even when a styryl group is available for

interaction. Although phenylethynyl migration occurs to the exclusion of detectable styryl migration, no reliable general relative migratory aptitude data for sp and sp^2 centers can be inferred from the results since other factors may play a role in determining the reaction selectivity (vide infra).

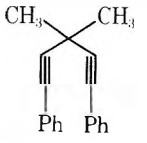
A useful qualitative valence bond representation for conventional concerted di-π-methane rearrangements, first recognized by Zimmerman and co-workers[17a,b] (Scheme II), is commonly invoked to characterize points along the potential energy hypersurface leading from the excited state reactant to ground state product. The fact that the di-π-methane photorearrangement of **7a** (and perhaps **7b**) occurs stereospecifically to produce the respective trans and cis cyclopropanes with retention of configuration at C-1[16] is assumed to be associated with a high degree of concertedness in the bond cleavage and bond formation processes required for atom reorganization of the di-π-methane type. Although the reaction stereospecificity is inconsistent with a sequential process, insufficient data are available to define the "degree of concertedness" (i.e., the reaction is concerted, but not synchronous). It should not be misconstrued that such formulations in Scheme II necessarily represent intermediates since it is not known that they correspond to energy minima. At most, they may represent shallow depressions in the energy surface. To the extent, however, that these species are useful in defining odd-electron disposition as the reaction course is traversed one should expect predictions based on this scheme to correlate with experiment. This approach has indeed stimulated extensive research and provides a qualitative model which allows one to visualize the overall gross molecular transformation along the reaction coordinate with extraordinary predictive success.

Application of this analysis to the concerted reorganization of **7a** and **7b** proves instructive. Initial π,π-bridging between C-2 and C-4 results in formation of **14** which incorporates a center with sp^2 character in the cyclopropyl ring and concomitant development of incipient arylcyclopropylcarbinyl and vinylphenyl radical sites, C-1 and C-5, respectively.

In pertinent cases previously studied[17b,c] the sole photoproducts isolated result from those pathways which involve migration of the less conjugated π moiety to the more conjugated one. Zimmerman and Pratt[17b] propose that the controlling feature in determining the overall regioselectivity is maintenance of odd-electron stabilization during the second step, i.e., cyclopropyl ring-opening process. In the case at hand (**14**) collapse of the cyclopropane ring by path a in which benzyl radical delocalization is maintained is apparently favored over cleavage by path b in which the corresponding residual radical is phenylvinyl in character; i.e., **15** is probably of lower energy than **16**. Cyclization of the diradical **15** with incorporation of the vinyl rather than ethynyl moiety into the cyclopropane ring of the product is not only consistent with Zimmerman's mechanistic representation of the process, but clearly in accord with our experimental results.

The effect of strain on the observed regioselectivity cannot be discounted and the preference for formation of cyclopropanes **8**, **9**, **10**, and **11** rather than cyclopropenes such as **17** from **7a** and **7b** may be attributed in whole or in part to unfavorable strain factors. As the reaction proceeds from the π–π bridged species **14** incorporating a single sp^2 center by path b to **16** the vinyl radical interacts and a cyclopropenyl photoproduct **17** must be generated possessing two such sp^2 centers. Path a may be operative and path b apparently circumvented simply because of the lower strain energy reflected in the transition state of the former. It is also possible that products formed through path b may escape detection as a result of the inherent photolability and higher absorptivity characteristic of such arylcyclopropenes (particularly those bearing conjugated styryl substituents including **17**) and the possible intervention of facile secondary photoreactions.[3,18]

In this connection it is noteworthy that atypical photobehavior was observed by Zimmerman and Pincock[1c] with a 1,4-pentadiyne (**17a**) which formally constitutes a di-π-methane system. For reasons of the type described above perhaps no di-π-methane rearrangement is observed upon irradiation of the diyne **17a**. When analyzed in the light of our



17a

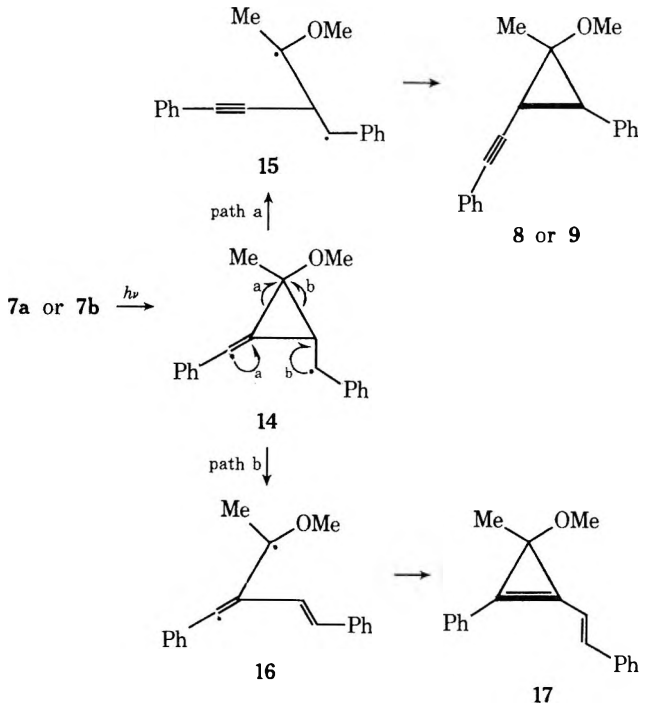
data conceivable 1,3 bridging in the Zimmerman and Pincock compound is reversible and/or insufficient driving force arising from adverse strain factors may exist which preclude the subsequent ring cleavage process. It is proposed that photoinduced 1,5 ethynyl–ethynyl bridging occurs to produce a diradical which acts as an energetic hydrogen abstractor to give as the ultimate product a 1,3-cyclopentadiene. It is significant that the dialkyne **17a** fails to undergo the di-π-methane rearrangement although arylacetylenic systems including **1a** (and **1b**) and acetylenic substrates such as **7a** (and **7b**) photorearrange.

Our data confirm that formation of the di-π-methane products **8**, **9**, **10**, and **11** from **7a** and **7b** occurs exclusively from the singlet excited state. This result is consistent with results obtained previously for other acyclic di-π-methane systems.[2,17a–e] Furthermore, the observation that cis–trans equilibration is a reaction which may occur from the triplet manifold also parallels the observations made by other investigators on related acyclic di-π-methane systems.

The stereochemical consequences observed for the di-π-methane rearrangement of the substrates **7a** and **7b** also constitute salient features of the photorearrangement process which occurs with these acetylenic systems. To reiterate, the trans isomer **7a** when irradiated at 254 nm yields the related trans cyclopropanes **8** and **9** exclusively. On the other hand the cis enyne **7b** yields the expected cis cyclopropanes **10** and **11** as well as the trans isomer **7a**. Isomerization of **7b** to **7a** competes efficiently with rearrangement. Thus from the results obtained to date reliable quantum yield data can only be extracted for the formation of **10** and **11** since **7a** is known to photorearrange to **8** and **9** under identical conditions and should begin to photoreact to some extent immediately upon production of **7b**. Therefore the value cited for **7a** must represent a minimum quantum yield because of the secondary photoreactions which must occur. The values presented in parentheses for **8** and **9** are not true quantum yields either since **8** and **9** undoubtedly do not arise directly and solely from **7b**. The possibility exists that **8** and **9** (Scheme I) are produced in part as a result of a single step rearrangement of **7b**. A third source for the photoproducts **8** and **9** obtained from **7b** may be the secondary photoisomerization of **10** and **11**. Such a process is not without precedent.[18] Owing to the complexity of the photoreactions of **7b** and the thermo- and photolability of the products and reactants, we have not been able to exclude conclusively the partial formation of **8** and **9** either directly from **7b** or from a secondary photoreaction of **10** and **11** formed initially. While the trans enyne **7a** unquestionably undergoes the di-π-methane rearrangement stereoselectively to produce trans cyclopropanes via the singlet state with retention of stereochemistry at C-5,[16] the question of whether the cis enyne **7b** behaves similarly is clouded by the efficient competing photoisomerization of **7b** to **7a** which provides the trans enyne **7a**, a known precursor for the corresponding trans cyclopropanes.

An equivalent representation to that depicted in Scheme II for the reactions under consideration is given in Scheme III

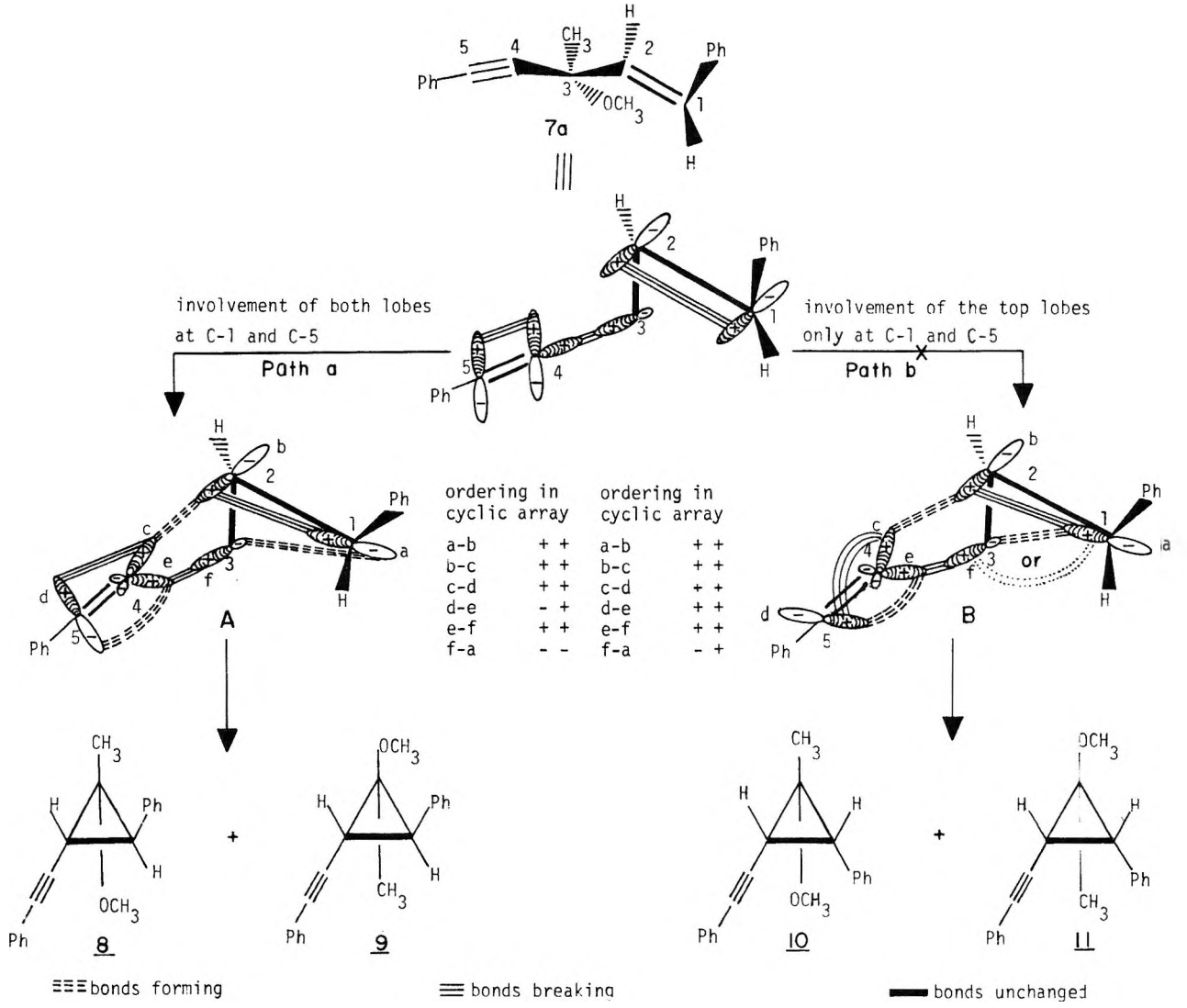
Scheme II



and depicts the change in basis orbitals as the reaction proceeds. It should be noted that the descriptions presented in the latter scheme represent cyclic arrays of six local orbitals containing $(4n + 2)$ π electrons. The basis orbital sets designated are of the form used for mixing through a secular determinant to give the final molecular orbitals and the selection of lobe orientation (i.e., + and − assignments) is arbitrary. Thus no overlap of a bonding or antibonding nature is implied by the interactions embodied in these formulations; the number of odd (plus-minus or minus-plus) interactions may be correlated with the final results of molecular orbital mixing.[17b] Moreover, this more sophisticated representation provides a different perspective from the valence bond approach of Scheme II and offers the added advantage of furnishing a theoretical interpretation for the observed stereochemistry and a more graphic rationale for the regioselectivity.

The significant orbitals involved (Scheme III) at the onset of the reaction are orbitals a and b (i.e., the original olefinic bond linking atoms 1 and 2), between orbitals e and f (the initial sp–sp^3 σ bond C_3–C_4) as well as that between c and d (the preexisting π-acetylenic C_4–C_5 bond). As the reaction ensues interactions may be written between orbitals b and c (constituting the π–π bridging between C_2 and C_4), between orbitals d and e (regenerating the acetylenic C_4–C_5 linkage), as well as between orbitals a and f (the formation of the C_1–C_3

Scheme III. Allowed Basis Orbital Arrays for the Di-π-methane Rearrangement for the Trans Enyne 7a



bond with emergence of the cyclopropyl ring). From available evidence Zimmerman proposes that the last interaction designated probably lags behind the other processes.[2a] This is not unreasonable since prior intervention of other steps in the reorganization should precede bonding to the saturated sp^3 hybridized C-3 atom of the reactant. The relative significance of this time lag may be magnified substantially by the increase in stability which should accrue as a result of the replacement of one methyl substituent of the geminal pair (normally present in conventional di-π-methane substrates) by a methoxy group such as found in **7**; i.e., an alkoxy substituent is more effective in stabilizing a free-radical center than a methyl group.

For purposes of illustration we have followed the precedent established by Zimmerman and Pratt[17b] in Scheme III, of (1) arbitrarily considering the syn rather than anti conformations of a given isomer in this case trans **7a** and (2) in utilizing one of two configurations at C-3 in depicting the basis orbital arrays; however, the overall stereochemical reasoning is independent of what conformation or even configuration is assumed with these racemic systems (vide infra). Two differing 6 π Möbius-like arrays with the requisite odd number of syn discontinuities (one in each case) may be generated depending on whether the same lobes or alternate lobes of the terminal π orbitals are utilized. The pair of six local orbital Möbius arrays a–b–c–d–e–f are categorized as antiaromatic in the ground state, but are aromatic and stable in the excited state, and thus the reorganizations depicted in Scheme III (≡ ≡ ≡ and ≡≡≡) are both allowed photochemical processes.

The question now arises as to which of the two alternative cyclic arrays (A or B) most accurately represents the preferred reaction course. In a series of previous papers Zimmerman and co-workers, and we independently, have established that the di-π-methane rearrangement proceeds with retention of configuration at carbons 1 and 5 of the 1,4-pentadienyl system.[2a,16,17b] For example, at carbon atom 5 (incorporated in the migrating moiety) it was confirmed that cis substitution remains cis on the π bond of the vinylcyclopropane product while the converse is true for the trans isomer; i.e., *at least superficially*[2a] the π bond of the reactant simply survives the reorganization (vide infra).[17b] Since the acetylenic bond of **7a** and **7b** is linear and radially symmetrical, the problem of stereochemistry at this center is meaningless in this context despite the participation invoked in the valence bond approach delineated in Scheme II.

In the case of the other terminal center 1 of the di-π-methane substrate the evidence compiled by Zimmerman and co-workers[16] and independently accumulated in our laboratory[1a,b,4a] using different substrates shows that cis reactant gives cis product while trans gives trans product in a stereospecific process. Thus the stereochemistry of a double bond of the reactant determines the configuration of the relevant cyclopropyl substituent of the product. That electronic factors rather than least motion considerations are responsible for this phenomenon has been demonstrated in an elegant and convincing manner by Zimmerman et al.[16]

Information which resolves the remaining question of stereochemical uncertainty, namely the configurational fate at C-3, has recently been assembled by Zimmerman and collaborators.[17d] The results verify the tentative conclusions drawn from data obtained earlier with cyclic substrates[17e] that inversion occurs at this insulating sp^3 center in the acyclic di-π-methane systems as well.[17a]

In light of these stereochemical data it is possible to deduce which array (A or B) displayed in Scheme III most accurately depicts the overall molecular reorganization in the case of **7a** and to validate the conclusions on the basis of the new experimental results obtained. It is apparent that the primary arrays of six local orbitals depicted in Scheme III at half-reaction are of Möbius character [one sign inversion between adjacent orbitals, e and d in the case of A, and a and f in B (≡ ≡ ≡)] and thus are allowed in the excited state. The torsional motion(s) at C-1 and 3 required by the interactions depicted in array A convert the trans enyne **7a** by path a into the cyclopropanes **8** and **9** bearing trans aryl and phenylethynyl groups which is the course anticipated on the basis of data cited and constitutes the results observed experimentally for **7a**. Moreover, since bond making and bond breaking occur at alternate lobes of orbital e on C-3 (≡ ≡ ≡) inversion of the type documented in a 1,4-pentadienyl system[17d] is incorporated in the display A. In contrast the angular rotation necessitated at C-1 and C-3 in B in order to achieve a–f orbital overlap of the type designated (≡ ≡ ≡) while ensuring the requisite sign discontinuity and inversion at C-3 does not accommodate the observed data and reveals the preferred route; i.e., path b is unacceptable since the net result is formation of "cis" cyclopropanes. This is contrary to precedent documented experimentally for a variety of systems including those described herein.

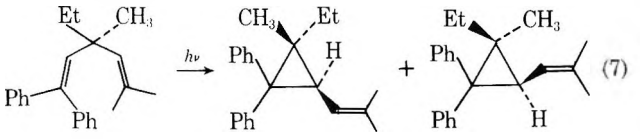
On the other hand, if the angular motions necessary to preserve trans stereochemistry in the product are imposed at C-1 and C-3 (: : : : :) the e–f orbital overlap becomes ++ (or −−) and the sign discontinuity is dissipated. This operation precludes inversion at C-3, since only one lobe of orbital f is implicated and furthermore, the electronic character of the entire array is altered; i.e., the system is rendered aromatic and of lowest energy in the ground state (Hückel in character with no sign discontinuities present in a six π electron system) and the reaction becomes excited state forbidden. Hence the preferred reaction stereochemistry would appear to involve disrotatory twisting of C-1 with respect to C-3 of the type shown in array A rather than B.

It is interesting to speculate on the possible effects of introducing the acetylenic π system into di-π-methane substrates. In considering 1,5-pentadienyl analogues, in order to accommodate all stereochemical data, it is convenient to select and compare basis orbital arrays for these $4n + 2$ π-electron systems in which the sign discontinuity is reserved for the migrating alkenyl moiety.[6,17b,d] In fact the resulting enforced rotation has led Hixson, Mariano, and Zimmerman[2a] to advance the esoteric proposal that the migrating double bond of the reactant merely appears to survive the rearrangement when indeed orbital reorganization with rotation has occurred in the process.

In cases such as **7a** and **7b**, however, where the presence of the radially symmetrical C_4–C_5 acetylenic bond may no longer impose such restrictions, additional sign discontinuities may be assimilated into this moiety. Perhaps then alternate allowed arrays may exist since no stereochemical repercussions are detectable. If in fact both C_4–C_5 π orbitals of the acetylenic bond are considered explicitly in **7a** and **7b** these systems then become $4n$ in character. Furthermore, regardless of any rehybridization which is invoked at the C_4 reaction center (sp and p, "sp^3 and sp^3" and "sp^5 and sp^5"),[16] it may be shown that introduction of an additional sign discontinuity into the reaction wave function is unavoidable and consequently the initial conclusions remain unchanged. Thus, while an additional sign disparity is introduced the array becomes $4n$ in character and remains aromatic and allowed (of lowest energy) in the excited state.

Perhaps the most intriguing stereochemical feature of the work described relates to the relative ratio of epimers formed as products in the rearrangement of **7a** and **7b**. The epimer which is formed in higher yield in the case of the isomeric pairs **8** and **9** as well as **10** and **11** is that bearing the methoxy and phenylethynyl groups affixed to the same side of the ring (**8** and **10**, respectively). It is interesting to speculate on the origin of this selectivity factor (~2.1 for **8**:**9** and **10**:**11**). Reference to

A values (conformational free-energy differences)[19] shows that a methyl group is much larger than a methoxy group and thus the intervention of adverse steric factors cannot be invoked to explain the results since the larger methyl group would be expected to encounter less interaction during cyclization with the collinear phenylacetylenic group than with the phenyl substituent. It is interesting in this regard that in the conversion of 18 to 19 and 20, Zimmerman found that the more stable isomer with the ethyl trans to isopropylidene is favored albeit only slightly (4:5) (eq 7).[17d] That a more pronounced



18 19 20

effect on the product ratio is not apparent with 18 in the di-π-methane reorganization could be due to the fact that an ethyl substituent is only slightly larger than a methyl group.[19] In summary, since the epimer selectivity favoring the photoproducts 8 and 10 obtained from **7a** and **7b**, respectively, manifest in these cases (2:1) is contrathermodynamic, we cannot ascribe the effect to steric factors and feel justified in invoking secondary electronic effects between the methoxy group and the incipient acetylenic bond to explain the magnitude of the observed specificity.

It should be noted that the syn-syn conformer of **7a** depicted in Scheme III is simply one of two such possible U-shaped geometries. An alternative one exists in which the pendant π moieties are rotated about the C_3–C_4 and C_2–C_3 bonds on the sp^3 hybrid center into the plane of the page. This simply has the effect of exchanging the methyl and methoxy substituents (i.e., methoxy becomes cis to phenyl), but the same epimer pairs (8 and 9 and 10 and 11) are generated from the corresponding enynes by the operations depicted (Scheme III). Additionally s-transoid conformations of **7a** leading to vinylalkynyl bridging may be written, but again this does not affect the configurational conclusions and the stereochemical predictions are invariant to the choice of conformer selected.

It should be noted that the photoreactions of **7a** and **7b** may also be designated as $4n + 2$ electron $[{}_\sigma 2_a + {}_\pi 2_a + {}_\pi 2_a]$ electrocyclic processes using the Woodward–Hoffmann analysis and are of lowest energy (allowed) in the excited state. This is a more favorable "cycloaddition" than the alternative $[{}_\sigma 2_s + {}_\pi 2_a + {}_\pi 2_a]$ interaction. The overall treatment in this manner represents an alternative, but equivalent approach to that formulated in valence bond (Scheme II) or MO terms (Scheme III) devised by Zimmerman.[2a,17a,b] Clearly a system with an odd number of sign inversions will also generate an odd number of antarafacial components and is Möbius while the converse holds true and a Hückel system is defined if an even number of (or zero) sign inversions is present.

In summary it is clear from the results obtained in this study that the traditional di-π-methane rearrangement incorporating only sp^2 hybrid di-π centers may be extended to include systems which also contain sp centers in which the acetylenic moiety migrates efficiently and cyclopropanes are produced. We had previously established[3] that an aryl.π system also cyclizes albeit less efficiently to the terminus of an acetylenic bond to give a cyclopropene. The present study in addition to providing new synthetic routes to acetylenic cyclopropanes also is of mechanistic significance and provides additional information with respect to the concerted character of di-π-methane reactions. The regioselectivity and stereospecificity of the photorearrangements of **7a** and **7b** reinforce the mechanistic proposals made by other workers in the field while our work in this area was in progress. For example, we have confirmed that the stereochemistry at the α position in the styryl chromophore (carbon atom 5 of the di-π-methane system) is maintained during the course of the reaction; i.e., the trans acetylenic alkene gives trans cyclopropanes while the alternate cis substrate gives the cis analogues. Furthermore, as others have found,[2] one may interpret the selectivity exhibited in the photoreactions of **7a** and **7b**, i.e., the migration of phenylethynyl to the exclusion of styryl, in terms of formation of the more stable of the two possible "diradical-like" transition states; however, this may be fortuitous and other factors such as steric effects or strain inherent in a potential cyclopropene nucleus may in fact be responsible for the specificity of the process. It is also of interest that the multiplicity dependent behavior of acyclic di-π-methane systems containing sp hybrid centers parallels that found for those containing only sp^2 hybrid unsaturated groups. It should be noted, however, that in the case of the allenes **3a** and **3b** an alternate reaction competes efficiently with the di-π-methane rearrangement.[4] Our efforts in this area continue with our eventual goal that of obtaining additional information on the migratory aptitudes of various groups in the di-π-methane rearrangement which in turn may shed additional light on the degree of concerted or sequential character of the reaction and extend its synthetic utility.

Experimental Section

General. All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 337 and 257 spectrophotometers and were calibrated against polystyrene. The ultraviolet spectra and absorbance values were determined on a Cary Model 17 spectrophotometer. The proton magnetic resonance spectra were obtained on Varian A-60, HA-100, and Hitachi Perkin-Elmer R-20B instruments using deuteriochloroform as the solvent with tetramethylsilane (1%) as the internal standard unless otherwise specified. The mass spectral studies were conducted using a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Woelm neutral alumina and added phosphor was used for column chromatographic separations which were conducted in Vycor columns to facilitate visualization with a hand-held ultraviolet scanning lamp. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Direct irradiations were conducted in serum-capped 15 cm × 12.5 mm i.d. fused quartz tubes. Sensitized irradiations were carried out in serum-capped Pyrex round-bottom flasks or Pyrex test tubes. A Rayonet photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with 16 8-W low-pressure lamps was used as a light source unless otherwise specified. The lamps were of the type G8 T5 (254 nm) or F8 T5 (broad emission at 350 nm). A Rayonet MGR-100 Merry-Go-Round or MGR-200 Mini-Go-Round apparatus (The Southern New England Ultraviolet Co., Middletown, Conn.) was utilized in all kinetic and quantum yield studies to ensure uniform exposure of individual samples, which were rotated at 5 rpm. The solutions to be irradiated were degassed either by nitrogen sparging for 25 min or by the multiple freeze–thaw technique.

***trans*-1,5-Diphenyl-3-methyl-1-penten-4-yn-3-ol (6).**[6] A solution of ethylmagnesium bromide was prepared under nitrogen by placing 2.2 g (0.09 mol) of magnesium turnings in 50 ml of anhydrous diethyl ether and slowly adding 10 g (0.09 mol) of ethyl bromide. The mixture was stirred for 2 h prior to careful addition of 8.4 g (0.08 mol) of phenylacetylene in 15 ml of anhydrous diethyl ether. This solution was stirred for 20 h before adding 8.4 g (0.05 mol) of benzalacetone[5] in 30 ml of anhydrous diethyl ether dropwise. The resulting reaction mixture was then stirred for 3 h and 100 ml of a 10% ammonium chloride solution was slowly added. The two phases were separated and the aqueous layer extracted with a 1:1 ether–pentane solution. The combined organic phases were washed with water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the excess phenylacetylene was removed by heating to 50–60 °C at 0.5 Torr for 1 h. The product **6** which solidified was recrystallized from hexane and 12.5 g (90%) was obtained: ir (KBr) 971 cm^{-1} (trans 1,2-disubstituted alkene); NMR (CCl_4) δ 7.45–6.95 (broad s, 10 H, aromatic), 6.76 (d, 1 H, J = 15.0 Hz, olefinic), 6.18 (d, 1 H, J = 15.0 Hz, olefinic), 2.35 (broad s, 1 H, hydroxyl), 1.69 (s, 3 H, methyl); mass spectrum m/e M^+ 248.

***trans*-1,5-Diphenyl-3-methyl-3-methoxy-1-penten-4-yne (7a).**

To a stirred solution of 12.6 g (0.05 mol) of the alcohol **6** in 100 ml of dimethyl sulfoxide was slowly added 8.2 g (0.05 mol) of iodomethane. This was followed by the addition of 1.8 g (0.04 mol) of solid sodium hydroxide. The flask was stoppered and stirred for 60–72 h at ambient temperature. The reaction mixture was then poured into 1 l. of water and extracted three times with 250-ml portions of a 1:1 ether–pentane solution. The organic extracts were combined and washed twice with water and then dried over anhydrous sodium sulfate. The residual yellow oil remaining after removal of the volatile solvents under reduced pressure crystallized upon trituration or standing. The product was recrystallized from a 1:1 ether–pentane solution to give 12.7 g (0.05 mol, 96%) of the white crystalline ether **7a**: mp 77–78 °C; ir (KBr) 970 cm^{-1} (trans 1,2-disubstituted alkene[8]); uv λ_{max} (EtOH) 252 nm (ϵ 30 000); NMR ($CDCl_3$) δ 7.60–7.18 (m, 10 H, aromatic), 6.93 (d, 1 H, J = 15.5 Hz, olefinic), 6.14 (d, 1 H, J = 15.5 Hz, olefinic), 3.40 (s, 3 H, methoxy), 1.72 (s, 3 H, methyl); mass spectrum m/e M^+ 262.

Anal. Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 87.07; H, 6.83.

***cis*-1,5-Diphenyl-3-methyl-3-methoxy-1-penten-4-yne (7b).** The cis acetylenic alkene **7b** was readily prepared by photoisomerization of the trans isomer **7a**. A solution of 2.5 g (0.01 mol) of **7a** in 1 l. of dry hexane and 125 ml of acetophenone was sealed in a 2-l. Pyrex round-bottom flask. The solution was purged with nitrogen for 0.5 h prior to irradiation, with stirring, at 350 nm for 12 h. The hexane and acetophenone were removed under reduced pressure and the pale yellow residual oil was found to consist of an equimolar mixture of **7a** and **7b**.[7] This mixture was then chromatographed on a 2.5 cm i.d. Vycor column packed to a height of 60 cm with Woelm grade III neutral alumina with added phosphor. The sample was eluted with hexane and the elution progress was followed by visualization with a 254-nm hand lamp. Only partial separation could be obtained and once elution of the sample began to occur from the column, 30-ml fractions were collected. The first one or two fractions contained pure **7b**; later fractions contained **7a** contaminated with **7b** with the concentration of **7a** constantly increasing as later fractions emerged. The last fractions consisted of pure **7a**. The hexane was allowed to evaporate at ambient temperature in a current of air in a hood. The chromatographic separation was repeated with samples enriched in **7b** in order to obtain greater amounts of pure **7b**. Finally **7b** was distilled at 100 °C and 5–10 μm in a bulb-to-bulb Kugelrohr apparatus to obtain pure **7b**, a colorless oil; bp 100 °C (5–10 μm); ir (KBr) absence of 970 cm^{-1} absorption (excludes trans-disubstituted alkene);[8] NMR ($CDCl_3$) δ 7.52–6.98 (m, 10 H, aromatic), 6.57 (d, 1 H, J = 12.0 Hz, olefinic), 5.72 (d, 1 H, J = 12.0 Hz, olefinic), 3.38 (s, 3 H, methoxy), 1.72 (s, 3 H, methyl); mass spectrum m/e M^+ 262.

Anal. Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.80; H, 7.01.

Direct Irradiations of *trans*- and *cis*-1,5-Diphenyl-3-methoxy-1-penten-4-yne (7a and 7b, Respectively). Procedure A. Solutions of **7a** and **7b** (0.037–0.045 M) dissolved in *tert*-butyl alcohol, benzene, and acetonitrile were irradiated at 254 nm for varying periods of time. A pale yellow semisolid oil was obtained upon removal of the volatile solvents in the case of **7a** and **7b**, respectively. The composition of each sample was established by NMR analysis. The data are summarized in Table I.

Procedure B. In a typical preparative irradiation, a solution of 3.5 g (7.6 mmol) of **7a** in 1320 ml of benzene was irradiated at 254 nm for 40 min. After removal of the solvent, the resulting mixture was chromatographed on a 2.5-cm i.d. Vycor column packed to a height of 60 cm with Woelm grade III neutral alumina with added phosphor. The progress of the separation of the sample on the column was followed with a 254-nm hand lamp during elution with hexane. Only partial separation could be achieved and 30-ml fractions were collected once the sample began to elute from the column. The early fractions contained **7b** followed by mixtures of **7b** and **7a**. Later samples contained **7a** while the final samples contained a mixture of *r*-1-methoxy-1-methyl-*t*-2-phenyl-*c*-3-phenylethynylcyclopropane (**8**) and *r*-1-methoxy-1-methyl-*c*-2-phenyl-*t*-3-phenylethynylcyclopropane (**9**). The last fractions were then rechromatographed on a 9-mm o.d. Vycor column packed with Woelm grade III neutral alumina to a height of 50 cm. The chromatography was performed as previously described. In each case bulb-to-bulb distillation of the cyclopropane fractions in a Kugelrohr apparatus at 100 °C and 5–10 μm was required before adequate purity could be achieved. The first compound to be eluted was shown to be **9**, a white, crystalline solid: mp 68–69 °C; ir (KBr) 2220 cm^{-1} (acetylene); uv λ_{max} (EtOH) 252 nm (ϵ 21 300); NMR ($CDCl_3$) δ 7.53–7.02 (m, 10 H, aromatic), 3.17 (s, 3 H, methoxy syn to phenyl), 2.21 (2 overlapping doublets discernible in benzene-d_6, J = 6.5 Hz, 2 H, cyclopropyl), 1.68 (s, 3 H, methyl, anti to phenyl); mass spectrum m/e M^+ 262.

Anal. Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.87; H, 7.16.

The second compound to be eluted was shown to be **8**, a white, crystalline solid: mp 36.5–37 °C; ir (KBr) 2225 cm^{-1} (acetylene); uv λ_{max} (hexane) 252 nm (ϵ 20 400); NMR ($CDCl_3$) δ 7.50–7.02 (m, 10 H, aromatic), 3.55 (s, 3 H, methoxy anti to phenyl), 2.71 (d, 1 H, J = 6.5 Hz, benzylic cyclopropyl H), 1.93 (d, 1 H, J = 6.5 Hz, phenylethynylcarbinyl H), 1.20 (s, 3 H, methyl syn to phenyl); mass spectrum m/e M^+ 262.

Anal. Calcd for $C_{19}H_{18}O$: C, 86.98; H, 6.92. Found: C, 86.71; H, 7.10.

Procedure C. In a typical preparative irradiation of **7b**, 1.0 g (3.8 mmol) in 90 ml of benzene was irradiated at 254 nm for 1 h. The resulting mixture was processed as described in B. The chromatographic fraction containing **8**, *r*-1-methoxy-1-methyl-*c*-2-phenyl-*c*-3-phenylethynylcyclopropane (**10**), and *r*-1-methoxy-1-methyl-*t*-2-phenyl-*t*-3-phenylethynylcyclopropane (**11**) was then rechromatographed as outlined in procedure B. The first compound to emerge was **10**, a white, crystalline solid: mp 48–49 °C; NMR ($CDCl_3$) δ 7.48–7.08 (m, 10 H, aromatic), 3.40 (s, 3 H, methoxy syn to phenyl), 2.62 (d, 1 H, J = 11.0 Hz, cyclopropyl benzilic H), 2.26 (d, 1 H, J = 11.0 Hz phenylethynylcarbinyl H), 1.40 (s, 3 H, methyl anti to phenyl); mass spectrum m/e M^+ 262.

Anal. Calcd for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.84; H, 7.09.

The second compound eluted, namely **11**, was obtained as a colorless liquid: ^1H NMR ($CDCl_3$) δ 7.58–7.09 (m, 10 H, aromatic), 3.43 (s, 3 H, methoxy anti to phenyl), 2.24 (d, 1 H, J = 9.5 Hz, benzylic cyclopropyl H), 2.00 (d, 1 H, J = 9.5 Hz, phenylethynylcarbinyl H), 1.57 (s, 3 H, methyl syn to phenyl); mass spectrum m/e M^+ 262. The third compound to elute was assigned structure **8**.

Sensitized Irradiations of *trans*- and *cis*-1,5-Diphenyl-3-methyl-3-methoxy-1-penten-4-yne (7a, 7b). The procedure followed and data obtained upon sensitized irradiation of **7a** and **7b** in hexane using acetophenone as a sensitizer are described in the procedure for the preparation of **7b**. Acetone also functions as a convenient sensitizer for **7a**, but affords a smaller percentage of **7b** even when irradiations were carried out for longer time periods.

Quantum Yield Determinations for the Rearrangement of *cis*- and *trans*-1,5-Diphenyl-3-methyl-3-methoxy-1-penten-4-yne (7a and 7b Respectively). Quantum yields were determined in *tert*-butyl alcohol solutions (0.11–0.15 M), contained in matched quartz cuvettes, at 254 nm. Potassium ferrioxalate actinometry[12] was employed. A Mini-Go-Round was used to ensure uniform irradiation of actinometer and sample solutions. The quantitative determination of the composition of the irradiated solutions was achieved by 100-MHz NMR. Quantum yields which are quoted in Scheme II represent an average of four determinations.

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Registry No.—**6**, 60184-29-4; **7a**, 42053-37-2; **7b**, 42053-36-1; **8**, 42053-40-7; **9**, 42053-41-8; **10**, 42053-38-3; **11**, 42053-39-4; ethyl bromide, 74-96-4; phenylacetylene, 536-74-3; benzalacetone, 122-57-6.

References and Notes

(1) (a) Presented in part at the 27th Southwest Regional Meeting of the American Chemical Society, San Antonio, Texas, Dec 1–3, 1971, Abstract No. 238, p 81. (b) A preliminary account of this work has appeared: J. Perretен, D. M. Chihal, G. W. Griffin, and N. S. Bhacca, *J. Am. Chem. Soc.*, **95**, 3427 (1973). (c) While this work was in progress, the photochemistry of a diphenylethynylmethane was reported [H. E. Zimmerman and J. A. Pincock, *J. Am. Chem. Soc.*, **95**, 3246 (1973)]. An unusual mechanistic departure (see ref 16) from the anticipated course of reaction was observed in which reductive cyclization to give a cyclopentadiene occurs with

obligatory initial 1,5 bonding at the acetylenic termini. (d) Taken in part from the Dissertation submitted in partial fulfillment for the requirements of the Ph.D. degree of D. M. Chihal, University of New Orleans, 1975.
(2) (a) For a comprehensive review of the di-π-methane rearrangement see S. S. Hixson, P. S. Mariano, and H. E. Zimmerman, *Chem. Rev.*, **73**, 531 (1973). (b) For a classic early example of the di-π-methane reaction see H. E. Zimmerman and P. S. Mariano, *J. Am. Chem. Soc.*, **91**, 1718 (1969).
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(4) (a) Presented in part at the 28th Southwest Regional Meeting of the American Chemical Society, Baton Rouge, La., Dec 6–8, 1972, Abstract No. 222, p 76. (b) D. C. Larkin, D. M. Chihal, G. W. Griffin, and N. S. Bhacca, *Tetrahedron Lett.*, 4009 (1973); D. C. Lankin, D. M. Chihal, N. S. Bhacca, and G. W. Griffin, *J. Am. Chem. Soc.*, **97**, 7133 (1975).
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(6) *Caution:* It has been noted in one case that the alcohol **6** induces an allergic reaction upon contact even with the vapors with the response becoming increasingly severe upon repeated exposure. Symptoms include periorbital edema, erythema, and nausea.
(7) Irradiation of **7b** under the same conditions likewise gives a mixture of **7a** and **7b** of similar composition.
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(10) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969, p 251.
(11) The nomenclature for the acetylenic cyclopropanes **8**, **9**, **10**, and **11** is in accord with "IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E. Fundamental Stereochemistry, Rule E-3.3", *J. Org. Chem.*, **35**, 2849 (1970). The designations *r*, *c*, and *t* refer to the reference center and cis and trans substituents, respectively.
(12) (a) C. G. Hatchard and C. A. Parker, *Proc. R. Soc. London, Ser. A*, **235**, 518 (1956). (b) It has been shown experimentally, ref 12c, and theoretically, ref 12d, that irradiation of samples in cylindrical cells in a Merry-Go-Round apparatus may seriously affect the observed quantum yield when the sample cell contains a solvent of different refractive index from that employed in the actinometer cell and similar criticisms might be advanced concerning our determinations with **7a** and **7b** despite the fact that the Mini-Go-Round was employed with flat quartz cuvettes. In view of our ability to reproduce the reported quantum yield data for the photoisomerization of 1,1,3-triphenyl-3,3-dimethyl-1-propene, it appears that such arguments are invalid here, perhaps because of the nearly monochromatic light source used and the flat cell surfaces exposed. (c) G. F. Vesley, *Mol. Photochem.*, **3**, 193 (1971). (d) M. D. Shetlar, *ibid.*, **5**, 287 (1973).
(13) (a) A sample of this compound was generously supplied by Professor H. E. Zimmerman, Department of Chemistry, University of Wisconsin, Madison, Wis. (b) We wish to thank Professors Zimmerman and Hixson for communication of data regarding the compounds **12a** and **12b** prior to publication and for fruitful correspondence and discussions during the preparation of this manuscript.
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(15) The risks inherent in relying solely on physical methods for structure elucidation have been detailed recently [H. E. Zimmerman and L. M. Tolbert, *J. Am. Chem. Soc.*, **97**, 5497 (1975), ref 12]. We feel, however, that our cyclopropane stereochemical assignments are secure in view of the availability of all isomers, the reliability of NOE experiments, the validity of coupling constant data, and the total self-consistency of the interpretation in the case of these unstable, compounds which are otherwise difficultly accessible by alternate synthetic means.
(16) During the preparation of our initial publication (see Acknowledgment and p 542, ref 2a) the results of an independent investigation of the stereochemistry of the di-π-methane rearrangement at carbon atom 1 of a diene were reported. See H. E. Zimmerman, P. Baeckstrom, T. Johnson, and D. W. Kurtz, *J. Am. Chem. Soc.* **94**, 5504 (1972); **96**, 1459 (1974).
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Formation of an Unusual Steroidal Oxetane and Its Transformation Products

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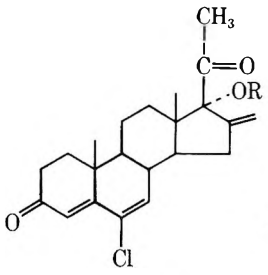
Chlorination of 6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione (**1b**) gave unexpectedly 12% of an oxetane **3a**. Treatment of **3a** with base gave a D-homo seven-membered ring system **7** which with acid afforded the 15-acetyl androstadiene **9a**. The elucidation of these structures, and related transformations, are discussed, together with the application of single-crystal x-ray analyses for unequivocal structural determination.

In connection with studies of structural and pharmacological modifications of the progestogen, 6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione acetate (**1a**),[1] two of us[2] sought to prepare 6-chloro-16β-chloromethyl-16α,17α-oxido-4,6-pregnadiene-3,20-dione (**2**).[3] Generation of the 16β-chloromethyl-16α,17α-oxido moiety from the 16-methylene-17-hydroxy unit has been accomplished previously by use of *N*-chlorosuccinimide[4] or chlorine.[3,5] With the 17-hydroxy **1b** available, it appeared that conversion to **2** might be effected, even though it was recognized that chlorination of the 4,6-dien-3-one system might also occur.[6] Using chlorine, the required compound **2** was obtained in moderate yield, but a significant amount of an unexpected oxetane, **3a**, was also produced. It is the formation of **3a**, its structural characterization, and subsequent transformation products (particularly **7** and **9**) which are the subject of this report. Elucidation of the constitution of **3a** was attempted initially by chemical transformations and interpretation of the various physical data presented in Tables I–III and Table X (elementary analyses, included in supplementary material), but this approach led to conflicting conclusions. Its structure, as well as structure **9a**, were finally established unequivocally by single-crystal x-ray analysis.

Treatment of **1b** with 1.1 equiv of chlorine (in the presence of 1.1 equiv of pyridine) for 5 min gave the 16β-chloromethyl 16α,17α-oxide (**2**) in 54% yield and another product in approximately 12% yield, as well as unreacted **1b**. Efforts to increase the yield of this minor product relative to the oxide **2**



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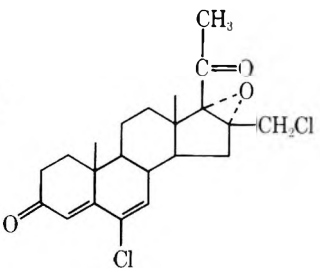
b, R = H



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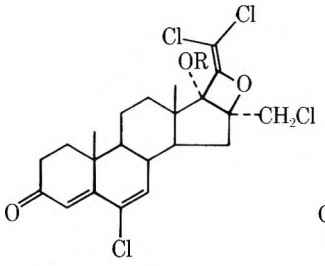

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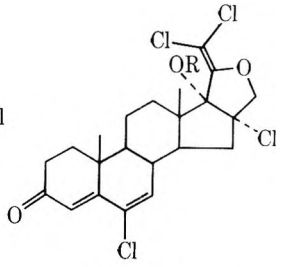

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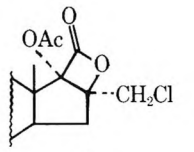

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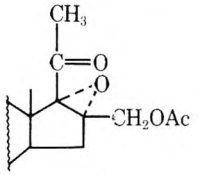

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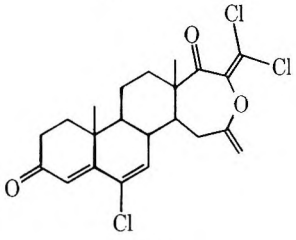

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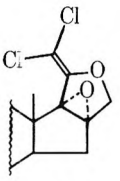

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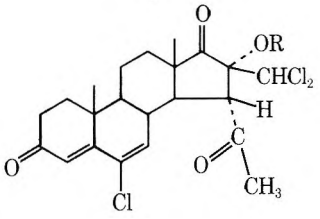
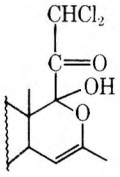


9a, R = H
b, R = CH_3CO



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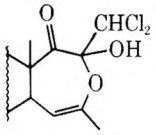

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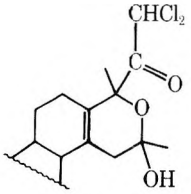
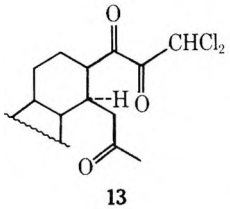
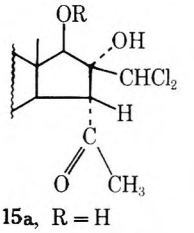


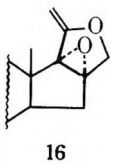
12



13



15a, R = H
b, R = CH_3CO



16

by varying medium and conditions proved fruitless. The analytical and spectral data revealed that this minor product possessed four chlorine atoms, a hydroxyl group, and the unchanged A/B ring system of **1b**, but lacked the 17-acetyl group. Of the structures accommodating these facts, the oxetane and tetrahydrofuran systems depicted in **3a** and **4a** seemed most reasonable.

Retention of the tertiary 17-hydroxyl function in the product was suggested by its conversion to the corresponding acetate with trifluoroacetic anhydride, acetic acid, and *p*-TSA,[7] but not with acetic anhydride in pyridine. However, its exposure to various acid media failed to provide further structural information. For example, treatment with either $HClO_4$ (at room temperature or at 60 °C) or acetic acid gave no reaction, whereas with HCl in acetic acid or with zinc in ethanol complex mixtures resulted; neither of these mixtures was investigated beyond TLC analysis.

It appeared that cleavage of the dichloromethylene moiety at C-20 by ozonolysis to produce the corresponding lactone would be instructive in the differentiation of **3** vis-à-vis **4**. However, while ozonolysis (EtOAc, pyridine, −60 °C) of the acetate gave in a single experiment a product which exhibited an ir band at 1852 cm^{-1} suggestive of the presence of a β-lactone as in **5**, this transformation proved to be irreproducible. Other attempts to distinguish between **3** and **4** by treatment with $Pb(OAc)_4$ were unsuccessful.

Consideration of structures **3** and **4** suggested that it should be possible to differentiate chemically between their respective primary and tertiary 16α-chloro substituents. In a model experiment, the primary chloride of **2** was converted to the primary acetate **6** with KOAc in DMF at 80 °C; by analogy, **3b** would be expected to yield the corresponding acetate. In contrast, however, **3b** afforded starting material as the only recognizable product. Failure to effect this transformation suggested structure **4b** rather than **3b**, in contrast to the results of the ozonolysis experiment.

Further support for structure **3a** came from physical data for a compound which was obtained from **3a** in 80% yield by use of KOAc in refluxing acetone and in 90% yield from the acetate derivative (**3b**) by use of NaOH in methanol at room temperature. These data showed that the reactions had proceeded with retention of the dichloromethylene unit, loss of a chlorine atom, and generation of a possible methylene system. In addition, an increased intensity in the absorption band at 283 nm was noted. While these data are more compatible with structure **7** (derivable from **3**) than with structure **8** (derivable from **4**), definitive assignment was still precluded by lack of convincing evidence. This uncertainty was intensified by analysis of the data obtained for another compound (Tables I–III, **9a**) generated in approximately 45% yield from proposed **7** (or **8**) with $HClO_4$ in THF at 60 °C. A most significant feature of **9a** was that it contained a methyl group having an anomalous chemical shift of 2.72 ppm. Esterification with acetic anhydride in pyridine for 48 h at room temperature gave approximately 65% yield of an acetate derivative in which the corresponding methyl signal appeared at 2.64 ppm. Possible structures which were considered, i.e., **10**–**12** (with **13** as the common precursor) did not accommodate the data for **9a** or its acetate. Subsequent reduction of **9a** with $NaBH_4$ at 5 °C gave a crude substance (**14**) in 80% yield. Allylic oxidation of the 3-hydroxy group with MnO_2 then produced a compound (Tables I–III, **15a**) which NMR revealed to contain a secondary hydroxyl group and a methyl group with a signal at 2.36 ppm which shifted downfield to 2.54 ppm upon esterification of **15a** with acetic anhydride in pyridine.

In order to resolve these structural ambiguities and thereby allow the sequence of transformations to be rationalized, **3a** and **9a** were subjected to single-crystal x-ray analyses. Both structures were solved by direct noncentrosymmetric phase-

Table I. Analytical Data

Registry no.	Compd	Mp, °C[a]	$[\alpha]D^b$	Ir, cm^{-1} [d]	Mol wt	m/e[e]
24431-77-4	**1b**	170–172 (sint 168)	−42	3448, 1718, 1653, 1600, 1585, 917, 909, 901	374.90	374
33146-09-7	**2**	137–139 (sint 135)	+57	1709, 1661, 1603, 1587, 1109, 877	409.34	408
60295-32-1	**3a**	275 dec	−1[c]	3448, 1770 (vw), 1698 (vw), 1650, 1610, 1587, 1412	478.24	476
60295-33-2	**3b**	227–230	+21 +11[c]	1757, 1672, 1618, 1595	520.28	518
60295-34-3	**5**			1852, 1761, 1669, 1618, 1600, 1235–1230	453.36	
60295-35-4	**6**	96–98 (sint 89)	+52.3	1754, 1718, 1667	432.93	
60295-36-5	**7**	216–218 (sint 214)	+24 +55[c]	1701, 1667, 1610, 1587, 1427, 1414, 1247, 1225, 990; ($CHCl_3$) 1701 (w), 1664, 1610, 1592	441.77	440
60295-37-6	**8**	200 dec (sint 160)		1664, 1613, 1595, 1053, 1043	441.80	440
60295-38-7	**9a**	232 dec (sint 228)	+107 +150[c]	3344, 3300, 1751, 1686, 1653, 1597, 1580	459.79	458
60295-39-8	**9b**	263 dec	+129[c]	1779, 1764, 1761, 1675, 1618, 1597	501.83	
60305-59-1	**15a**	222 dec		3390, 1695, 1669, 1610, 1587	461.81	460
60295-04-7	**15b**			3268, 3172, 1754, 1701, 1668, 1621, 1197, 1232, 1073	503.84	502
60295-05-8	**16**	205–211 (sint 180)	+107	1681, 1664, 1639 (sh), 1610, 1787, 1410, 1025, 1010, 891.3	372.88	

[a] Kofler hot-stage microscope or capillary melting point apparatus and are uncorrected. [b] Dioxane, unless otherwise indicated, at 25 °C at about 1% concentration. [c] Pyridine. [d] Nujol. [e] Varian MAT CH5 spectrometer using electron impact source at 70 eV and at 2.5 °C.

Table II. Analytical Data—Ultraviolet Absorption

Compd	λ_{max}	$\epsilon^{a,b}$	λ_{max}	$\epsilon^{c,f}$
1b	285	22 200		
2	283	21 400	278	22 100
			208[d]	4 400
3a	283	22 700[c]	278	23 700
	207.5	16 000[c]	208	15 100
3b	282.5	22 980[c]	278	23 500
	209	14 800[c]	208	14 700
5	282	17 400		
6	282	21 700		
7	283	25 800		
8	283	20 800[c]	278	21 200
	223	14 300[c]	223	13 800
			207[e]	10 100
9a	283	23 000		
9b	282	17 750		
15a	284	22 400		
15b	283	17 000		
16	283	20 400[c]	283	22 100
	206.5	13 700[c]	206.5	13 700

[a] MeOH as solvent. [b] Unless otherwise indicated, Cary 11 spectrometer. [c] Cary 118CX spectrometer. [d] Point on rising slope to 190 nm. [e] Inflection. [f] CH_3CN as solvent.

determining procedures and the nonhydrogen atom positional and thermal parameters were refined by full-matrix least-squares 1 and 2. Final positional and thermal parameters for the carbon, chlorine, and oxygen atoms (Tables V and VI) and calculated positions for the hydrogen atoms (Tables VII and VIII) are included in the supplementary material.[8]

Corresponding interatomic distances and valency angles, presented in Table IV, all agree well for chemically equivalent bonds and lie close to accepted values except in the oxetane ring of **3a** and ring D of **9a**. The strain involved in the oxetane ring of **3a** results in elongated C(16)–O(25) [1.54 (2) Å] and C(16)–C(17) [1.59 (2) Å] bonds. In **9a** bonds C(15)–C(16) [1.584 (11) Å] and C(16)–C(17) [1.574 (11) Å] are longer than normal owing to the highly substituted nature of ring D.

Complete lists of torsion angles defining the molecular conformations are in Table IX.[8] In **3a**, ring A with $\Delta(C_2)$ = 31°, $\Delta(C_s)$ = 25°,[9] and ring B with $\Delta(C_2)$ = 25°, $\Delta(C_s)$ = 25°, are intermediate between half-chair and envelope[10] conformations. In **9a**, ring A approximates to a C(1)α envelope form [$\Delta(C_2)$ = 51°, $\Delta(C_s)$ = 4°] while ring B has a conformation which lies closer to a C(9)α–C(10)β half-chair form [$\Delta(C_2)$ = 26°, $\Delta(C_s)$ = 40°]. In both compounds ring C has a distorted chair conformation, and ring D adopts a form intermediate between a C(14) envelope (C_s) and a C(16) half-chair (C_2) form characterized[11] by ϕ_{max} = 49°, Δ = −22° in **3a**, and ϕ_{max} = 48°, Δ = −56° in **9a**. The oxetane ring of **3a** has endocyclic torsion angles of ±9° and accordingly deviates by a small amount from planarity, the displacement of C(20) being to the α side of the C(17),C(16),O(25) plane in order to minimize nonbonded interactions with the C(13)-methyl group.

In the solid state molecules of **3a** and **9a** are linked by O–H···O hydrogen bonds between the tertiary hydroxyl group and the carbonyl oxygen of ring A. For **3a** the association occurs between molecules related by unit translations along both the *b* and *c* directions with O(24)···O(23′) = 3.12 Å,[12] and a C(17)–O(24)···O(23′) angle of 98°. In crystals of **9a** the molecules are associated by hydrogen bonding around the 2_1 screw axis along the c direction with O(25)···O(23″) = 2.97 Å,[12] and a C(16)–O(25)···O(23″) angle of 124°. All other short intermolecular separations are of the van der Waals type.

With the structures of **3a** and **9a** firmly established by the

Table III. ^{1}H NMR Data[a]

Compd	
1b	0.86 (13-CH_3), 1.18 (10-CH_3), 2.34 (20-CH_3), 5.10, 5.30 (16-CH_2), 6.31 (4-H), 6.31 (7-H), 3.28 (17-OH)
2	1.12 (13-CH_3), 1.17 (10-CH_3), 2.26 (20-CH_3), 6.33 (4-H), 6.26 (d, J = 2.2 Hz) (7-H), 3.68, 3.76 (ab doublets, J = 12.5 Hz) (16-CH_2Cl)
3a	0.99 (13-CH_3), 1.04 (10-CH_3), 6.05 (4-H), 6.44 (d, J = 2 Hz) (7-H), 6.57 (17-OH), 3.91, 4.06 (ab doublets, J = 12.5 Hz with D_2O sharpened) (16-CH_2Cl)
3b	1.19 (13-CH_3), 1.26 (10-CH_3), 2.16 (17-OCOCH_3), 6.35 (4-H), 6.26 (d, J = 1.5 Hz) (7-H), 3.98, 4.06 (ab doublets, J = 11.8 Hz) (16-CH_2Cl)
6	1.09 and 1.13 (10-CH_3 and 13-CH_3), 2.09 (16-CH_2O-C(=O)CH_3), 2.26 (20-CH_3), 4.21 and 4.50 (J = 12 Hz) (16-CH_2OAc), 6.25 (J = 2 Hz) (7-H), 6.33 (4-H)
7	1.17 (13-CH_3), 1.26 (10-CH_3) 6.37 (4-H), 6.47 (broad) (7-H), 5.04 and 4.90 (2 triplets, J = 1.8 Hz) (16-CH_2)
8	1.08 (13-CH_3), 1.13 (10-CH_3), 4.09 and 4.34 (ab doublets, 10.5 Hz) (16-CH_2), 6.15 (d, J = 2 Hz) (7-H), 6.29 (4-H)
9a	1.18 (13-CH_3, and 10-CH_3), 6.44 (4-H), 5.93 (d, J = 2 Hz) (7-H), 5.98 (16-$CHCl_2$), 5.34 (16-OH) (disappears with D_2O), 3.82 (d, 12 Hz) (15-H), 2.72 (15-$COCH_3$)
9b	1.15 and 1.18 (10-CH_3 and 13-CH_3), 6.30 (4-H), 5.89 (broad) (7-H), 5.93 (16-$CHCl_2$), 3.84 (d, 12 Hz) (slightly broadened, J = 12 Hz) (15-H), 2.64 (15-$COCH_3$)
15a	0.87 (13-CH_3), 1.09 (10-CH_3), 6.01 (4-H), 5.93 (d, J = 2.0 Hz) (7-H), 3.35 (d, J = 12 Hz) (15-H), 3.67 (d, J = 5.5) (singlet with D_2O) (17-H), 6.07 (16-$CHCl_2$), 2.36 (15-$COCH_3$), 5.20 (d, J = 5.5) (17-OH), 5.60 (16-OH) (disappears with D_2O)
15b	1.02 (13-CH_3), 1.15 (10-CH_3), 2.12 (17-OCOCH_3), 2.54 (15-$COCH_3$), 3.34 and 3.54 (15-H), 4.96 (17-H), 4.64 (16-OH), 5.82 (16-$CHCl_2$), 5.85 (d, J = 2 Hz) (7-H), 6.30 (4-H)
16	1.09 (13-CH_3), 1.16 (10-CH_3), 4.20 and 4.54 (ab doublets, J = 1.8 Hz) (20 = CH_2), 3.97 and 4.21 (ab doublets, 10.5 Hz) (16-CH_2), 6.20 (d, J = 2.2 Hz) (7-H), 6.32 (4-H)

[a] Varian A-60A spectrometer and $CDCl_3$ (unless otherwise stated), with chemical shifts given in parts per million downfield from Me_4Si (δ). [b] Me_2SO-d_6. [c] NMR taken on crude product.

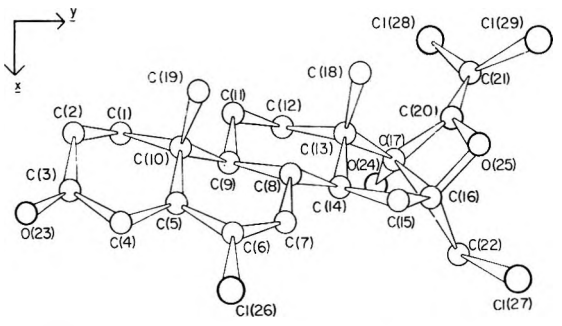


Figure 1. Atom numbering scheme and conformation of 3a.

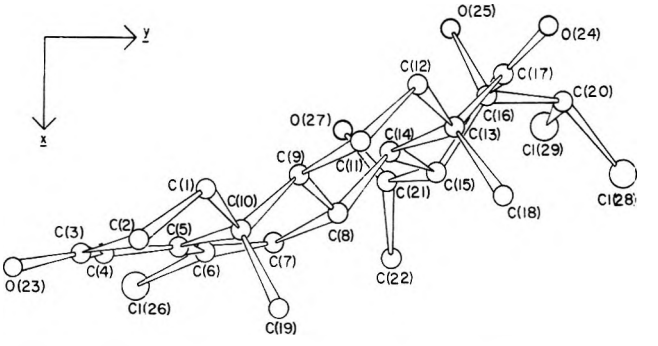
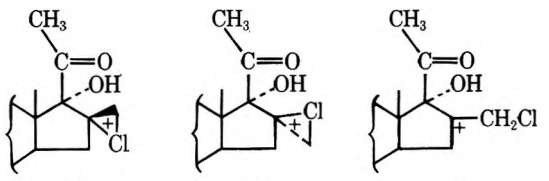


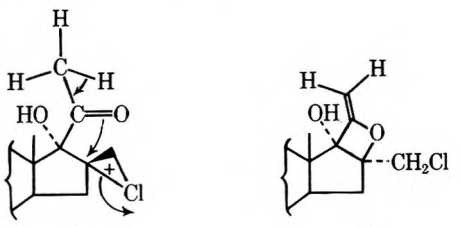
Figure 2. Atom numbering scheme and conformation of 9a.

x-ray analyses, the sequence of transformations may be rationalized in the following manner.

Chlorination of 1b may afford an α- or β-chloronium species such as depicted in 17 or 18. Attack by the 17α-hydroxyl group



17 18 19

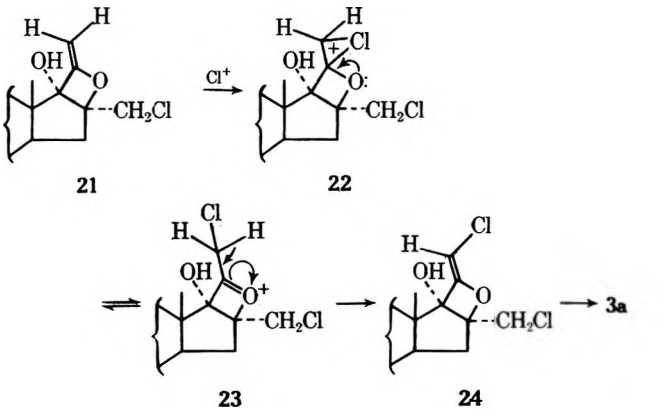


20 21

at the incipient C(16) carbonium species of 18 would readily produce oxide 2. Transformation of 17 to 2 would appear less likely to occur except through the formation of a species which approaches canonical form 19. However, polarization of the C(20) carbonyl bond with subsequent attack at C(16) as shown in 20 would lead to 21.

Chlorination of the C(20) methylene group may be visualized as proceeding in a stepwise manner involving electron donation by the oxetane oxygen as shown in the sequence 21 → 22 → 23 → 24 (Scheme I), with repetition of this process

Scheme I



to yield 21,21-dichloro 3a. (Reference 13 includes a less preferred process.)

Transformation of 3 to 7 may be visualized as proceeding

Table IV. Interatomic Distances (Å) and Valency Angles (deg), with Estimated Standard Deviations in Parentheses

A. Bond Lengths

	3a	9a		3a	9a
C(1)–C(2)	1.51 (3)	1.540 (15)	C(13)–C(18)	1.54 (2)	1.553 (12)
C(1)–C(10)	1.54 (2)	1.590 (13)	C(14)–C(15)	1.52 (2)	1.563 (11)
C(2)–C(3)	1.50 (2)	1.469 (15)	C(15)–C(16)	1.55 (2)	1.584 (11)
C(3)–C(4)	1.44 (3)	1.489 (17)	C(15)–C(21)		1.514 (12)
C(3)–O(23)	1.26 (2)	1.216 (11)	C(16)–C(17)	1.59 (2)	1.574 (13)
C(4)–C(5)	1.37 (2)	1.355 (13)	C(16)–C(20)		1.511 (13)
C(5)–C(6)	1.45 (2)	1.466 (12)	C(16)–C(22)	1.51 (2)	
C(5)–C(10)	1.53 (2)	1.501 (13)	C(16)–O(25)	1.54 (2)	1.405 (10)
C(6)–C(7)	1.33 (2)	1.307 (12)	C(17)–C(20)	1.52 (2)	
C(6)–Cl(26)	1.76 (2)	1.767 (8)	C(17)–O(24)	1.38 (2)	1.200 (11)
C(7)–C(8)	1.52 (2)	1.523 (12)	C(20)–C(21)	1.29 (2)	
C(8)–C(9)	1.57 (2)	1.552 (12)	C(20)–O(25)	1.40 (2)	
C(8)–C(14)	1.53 (2)	1.511 (10)	C(20)–Cl(28)		1.767 (10)
C(9)–C(10)	1.57 (2)	1.541 (12)	C(20)–Cl(29)		1.778 (11)
C(9)–C(11)	1.52 (2)	1.561 (12)	C(21)–C(22)		1.432 (12)
C(10)–C(19)	1.57 (2)	1.526 (11)	C(21)–O(27)		1.247 (11)
C(11)–C(12)	1.54 (2)	1.552 (13)	C(21)–Cl(28)	1.69 (2)	
C(12)–C(13)	1.54 (2)	1.512 (12)	C(21)–Cl(29)	1.75 (2)	
C(13)–C(14)	1.54 (2)	1.540 (11)	C(22)–Cl(27)	1.83 (2)	
C(13)–C(17)	1.57 (2)	1.511 (12)			

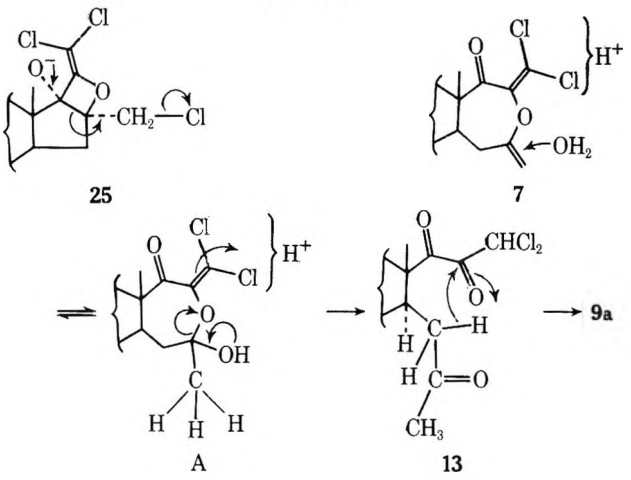
B. Valency Angles

	3a	9a		3a	9a
C(2)–C(1)–C(10)	111.8 (15)	109.9 (8)	C(8)–C(14)–C(15)	117.4 (14)	121.6 (6)
C(1)–C(2)–C(3)	112.0 (14)	113.3 (9)	C(13)–C(14)–C(15)	105.2 (12)	103.8 (6)
C(2)–C(3)–C(4)	118.3 (15)	118.8 (8)	C(14)–C(15)–C(16)	99.8 (13)	99.4 (6)
C(2)–C(3)–O(23)	122.3 (15)	122.8 (11)	C(14)–C(15)–C(21)		115.4 (6)
C(4)–C(3)–O(23)	119.1 (16)	118.3 (10)	C(16)–C(15)–C(21)		113.8 (6)
C(3)–C(4)–C(5)	122.5 (9)	120.8 (9)	C(15)–C(16)–C(17)	109.1 (12)	103.6 (7)
C(4)–C(5)–C(6)	123.6 (15)	121.7 (9)	C(15)–C(16)–C(20)		115.7 (7)
C(4)–C(5)–C(10)	121.3 (14)	123.7 (9)	C(15)–C(16)–C(22)	119.8 (13)	
C(6)–C(5)–C(10)	115.1 (13)	114.5 (7)	C(15)–C(16)–O(25)	113.3 (12)	113.9 (6)
C(5)–C(6)–C(7)	126.8 (15)	125.5 (8)	C(17)–C(16)–C(20		111.8 (7)
C(5)–C(6)–Cl(26)	116.2 (12)	116.8 (6)	C(17)–C(16)–C(22)	114.4 (13)	
C(7)–C(6)–Cl(26)	117.0 (12)	117.5 (6)	C(17)–C(16)–O(25)	87.3 (10)	104.8 (7)
C(6)–C(7)–C(8)	119.9 (13)	122.9 (7)	C(20)–C(16)–O(25)		106.6 (7)
C(7)–C(8)–C(9)	111.2 (11)	107.5 (7)	C(22)–C(16)–O(25)	108.5 (11)	
C(7)–C(8)–C(14)	114.8 (7)	115.6 (7)	C(13)–C(17)–C(16)	102.3 (12)	108.7 (7)
C(9)–C(8)–C(14)	109.9 (13)	108.8 (6)	C(13)–C(17)–C(20)	116.4 (11)	
C(8)–C(9)–C(10)	109.4 (12)	112.0 (6)	C(13)–C(17)–O(24)	112.9 (11)	128.9 (9)
C(8)–C(9)–C(11)	112.6 (11)	112.7 (7)	C(16)–C(17)–C(20)	85.0 (10)	
C(10)–C(9)–C(11)	114.7 (11)	113.8 (7)	C(16)–C(17)–O(24)	119.8 (11)	122.4 (8)
C(1)–C(10)–C(5)	110.8 (12)	109.7 (7)	C(20)–C(17)–O(24)	117.1 (13)	
C(1)–C(10)–C(9)	109.5 (14)	109.8 (7)	C(16)–C(20)–Cl(28)		113.3 (7)
C(1)–C(10)–C(19)	109.9 (12)	109.0 (7)	C(16)–C(20)–Cl(29)		112.1 (7)
C(5)–C(10)–C(9)	108.3 (11)	108.6 (7)	C(17)–C(20)–C(21)	138.1 (15)	
C(5)–C(10)–C(19)	106.4 (13)	108.5 (6)	C(17)–C(20)–O(25)	95.2 (11)	
C(9)–C(10)–C(19)	111.8 (11)	111.1 (7)	C(21)–C(20)–O(25)	126.6 (14)	
C(9)–C(11)–C(12)	112.3 (12)	112.6 (7)	Cl(28)–C(20)–Cl(29)		109.0 (5)
C(11)–C(12)–C(13)	112.2 (14)	110.3 (7)	C(15)–C(21)–C(22)		117.9 (7)
C(12)–C(13)–C(14)	106.7 (12)	111.0 (7)	C(15)–C(21)–O(27)		119.1 (8)
C(12)–C(13)–C(17)	115.3 (14)	114.6 (7)	C(20)–C(21)–Cl(28)	123.0 (13)	
C(12)–C(13)–C(18)	109.6 (12)	109.4 (7)	C(20)–C(21)–Cl(29)	121.4 (13)	
C(14)–C(13)–C(17)	101.1 (11)	102.3 (7)	C(22)–C(21)–O(27)		123.0 (8)
C(14)–C(13)–C(18)	112.9 (14)	113.4 (6)	Cl(28)–C(21)–Cl(29)	115.6 (9)	
C(17)–C(13)–C(18)	110.9 (12)	106.0 (7)	C(16)–C(22)–Cl(27)	108.7 (11)	
C(8)–C(14)–C(13)	112.0 (11)	111.3 (6)	C(16)–O(25)–C(20)	91.3 (10)	

from the base generated anion **25** as depicted via ketonization of the 17α-hydroxyl group. The coupling exhibited in the NMR is consistent with the presence of an exocyclic methylene group. The increase in intensity of the band at 283 nm may be attributed to the chromophoric contribution of the conjugated unit contained in ring D of **7**.

Formation of **9a** may be considered to occur by the acid-catalyzed hydration of **7** followed by cleavage of species "A" to **13** and then recyclization to **9a** (Scheme II). The chemical shift of 2.72 ppm for the 15-acetyl methyl in **9a** is significantly further downfield than is usually found for methyl ketones (2.00–2.20 ppm) and merits some comment. Since the corresponding signal in acetate **9b** occurs at 2.64 ppm it does not appear likely that the deshielding effect is due to intramo-

Scheme II



lecular hydrogen bonding involving the hydroxyl group of **9a**. Although it is not revealed in the crystalline rotamer as shown by x-ray analysis (Figure 2), Dreiding model orientation of the 15-acetyl group indicates that in solution this grouping may lie close to the chlorine atoms of the 16β-dichloromethyl group, a feature reflected in solution NMR as a deshielding effect. A like conclusion would apply to **15a** and **15b** in which the ring D conformations would differ slightly from those in **9a** and **9b** owing to the absence of the 17-keto group. A substantial shielding effect would be expected from the spatial orientation of the 15-acetyl carbonyl relative to the 7 hydrogen and this is indeed observed in the chemical shifts for this proton in **9a, 9b, 15a,** and **15b,** all of which display signals more upfield than those in **1, 2, 3a, 3b, 6,** and **7.**

The presence of a singlet absorption at 2.36 ppm in **15a** indicates that mild $NaBH_4$ reduction (vide supra) of **9a** occurred selectively at the 17 carbonyl in preference to the 15 carbonyl. Reduction to form a 15(1′-hydroxyethyl) unit in this reaction would have been indicated by coupling of the terminal methyl group with the hydrogen geminal to the hydroxy group.

The 17-hydroxy group in **15a** is probably β oriented since approach of the reducing agent from the β side of **9a** would be severely hindered by the combined steric effects of the 16β-dichloromethyl and 13-methyl groups and would thus be more likely to occur from the α side which has the less bulky 16α-hydroxy group.

Finally, we note (Table II) the lower wavelength ultraviolet absorptions for compounds **3a** and **3b,** as well as **8** and **16,** which are attributable to the exocyclic methylene unit. The dichloromethylene moiety exocyclic to the four-membered ring system in **3a** and **3b** has its maximum at 208 nm. The exocyclic dichloromethylene grouping of the five-membered ring system in **8,** however, has an ultraviolet maximum at 223 nm, with an inflexion at 207 nm, whereas the related methylene (hydrogens attached to the 20 carbon) has its lower wavelength absorption at 206.5 nm. The effect of the allylic 16,17-oxide unit on the lower wavelength absorption of the methylene group in **8** and **16** has not been defined.

Experimental Section

Crystal Data. $C_{22}H_{24}Cl_4O_3$ **(3a),** mol wt 478.3. Orthorhombic, a = 26.95 (3), b = 10.83 (2), c = 7.44 (2) Å, U = 2172 Å^3, d_m (flotation) = 1.45 g cm^{-3}, Z = 4, d_c = 1.463 g cm^{-3}, $F(000)$ = 992. Cu Kα radiation, λ = 1.542 Å; absorption coefficient for Cu Kα radiation, μ = 51.2 cm^{-1}. Space group $P2_12_12_1(D_4^2)$ uniquely established from the systematic absences: $h00$ when $h \neq 2n$, $0k0$ when $k \neq 2n$, $00l$ when $l \neq 2n$.

$C_{22}H_{25}Cl_3O_4$ **(9a),** mol wt 459.8. Orthorhombic, a = 13.09 (1), b = 17.69 (1), c = 9.47 (1) Å, U = 2193 Å^3, d_m (flotation) = 1.39 g cm^{-3}, Z = 4, d_c = 1.393 g cm^{-3}, $F(000)$ = 960. Mo Kα radiation, λ = 0.7107 Å; absorption coefficient for Mo Kα radiation, μ = 4.5 cm^{-1}. Space group $P2_12_12_1(D_4^2)$ established by the systematic absences which were the same as for **3a.**

Crystallographic Measurements. Unit-cell dimensions for **3a** were obtained from rotation and zero-level Weissenberg photographs taken with Ni-filtered Cu Kα radiation. For **9a** preliminary unit-cell dimensions derived in a like manner were refined by least-squares treatment of the θ, χ, and ϕ angles for 40 reflections accurately centered on an Enraf-Nonius CAD 3 automated diffractometer (Zr-filtered Mo Kα radiation; 3° take-off angle).

Intensity data for the hk0-6 reciprocal lattice nets of **3a** were recorded photographically by the multiple-film equi-inclination Weissenberg method and estimated visually by comparison with a calibrated intensity strip. These data were assumed initially to be on a common scale as each level had been given approximately equal exposure times; absolute layer scales were derived at the end of the isotropic refinement cycles by correlation of $\Sigma|F_o|$ with $\Sigma|F_c|$. Application of spot-shape corrections and the usual Lorentz and polarization factors yielded 1402 independent structure amplitudes which were used in the structure analysis and refinement. No corrections were made for absorption or extinction.

For **9a** all unique intensity data up to 2θ 50° were measured on an Enraf-Nonius CAD 3 automated diffractometer (Zr-filtered Mo Kα radiation; 3° take-off angle) with a crystal of dimensions ca. 0.20 × 0.80 × 0.30 mm oriented so that the crystal b axis was parallel to the diffractometer ϕ axis. Data were recorded by the θ–2θ scanning technique with scan widths (1.00 + 0.50 tan θ); stationary background measurements were made at each end of the scan range for a time equal to half the scan period. Instrument and crystal stability were monitored throughout by remeasuring the intensity of a strong standard reflection after each batch of 99 reflections; no significant variation was noted. From a total of 2222 measurements, 1243 reflections for which $I > 2.0\sigma(I)$, where $\sigma(I)$ = (scan count + total background count)$^{1/2}$, were used in the structure analysis and refinement. Absorption corrections determined from the ϕ dependence of the 0 8 0 reflection measured at χ = 90° were applied to these data which were then corrected for Lorentz and polarization effects.

Structure Analyses. The crystal structures were solved by direct noncentrosymmetric phase-determining procedures using MULTAN[14] with the 251 (**3a**) and 243 (**9a**) largest $|E|$ values. In each case the program was allowed to select four reflections in addition to the three origin defining reflections and the correct solutions corresponded to those sets with the highest figures-of-merit and lowest residuals.

For **3a** the initial structure model gave R = 0.351 when structure factors were calculated and this was reduced to 0.147 by full-matrix least-squares refinement of the atomic positional and isotropic thermal parameters. Inclusion of the hydrogen atoms at their calculated positions, with B = 4.0 Å^2, then decreased R to 0.141. After two more cycles of refinement during which the chlorine atoms were allowed to assume anisotropic thermal parameters, the anomalous scattering corrections for chlorine were introduced, and for structure factors calculated with coordinates corresponding to the known natural steroid absolute configuration R at 0.116 was significantly lower than for the mirror image (R = 0.120). Several further rounds of least-squares calculations during which the nonhydrogen atom parameters were varied brought the refinement to convergence at R = 0.101 when no parameter shift exceeded 0.10 times its estimated standard deviation. The analysis of **9a** followed a similar course from an initial R value of 0.286 to a final value of 0.059. Fractional atomic coordinates and thermal parameters for the nonhydrogen atoms (Tables V and VI) and calculated hydrogen atom coordinates (Tables VII and VIII) are included in the supplementary material. The lists of observed and calculated structure amplitudes (Tables XI and XII) are available upon request.[18]

Scattering factors used in all the structure-factor calculations were those for C, O, and Cl in the Cromer and Waber[15] compilation, with that for Cl corrected for anomalous dispersion;[16] for H the Stewart, Davidson, and Simpson[17] values were used. In the least-squares calculations $\Sigma w\Delta^2$ ($\Delta = |F_o| - |F_c|$) was minimized, the weights w being assigned according to the scheme $\sqrt{w} = 1$ for $F_o < K$, and $\sqrt{w} = K/|F_o|$ for $|F_o| > K$ (K = 25.0 for **3a,** = 15.0 for **9a**).

Reaction of 16-Methylene-6-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione (1b) with Chlorine. Preparation of 6-Chloro-16β-chloromethyl-16α,17α-oxido-4,6-pregnadiene-3,20-dione (2) and 6,21,21-Trichloro-16α-chloromethyl-16β,20-oxido-17α-hydroxy-4,6,20-pregnatrien-3-one (3a). A solution containing 2.08 g of chlorine in CCl_4 (57.7 ml) was added to a solution of 10 g of **1b** contained in 500 ml of CH_2Cl_2 and 2.37 ml of pyridine. Consumption of chlorine occurred almost instantaneously. After approximately 7 min the solution was washed with water and evaporated to a residue which was chromatographed on 1100 g of silica

gel eluting with ether–hexane (1:1 to 8.5:1.5) to obtain 2.3 g of unreacted **1b**, 5.9 g (54%) of **2**, crystallized from ether, and 1.5 g (11.5%) of the tetrachloro **3a**, crystallized from EtOAc.

Preparation of 6,21,21-Trichloro-16α-chloromethyl-16β,20-oxido-17α-hydroxy-4,6,20-pregnatrien-3-one 17-Acetate (3b). Trifluoroacetic anhydride (32 ml) was added dropwise in a 15-min time interval to a mixture consisting of 2.63 g of **3a**, 0.79 g of *p*-TsOH·H_2O, and 79 ml of AcOH with stirring, then stirring was maintained for 19 h. The reaction mixture was added to a 1-l. aqueous saturated sodium chloride solution. Insolubles were collected and dried (2.87 g) and then chromatographed on 287 g of silica gel, eluting with ether–hexane (2:3–3:2) to obtain after crystallization from EtOAc 2.14 g (75%) of **3b**.

Preparation of 6-Chloro-16-methylene-17-oxa-17a-dichloromethylenedi-D-homo-4,6-androstadiene-3,17b-dione (7). From 3a. A mixture consisting of 1.44 g of **3a**, 14.4 g of anhydrous KOAc, and 216 ml of acetone was refluxed for 2 h. The mixture was filtered, and the filtrate evaporated to dryness. The residue was taken up in CH_2Cl_2, washed with water, and evaporated to give a residue which was crystallized from EtOAc, 1.1 g (80%) of **7**.

From 3b. Exposure of 1.3 g of **3b** to 5 equiv of NaOH, in MeOH–CH_2Cl_2 for 15 min and workup gave **7** in approximately 90% conversion.

Preparation of 6-Chloro-15α-acetyl-16β-dichloromethyl-16α-hydroxy-4,6-androstadiene-3,17-dione (9a). A mixture consisting of 550 mg of **7**, 11 ml of H_2O, 5.5 ml of 70% $HClO_4$, and 38.5 ml of THF was heated at 60 °C for 29 h, then added to 10 volumes of water and extracted with CH_2Cl_2. Evaporation gave a residue of 585 mg which was chromatographed with 1000-μ silica gel plates, eluting with acetone–CH_2Cl_2, giving 430 mg (78%) of **9a**, crystallized from MeOH.

Preparation of 6-Chloro-15α-acetyl-16β-dichloromethyl-16α-hydroxy-4,6-androstadiene-3,17-dione 16-Acetate (5b). A solution consisting of 100 mg of **9a**, 2 ml of pyridine, and 1.0 ml of Ac_2O was kept at room temperature for 18 h. Usual workup gave a crude residue (98 mg). Crystallization from MeOH afforded 70 mg of 16-acetate **9b**.

6-Chloro-15α-acetyl-16β-dichloromethyl-16α,17β-dihydroxy-4,6-androstadien-3-one (15a). A. Reduction of 9a with $NaBH_4$. $NaBH_4$ (250 mg solid) was added to a solution of 0.5 g of **9a** in 5 ml of CH_2Cl_2, 5 ml of MeOH, and 1 ml of water, at 5 °C with stirring. After 25 min, dilute acetic acid was added to neutrality, most of the solvent was evaporated, water was added, and insolubles were collected. Crystallization from EtOAc gave 230 mg of **14** (uv showed no 3-keto-$\Delta^{4,6}$ absorption).

B. Generation of 15a with MnO_2. Activated MnO_2 (450 mg) was added to a solution of 150 mg of **14** in 15 ml of CH_2Cl_2, and the mixture stirred at room temperature for 1 h, then the insolubles were separated by filtration. Workup of the filtrate gave 120 mg (TLC, mainly one component), crystallized from EtOAc to yield 61 mg (41%) of **15a**.

6-Chloro-15α-acetyl-16β-dichloromethyl-16α,17β-dihydroxy-4,6-androstadien-3-one 17-Acetate (15b). The 17-hydroxy **15a** (20 mg) was added to 0.2 ml of Ac_2O and 0.4 ml of pyridine and maintained at room temperature for 61 h. The usual workup gave 21 mg of **15b** (TLC, approximately 5–10% impurity, visually).

Preparation of 6-Chloro-16α,17α:16a,20-dioxido-4,6,20-pregnatrien-3-one (16). *t*-BuOK (1.2 g) was added to a stirred solution consisting of 1.4 g of **2** and 118 ml of *t*-BuOH, under N_2, at room temperature. After 30 min, the mixture was added to 10 volumes of water and worked up in the usual way, giving 1.4 g of crude residue. Chromatography on 140 g of silica gel, eluting with mixtures of ether–hexane, gave, after crystallization from EtOAc, 0.48 g (37%) of **16**.

Preparation of 6-Chloro-21,21-dichloromethylene-16α,17α:16a,20-dioxido-4,6,20-pregnatrien-3-one (8). A 1.89-ml solution of chlorine (1.18 mmol) in CCl_4 was added to a solution consisting of 207 mg (0.555 mmol) of **16**, 100 mg of pyridine, and 11 ml of CH_2Cl_2, and the solution was stirred for 7 min. Although starch–iodide test paper was still positive, the solution was added to 10 ml of 0.1 N $Na_2S_2O_3$ solution and the mixture extracted with CH_2Cl_2. The residue from CH_2Cl_2 exhibited several components by TLC (silica gel). Separation of the components on 1000-μ silica gel preparative plate, developing with C_6H_{12}–EtOAc (4:1), then rechromatographing selected areas with $CHCl_3$ gave 23 mg of **8**, TLC indicating (H_2SO_4–MeOH stain) approximately 90–95% purity.

Reaction of 3b with Ozone. Attempted Preparation of 5. Ozone was added to a solution of 260 mg of **3b** in 16 ml of EtOAc and 5 ml of pyridine at −60 °C. Ten minutes after the development of blue solution, 6 ml of AcOH and 1 g of zinc dust were added and the solution was worked up in the usual way to afford a neutral fraction from which 14 mg (designated as **5**) was obtained after silica gel preparative plate [1000 μ, $CHCl_3$–EtOAc (9:1)] which still appeared by visual inspection of TLC to have 20–30% impurities.

Acknowledgments. We thank Dr. M. Yudis and Mrs. H. Marigliano for instructive NMR discussions.

Registry No.—**14**, 60295-06-9.

Supplementary Material Available. Tables of atomic coordinates and thermal parameters for the nonhydrogen atoms (Tables V and VI), hydrogen atom coordinates (Tables VII and VIII), torsion angles (Table IX), and elementary analyses (Table X) (10 pages). Ordering information is given on any current masthead page.

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(8) See paragraph at end of paper regarding supplementary material.

(9) Deviations from ideal half-chair (C_2) and envelope (C_s) conformations are expressed in terms of the endocyclic torsion angles, ω_{ij}, about the bonds between atoms C(*i*) and C(*j*). In ring A, $\Delta(C_2) = |\omega_{2,3} - \omega_{1,10}| + |\omega_{3,4} - \omega_{5,10}|$, $\Delta(C_s) = |\omega_{1,2} + \omega_{1,10}| + |\omega_{2,3} + \omega_{5,10}| + |\omega_{3,4} + \omega_{4,5}|$. In ring B, $\Delta(C_2) = |\omega_{5,10} - \omega_{8,9}| + |\omega_{5,6} - \omega_{7,8}|$, $\Delta(C_s) = |\omega_{8,9} + \omega_{9,10}| + |\omega_{5,10} + \omega_{7,8}| + |\omega_{5,6} + \omega_{6,7}|$.

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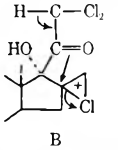
(12) O(23′) in **3a** requires transformation of the coordinates of Table V to $x, -1 + y, 1 + z$; for O(23″) in **9a** the coordinates of Table VI should be transformed to $\frac{1}{2} - x, 2 - y, \frac{1}{2} + z$.

(13) A less attractive process for the formation of 3a would require mono- or dichlorination at C(21) to precede oxetane formation via a species such as B. However, supportive for our preferred sequence for **3a** formation



B

(although not proof) is the following. (a) When **2** was subjected to the same conditions as were employed for the **1a** → **3** transformation no reaction resulted. (b) Similar treatment of **1a** produced no 16,20-oxide **3b**, and **1a** was substantially recovered. (c) On the other hand, 21,21-dichloro **8** was obtained (9% yield) when **16** was treated similarly. [This furan system was first reported by D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Org. Chem.*, **29**, 3486 (1964). In essence, we utilized their process for the preparation of **16** from **2**.] Although **16** contains a tetrahydrofuran system in contrast to the oxetane ring of **21**, it does not seem unreasonable to extend this transformation to the latter system.

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Studies Directed toward the Synthesis of Prostaglandins. Useful Boron-Mediated Olefin Syntheses

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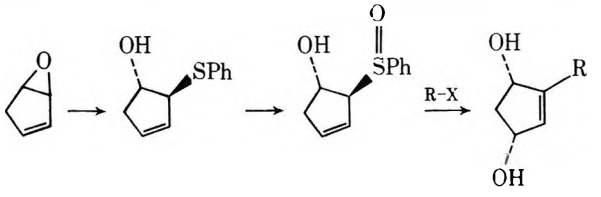
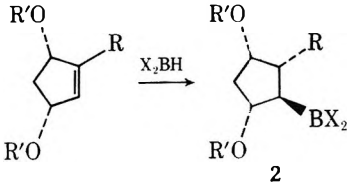
The reactions of bis(2-ethylcyclopentyl)borane, dicyclopentylborane, with 3-(*tert*-butydimethylsiloxy)-1-octyne and subsequent iodine-promoted rearrangement to *Z* olefins or unsymmetrical acetylenes are reported. Mixed dialkylboranes are also examined in this olefin–acetylene cross process. Significant amounts of thexyl-migrated acetylenic by-products are observed in several instances. The synthesis of either *E*- or *Z*-1,2-disubstituted olefins by reaction of boronic esters with both (*E*)- and (*Z*)-alkenyllithium reagents is examined. This study demonstrates that 50–70% yields of either *E*- or *Z*-1,2-disubstituted olefins are obtainable from the aforementioned reagents. The overall objectives in this investigation are to assess the potential of emplcying organoborane intermediates in the coupling of the C_{13}–C_{20} prostaglandin olefinic side chain to cyclopentenoid precursors.

As part of our program directed toward the total synthesis of prostaglandin hormones we recently reported a general stereospecific approach to the synthesis of *cis*-2-alkyl-2-cyclopentene-1,4-diols (1) via the three-step sequence illustrated below.[2] This expeditious synthetic scheme readily affords a



1

variety of functionalized cyclopentene derivatives which should be amenable to further elaboration to various prostanoids and known intermediates in published prostaglandin syntheses.[3] Based upon the multitude of cross-coupling reactions that have been developed in recent years which have employed organoboranes,[4] we have initiated studies aimed at transforming olefins such as 1 to organoborane intermediates (cf. 2). These intermediates could serve as versatile precursors to elaborated prostanoid intermediates such as 3–5.



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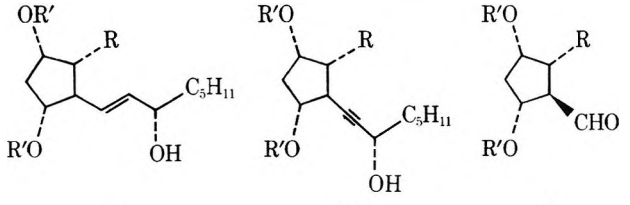
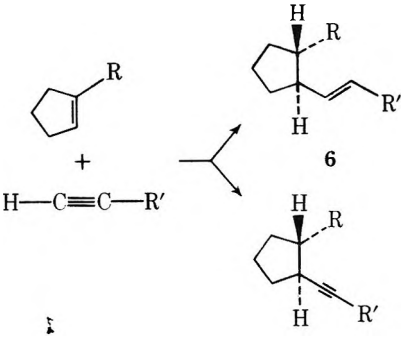


3 4 5

At the present time it is a rare occurrence when boron-mediated carbon–carbon bond constructions are employed in a multistage organic synthesis. This underutilization of a potentially powerful class of reactions generally is due to the relative inefficiency with which a single carbon ligand on a given boron atom can be coupled to other carbon substrates. Partial solutions to this shortcoming have been provided via the design of boron-bound carbon ligands such as 9-BBN[5] and thexyl[6] which generally exhibit low migratory aptitudes in organoborane transformations; however, in specific cases even these ligands lead to unwanted side reactions (vide infra). The purpose of this study has been to survey those organoborane cross-coupling processes which could be ultimately applicable to coupling the C_{13}–C_{20} prostaglandin side chain (cf. **3**, **4**) to cyclopentene precursors in high efficiency with respect to the cyclopentene moiety.

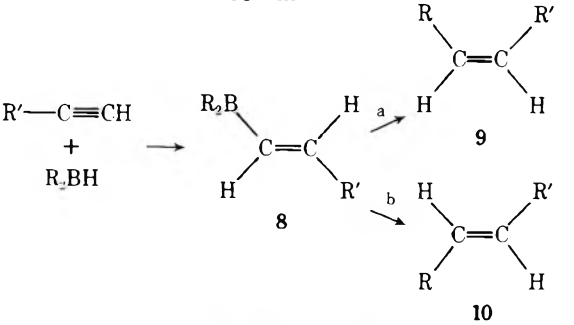
Boron-Mediated Olefin Synthesis. The application of organoboranes to carbon–carbon bond construction has been extensively studied, and a wide variety of processes are becoming available for carbon skeletal assemblage.[4] Of particular interest in the present study were those processes which assemble cyclic olefinic and acetylenic moieties to *E* olefins and internal acetylenes as schematically represented below (cf. **6** and **7**).



6 7

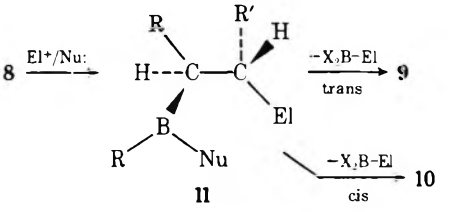
Recently, an elegant approach to the synthesis of both *E*- and *Z*-1,2-disubstituted olefins from common intermediates has been reported by Zweifel (Scheme I).[7] Dialkylborane–

Scheme I

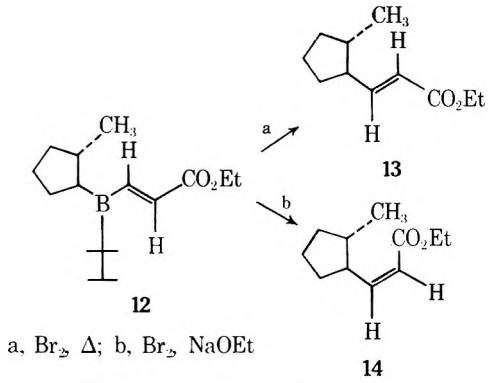


a, I_2, ^-OH; b, BrCN

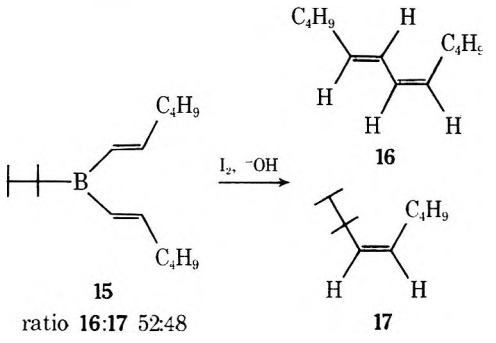
Stereochemistry



acetylene hydroboration has been shown to readily produce vinylborane intermediates **8**. In situ electrophile-induced (El^+) rearrangements of these species has been postulated to proceed via **11** to either the *Z* olefin **9** by base-induced trans fragmentation or to the *E* olefin **10** by thermal cis elimination of the boron and electrophile functions.[7] Both processes have been shown to be highly stereoselective and afford olefins of high (92–99%) stereochemical purity. Recently Negishi has employed this olefination sequence in the synthesis of the α,β-unsaturated esters **13** and **14** in 91–95% isomeric purity.[8]

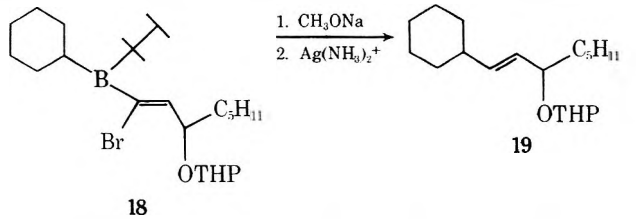


It is noteworthy that less than 3% of competitive thexyl migration was observed in the rearrangement of **12**. In various related olefination processes it has been reported that competitive thexyl ligand migration has not posed serious problems.[9-11] One notable exception is the diene synthesis shown below where the alkenyl and thexyl ligands in **15** exhibit

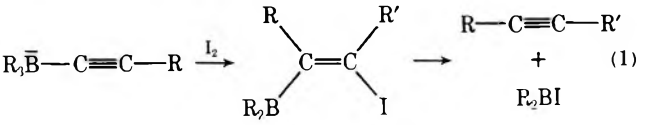


comparable migratory aptitudes.[7b] With respect to results which are to be presented (vide infra) we have observed a similar competition between thexyl and secondary alkyl ligands in analogous vinylborane rearrangements.

In a preliminary communication closely related to the present study, Corey[11] has reported that the base-catalyzed rearrangement of vinylborane **18** and subsequent deboronation afforded the *E* olefin **19** in 65% yield with no mention of the thexyl-migrated olefin.



Mechanistically related olefin–acetylene coupling reactions have recently been reported by several investigators.[12,13] Lithium alkynyltrialkylboronates have been shown to rearrange and undergo subsequent cis elimination upon treatment with either iodine[12] or methanesulfinyl chloride to afford good yields of internal acetylenes (eq 1). Superficially, such acetylene syntheses appear to be attractive candidates for appending alkenyl side chains to cyclic olefinic substrates. This mode of bond construction, however, loses much of its appeal

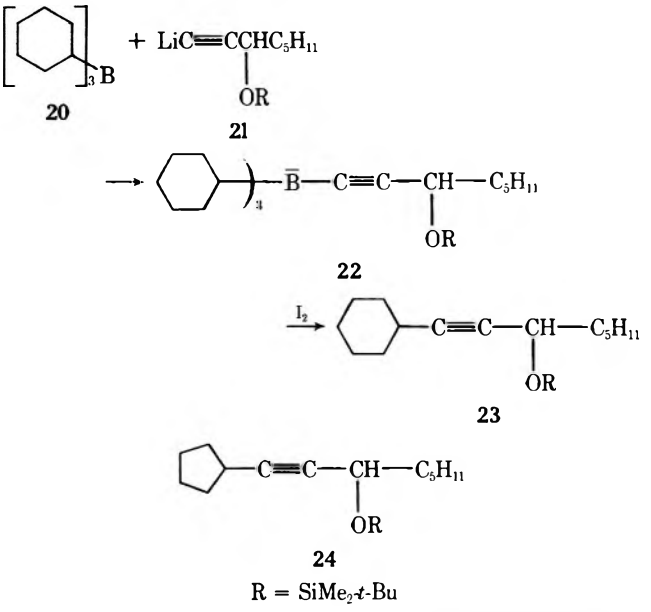


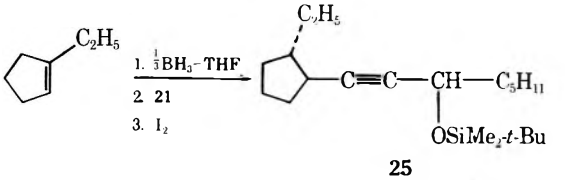
with the realization that only one of the three carbon ligands on boron can be effectively utilized in the cross-coupling process. Studies directed toward defining practical "nonmigrating" carbon ligands have met with mixed success in the above process.[13b,14]

In an effort to ascertain whether any or all of the above olefination sequences could be efficiently applied to the elaboration of the C_{13}–C_{20} olefinic prostanoid side chain onto cycloalkene derivatives (cf. **1** → **3**), the following general studies were undertaken.

Synthesis of Internal Acetylenes. The reaction sequence chosen for initial study was the acetylene synthesis illustrated in eq 1.[12,13] Following the procedure of Brown and co-workers,[12] reaction of tricyclohexylborane (**20**) with the lithium acetylide **21** followed by iodine-promoted decomposition of ate complex **22** afforded acetylene **23** in greater than 65% yield. The corresponding cyclopentyl acetylene **24** was also produced in comparable yield from tricyclopentylborane.[15] These preliminary experiments firmly establish that the *tert*-butyldimethylsilyloxy function does not interfere with the desired coupling reaction. Extension of this acetylene–olefin cross-coupling to trisubstituted olefins was next examined. Reaction of ethylcyclopentene (3 equiv) with BH_3–THF (1 equiv)[16] followed by successive addition of lithium acetylide **21** (R = $SiMe_2$-*t*-Bu) and iodine afforded the desired acetylene **25** in

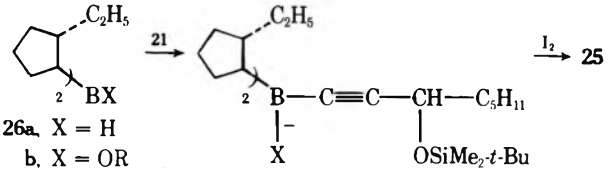
Scheme II





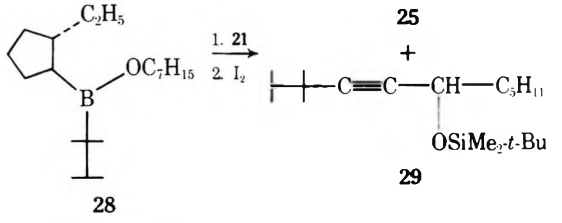
only 31% yield. The lower yields encountered in this instance could have been associated with difficulties in the formation of the trialkylborane with this olefin,[17] or due to possible steric factors associated with either formation or rearrangement of the intermediate ate complex.[18] Since the penultimate intermediate in the acetylene coupling reaction is the presumed ate complex **27** (X = C_7H_{13}) (Scheme III), various alternate approaches to **27** from the dialkylborane **26a**[17] were investi-

Scheme III

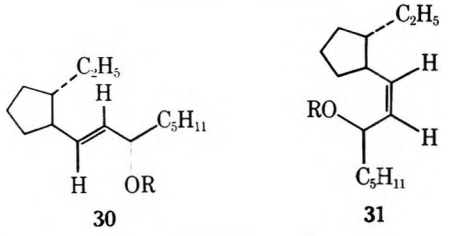


Procedure	Yield of 25, %
A: 1, n-C_4H_9OH; 2, **21**; 3, I_2	20
B: 1, **21**; 2, n-$C_6H_{13}CHO$; 3, I_2	25
C: 1, n-$C_6H_{13}CHO$; 2, **21**; 3, I_2	72

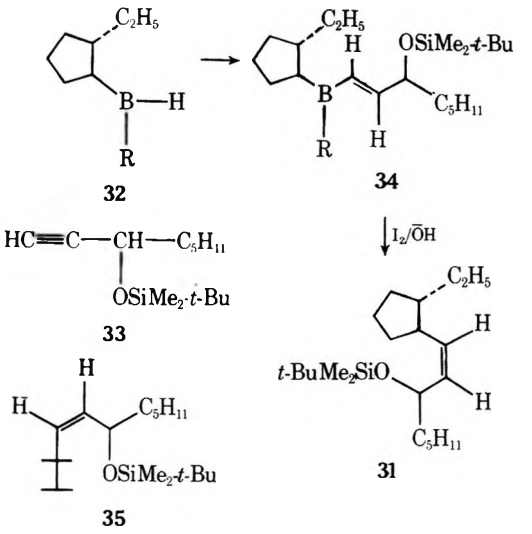
gated. In order to avoid competitive ligand migration in the rearrangement of **27**, an alkoxyl group was chosen as the nonmigrating ligand in the ate complex.[19] In situ generation of dialkylborane **26a** followed by the successive addition of 1-butanol (1 equiv) and lithium acetylide **21** afforded the presumed complex **27b** (X = OC_4H_9). Subsequent rearrangement afforded acetylene **25** in only 20% yield (procedure A). An alternate procedure was examined within **27a**, produced via the addition of **21** to **26a**, was transformed into the alkoxy ate complex **27b** (X = OC_7H_{15}) by reaction with heptanal. However, after stirring the borohydride complex in the presence of 1-heptanal (1 equiv, 0 °C, 1 h), the addition of iodine gave only a 25% yield of acetylene **25** (procedure B). A successful variant of this latter procedure involving initial generation of a borinate ester **26b** via reduction of heptanal with **26a** followed by the successive addition of **21** and iodine was found to afford the desired coupled acetylene in 72% yield (procedure C). This latter experiment demonstrates that dialkyl borinic esters (cf. **26b**) *can* serve as valuable substrates in such acetylene coupling reactions. In addition, the olefin: acetylene stoichiometry has been improved by this modification from 3:1 (Scheme II) to 2:1 (Scheme III) while comparable yields have been maintained. In an effort to achieve cross-coupling stoichiometry of unity for olefinic and acetylenic moieties, the mixed dialkylborinic ester **28** was prepared in analogous fashion (cf. Scheme III, procedure C). Reaction of **28** with acetylide **21** and subsequent iodine-induced rearrangement afforded acetylene **25** (34%) and **29** (6%), the latter having been formed as a result of thexyl ligand migration.



Stereoselective Olefin Synthesis. Attention was next turned to the application of the Zweifel olefin synthesis (Scheme I)[7] to the construction of the prostanoid olefin models **30** and **31** (R = H). Hydroboration of acetylene **33** with the dialkylborane derived from 1-ethylcyclopentene (**32**, R = C_7H_{13}) afforded the presumed vinyl borane **34** which was rearranged to the *Z* olefin **31** in 73% yield (Scheme IV). However, the use of thexyl-2-ethylcyclopentylborane (**32**, R = C_6H_{13}) in the *same* reaction sequence resulted in only a 30% yield of olefin **31** which was accompanied by 14% of the olefin

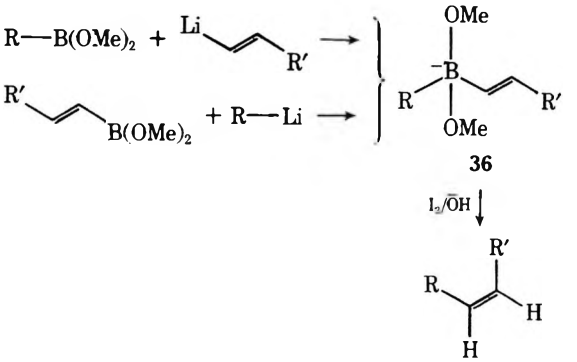


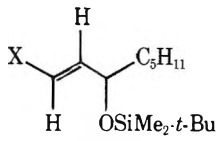
Scheme IV



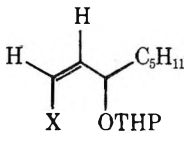
35. These results demonstrate excellent internal consistency with our acetylene cross-coupling study (Scheme III). Iodine-promoted rearrangement of dicyclopentylvinylborane **34** (R = C_7H_{13}) and acetylene ate complex **27** afforded good yields of *Z* olefin **31** and acetylene **25**, respectively. However, attempts to execute analogous reactions on the "mixed" thexylcyclopentylboranes (cf. **28** and **32**, R = C_6H_{13}) resulted in lower yields of both the desired acetylene **25** and olefin **31** and, in addition, products derived from competitive thexyl migration **35** and **29** were formed. Further complications were encountered in attempts to rearrange the dicyclopentylvinylborane **34** (R = C_7H_{13}) to the silyl-protected *E* olefin **30** with cyanogen bromide according to literature precedent.[14d] The major product from this reaction, although not fully characterized, was consistent with the expected olefinic product which had incorporated a nitrile function with concomitant loss of the silyloxy moiety.

As a result of the problems encountered in applying precedented borane cross-coupling reactions to the specific types of olefin syntheses under discussion, we turned to a study of the potential olefin synthesis illustrated below.[20] Based upon analogy, the boronic ester-derived ate complex **36**, readily obtained via alkyl or alkenylboronic ester precursors, might be expected to undergo stereospecific rearrangement to olefinic products in the presence of iodine–base. In this overall olefin construction the final olefin geometry may be defined by the stereochemistry of either the alkenyllithium or vinylboronic boronic ester moieties chosen for the synthesis of the ate complex **36**. An important feature of this process is the *absence* of ligands in the ate complex which can compete with the illustrated boron extrusion process.[19] To test the viability of the illustrated olefin synthesis, vinyllithium reagents **37b** and **38b** were prepared from the corresponding iodides **37a**[21] and **38a**[22] by metal–halogen exchange, and boronic ester **39**





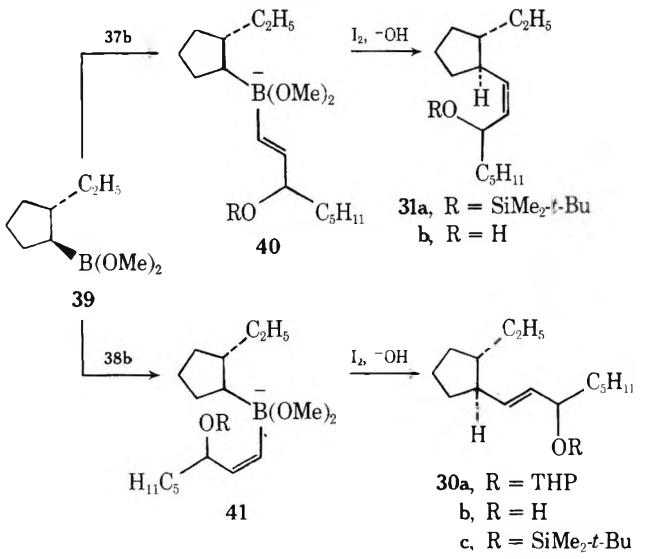
37a, X = I
b, X = Li
c, X = H



38a, X = I
b, X = Li
c, X = H

was prepared by analogy to the procedure of Brown (Scheme V).[5c] Addition of 1 equiv of boronic ester **39** to a tetrahydrofuran (THF) solution of *E* vinyllithium reagent **37b** (0 °C) followed by the addition of iodine (1 equiv) and subsequent stirring at 25 °C (3 h) afforded the *Z* olefin **31a** (22%) as well

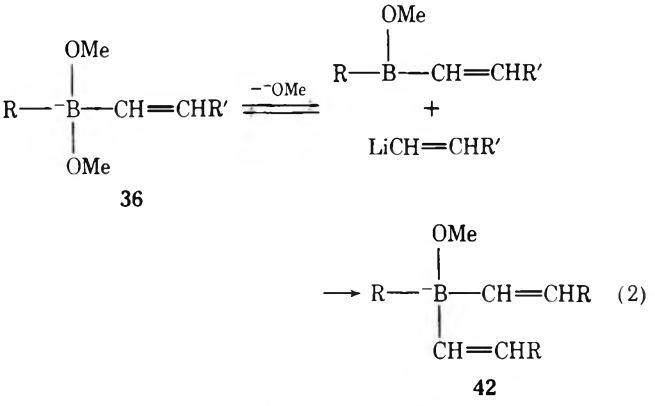
Scheme V



30a, R = THP
b, R = H
c, R = $SiMe_2$-*t*-Bu

as vinyl iodide **37a** (22%) and olefin **37c** (11%). Although these results were encouraging, the presence of vinyl iodide suggested that, under the reaction conditions, either the formation of ate complex **40** was not complete or "direct iodination" of the alkenyl–boron bond was competing *directly* with the desired rearrangement. Control experiments implicated the latter explanation. Brown and co-workers have reported a related process in the reaction of vinylboronic acids with iodine and base.[23] It is noteworthy that "direct iodination" of vinylborane **34** or its ate complex was *not* observed to be a significant side reaction, although we have observed **37a** as a minor by-product in this reaction. Minor improvements in the olefination reaction were made when the ate complex **40** was treated with iodine in the presence of sodium hydroxide. After a careful study of the iodine-promoted rearrangement of both **40** and **41**, we have found the overall process to be dramatically solvent dependent. Rearrangement of **40** with iodine in a methoxide–methanol medium afforded a 75% yield of desired olefin **31a**, accompanied by only 15% of the "direct iodination" product **37a**. GLC analysis of the *Z* olefin **31a** indicated that the *Z*:*E* isomer ratio was greater than 96:4, indicating that olefins of high geometric purity are accessible via this route.[24]

Mechanistically, it was predicted that the *E* olefin would result from the iodine-promoted rearrangement of ate complex **41**. Indeed, the addition of 1 equiv of boronic ester **39** to *Z* vinyllithium reagent **38b** generated in ether,[25] followed by iodine-promoted rearrangement in methanol–methoxide solution, afforded the desired *E* olefin **30a** in 58% yield. The *E*:*Z* olefinic isomer ratio was greater than 99:1 in this instance. The successful synthesis of **30a** via this route, as contrasted by the failure to obtain the same compound via the cyanogen bromide rearrangement of vinylborane **34** (Scheme IV), is noteworthy. Other mechanistic points in the olefination sequence illustrated in Scheme V are worthy of discussion. Heteroatom-substituted boronate complexes are known to be labile intermediates.[26] The potentially serious ligand exchange reaction shown below (eq 2) could complicate these and related boronic ester cross-coupling reactions. Ligand exchange on **36** which can occur via tricoordinate borane in-



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termediates could lead to alternate ate complex **42.** Based upon the known migratory aptitudes of alkyl and alkenyl ligands,[7b] the presence of **42** would be implicated by the observation of dienes subsequent to iodine-promoted rearrangement. Careful examination of the products of the boronic ester mediated olefination sequence (Scheme V) revealed that diene by-products are not significant contaminants. Hence, the ate complexes **40** and **41** do not undergo ligand exchange under the stated reaction conditions. With simple procedures now available for the synthesis of both alkyl and alkenylboronic esters,[27] the results of this study indicate that such organoboranes will be useful substrates for olefin synthesis.

Conclusion

Over the last several years boron-mediated cross-coupling reactions which result in the stereospecific synthesis of olefins and acetylenes have been developed by numerous investigators. The major limitations of these synthetic methods relate to the overall cross-coupling stoichiometry. The present study has sought to solve some of the inherent problems associated with these highly useful bond construction reactions. In particular, the use of boronic esters in hydrocarbon coupling reactions shows considerable promise. The application of the chemistry detailed herein to the synthesis of prostaglandin hormones will be detailed elsewhere.

Experimental Section

Materials. THF and ether were dried by distillation under nitrogen from lithium aluminum hydride or benzophenone ketyl. Dry methanol was anhydrous reagent or spectral grade and was stored over 3 Å molecular sieves. Alkyllithium reagents were purchased from Ventron as solutions in *n*-hexane or cyclohexane, and were standardized by the procedure of Gilman.[28]

Procedure. GLC analyses were run on a Varian Aerograph Model 1400 gas chromatograph equipped with a flame ionization detector using a 6 ft by 0.125 in. stainless steel column of 6% SE-52 or Carbowax 20M on 60–80 mesh acid-washed dimethyldichlorosilanized Chromosorb W. Preparative GLC was carried out using a Varian Aerograph Model 90-P gas chromatograph. Detector response calibrations were determined by comparison of the peak areas (measured by triangulation) of the compound and standard at a variety of weight ratios. Infrared spectra were recorded using a Perkin-Elmer Model 700 or a Beckman IR 4210 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian Associates Model T-60, A-60, or A-60D spectrometer. Chemical shifts are reported in parts per million on the δ scale relative to tetramethylsilane internal standard or chloroform internal standard for silicon-containing compounds. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants, and interpretation.

3-(*tert*-Butyldimethylsiloxy)-1-octyne (33). To a dry 100-ml flask containing 15 ml of dry DMF was added 6.99 g (55.5 mmol) of 1-octyn-3-ol, 9.2 g (61 mmol) of *tert*-butyldimethylchlorosilane, and 9.4 g (139 mmol) of imidazole (freshly sublimed). The reaction mixture was stirred under nitrogen for 36 h. Hexane (150 ml) was added, and the solution was washed five times with water and dried (brine, Na_2SO_4). Removal of the solvent and molecular distillation of the remaining liquid at 45 °C (12 mmHg) afforded 12.34 g (51.4 mmol, 92%) of acetylene **33**. Analytically pure material was obtained by a second molecular distillation of the above liquid: ir (neat) 3320 cm^{-1}; NMR ($CDCl_3$) δ 0.13 (d, 6, CH_3Si–), 0.93 (s, 12, $-CH_3$), 1.12–1.92 (m, 8), 2.35 (d, 1, $-C{\equiv}CH$), 4.34 (m, 1, –CHO–).

Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.92; H, 11.74. Found: C, 70.20; H, 11.58.

1-Cyclohexyl-3-(*tert*-butyldimethylsiloxy)-1-octyne (23). Tricyclohexylborane was prepared by adding 0.67 ml (6.6 mmol) of cyclohexene to 1.8 ml of 1.1 M solution of borane (2.0 mmol) in THF at −20 °C. After 5 min, the heterogeneous solution was warmed to room temperature and was stirred for 12 h. The resulting homogeneous solution was cooled to 0 °C. In another flask containing 4 ml of dry THF and 0.483 g (2.0 mmol) of acetylene **33** under nitrogen was added at −20 °C 2.0 mmol of *n*-butyllithium in hexane. The solution was warmed to room temperature and after 10 min was added to the solution containing the tricyclohexylborane. After 5 min this solution was cooled to −60 °C and 0.513 g (2.02 mmol) of iodine in 3 ml of dry THF was added. After stirring at −60 °C for 70 min and room temperature for 20 min, 80 ml of ether was added, and the organic phase was extracted with 15 ml of 5% sodium hydroxide. The basic layer was extracted with 30 ml of ether, and the combined ether layers were extracted with 13 ml of base, 5 ml of base and 2 ml of 30% hydrogen peroxide, and brine. Benzene (50 ml) was added, and the organic layer was dried ($MgSO_4$). Removal of the solvent and chromatography of the remaining liquid on 15 g of alumina (hexane) afforded 0.574 g (1.78 mmol, 89%) of acetylene **23** as a clear liquid (greater than 75% pure by GLC). Analytically pure material was obtained by preparative gas chromatography: ir (neat) 2245 cm^{-1}; NMR (CCl_4) δ 0.12 (s, 6, CH_3Si), 0.93 (s, 12, $-CH_3$), 1.02–2.00 (m, 18), 2.36 (m, 1, $-C{\equiv}CCH-$), 4.36 (m, 1, –CHO–); MS *m/e* 322 (less than 1), 266 (25), 265 (100), 165 (29), 75 (39), 73 (22).

Anal. Calcd for $C_{20}H_{38}OSi$: C, 74.46; H, 11.87. Found: C, 74.42; H, 11.92.

1-Cyclopentyl-3-(*tert*-butyldimethylsiloxy)-1-octyne (24). Acetylene **24** was prepared using the same precedure that was used to prepare acetylene **23**. Tricyclopentylborane (2.2 mmol) and the lithium salt of acetylene **33** were combined and iodine was added. After workup, 0.623 g (2.02 mmol, 92%) of crude liquid was obtained. A portion of this crude material (0.238 g, 0.765 mmol) was molecularly distilled at 39 °C (0.001 mmHg) to afford 0.210 g (0.68 mmol) of octyne **24** which was greater than 92% pure by GLC (75% isolated yield). An analytical sample was prepared by preparative GLC: ir (neat) 2240 cm^{-1}; NMR ($CDCl_3$) δ 0.12 (s, 6, CH_3Si–), 0.93 (s, 12, $-CH_3$), 1.03–2.02 (m, 16), 2.68 (m, 1, $-CHC{\equiv}C-$), 4.36 (m, 1, –CHO–).

Anal. Calcd for $C_{19}H_{36}OSi$: C, 73.95; H, 11.76. Found: C, 73.86; H, 11.72.

1-(*trans*-2-Ethylcyclopentyl)-3-(*tert*-butyldimethylsiloxy)-1-octyne (25). Procedure A. From Tris(*trans*-2-ethylcyclopentyl)borane. To a solution of 288 mg (3.0 mmol) of 1-ethylcyclopentene in 1.5 ml of THF stirred at 0 °C under nitrogen was added 0.91 ml (1.0 mmol) of 1.1 M borane in THF solution. The reaction mixture was stirred for 15 h (25 °C). In a separate flask, a solution of 240 mg (1.0 mmol) of acetylene **33** in 1.5 ml of THF at 0 °C was treated with 0.46 ml (1.0 mmol) of a 2.2 M solution of *n*-BuLi in hexane. The resulting acetylide **21** was transferred to the borane mixture at 0 °C, stirred for 5 min, and cooled to −65 °C. The reaction mixture was treated with a solution of 260 mg (1.0 mmol) of iodine in 2 ml of THF for 1 h at −65 °C and 2 h at room temperature. The solution was poured into 50 ml of ether washed with aqueous sodium thiosulfate, water, basic hydrogen peroxide solution, water, and brine. The ether layer was dried ($MgSO_4$) and filtered and solvent removed in vacuo to yield 580 mg of colorless oil. Analysis by GLC with eicosane as an internal standard showed a 31% yield of acetylene **25** and a large amount of acetylene **33**. Preparative GLC (6 ft, 15% SE-52, 240 °C) gave an analytical sample: ir (neat) 2960, 2940, 2870, 1470, 1355, 1260, 1090, 845, 785 cm^{-1}; NMR ($COCL_3$) δ 4.33 (t, 1), 0.8–2.4 (m, 24), 0.92 (s, 9), 0.13 (s, 6).

Anal. Calcd for $C_{21}H_{40}OSi$: C, 74.93; H, 11.98. Found: C, 74.67; H, 12.03.

Procedure B. From Borane 26a. To a three-necked 25-ml pear-shaped flask under N_2 was added 194 mg (2.0 mmol) of ethylcyclopentene and 1 ml of dry THF. The solution was cooled to 0–5 °C and 0.92 ml (1 mmol) of 1.1 M borane in THF solution was added dropwise. After 1 h stirring, a solution of acetylide **21** [prepared from 240 mg (1.0 mmol) of acetylene (**33**) and 0.46 ml (1.0 mmol) of 2.2 M *n*-BuLi in hexane solution in 1.5 ml of THF at <0 °C] was added dropwise with stirring. After 5 min at 0–5 °C, 0.135 ml (1.0 mmol) of heptanal was introduced dropwise and the solution was stirred for an additional 1 h. The reaction was then cooled to <−60 °C and a solution of 255 mg (1.0 mmol) of iodine in 2 ml of THF was added. After 2 h at 25 °C the mixture was poured into 50 ml of Et_2O and 25 ml of aqueous thiosulfate solution. Workup as previously described gave 700 mg of colorless oil which darkened on standing. By GLC internal standard (eicosane) the yield of **25** was 27%.

Procedure C. From Borinate 26b. To 196 mg (2.0 mmol) of ethylcyclopentene and 1 ml of dry THF in a 25-ml pear-shaped flask stirred under nitrogen at 0–5 °C was added 0.92 ml (1.0 mmol) of a 1.1 M borane in THF solution. After 2 h, 0.135 ml (1.0 mmol) of heptanal was added dropwise and the solution was stirred for 1.75 h. A solution of acetylide **21** [prepared from 242 mg (1.0 mmol) of acetylene **33** and 0.46 ml (1.0 mmol) of a 2.2 M *n*-BuLi in hexane solution, in 1.5 ml of THF] was then added. After 10 min the mixture was cooled to <−70 °C and a solution of 258 mg (1.0 mmol) of iodine in 2 ml of dry THF was added dropwise. The mixture was stirred for 1 h and then brought to room temperature for 2 h. The product was isolated as previously described to give 680 mg of colorless oil which darkened on standing. By GLC internal standard (eicosane) the yield of **25** was 72%.

Procedure D. From Ethylcyclopentylthexylborane (28). To 89 mg (1.07 mmol) of 2,3-dimethyl-2-butene stirred under N_2 at 0–5 °C was added 0.92 ml (1.0 mmol) of a 1.1 M borane in THF solution. After 1.5 h, 0.12 ml (1.0 mmol) of ethylcyclopentene was added and stirring was continued for 1.25 h. Heptanal (0.13 ml, 1.0 mmol) was then added and the solution was stirred for 1.5 h at 0–5 °C. To the resulting solution was added a solution of 1.0 mmol of acetylide 21 in 2 ml of THF. After 5 min, the reaction was cooled to <−65 °C and a solution of 260 mg (1.0 mmol) of iodine in 2 ml of THF was added. The mixture was brought to room temperature after 1 h and was stirred for another 2 h. Workup as previously gave 640 mg of colorless oil which darkened on standing. By GLC internal standard (eicosane) the yield of **25** was 34%.

In addition, the thexyl-migrated acetylene **29** (ca. 6%) was identified by GLC–MS: *m/e* 323, 309, 267, 253, 167, 157.

1-(*trans*-2-Ethylcyclopentyl)-3-(*tert*-butyldimethylsiloxy)-1-(*Z*)-octene (31). Procedure A. From Bis(*trans*-2-ethylcyclopentyl)borane. To 194 mg (2.0 mmol) of 1-ethylcyclopentene stirred under nitrogen in a 25-ml pear-shaped flask was added 1 ml of THF. The reaction mixture was stirred at −30 °C and 0.46 ml (1.0 mmol) of a 2.2 M solution of borane in THF was added. The solution was brought to 0 °C and stirred for 1.5 h. Acetylene **33** (250 mg, 1.1 mmol) was added and the reaction mixture was stirred for 1 h at 25 °C. The solution was cooled to −40 °C and 0.4 ml (2.4 mmol) of 6 N aqueous sodium hydroxide was added followed by a solution of 260 mg (1.0 mmol) of iodine in 2 ml of THF. The solution was stirred for 2 h at room temperature. Ether (50 ml) was added and the solution was washed with 5% sodium hydroxide, 5% sodium hydroxide with ~10% hydrogen peroxide, and brine. The ether layer was dried ($MgSO_4$) and filtered, and solvent removed in vacuo to yield 530 mg of colorless oil. Analysis by GLC with eicosane as an internal standard showed a 73% yield of **31**. Preparative GLC afforded an analytical sample: ir (neat) 1650, 1452, 1250, 1075, 835, 770, 670 cm^{-1}; NMR ($CDCl_3$) δ 5.33 (m, 2, vinyl) 4.50 (m, t, –CHO–), 1.20–2.30 (m, 18), 0.85 (s, 15, $-CH_3$), 0.12 (s, $-SiCH_3$).

Anal. Calcd for $C_{21}H_{42}OSi$: C, 74.48; H, 12.50. Found: C, 74.26; H, 12.20

Procedure B. From (*trans*-2-Ethylcyclopentyl)thexylborane. To 91.4 mg (1.09 mmol) of 2,3-dimethyl-2-butene stirred under nitrogen at 0 °C in a 25-ml three-necked pear-shaped flask was added 0.48 ml (1.05 mmol) of a 2.19 M solution of borane in THF. The reaction mixture was stirred for 2.5 h and cooled to −20 °C, and 0.12 ml (1.0 mmol) of 1-ethylcyclopentene was added dropwise. The solution was stirred for 1.75 h, 250 mg (1.1 mmol) of acetylene **33** was added, and stirring was continued for 2 h at −20 °C and 1.5 h at 0 °C. The solution was cooled to −50 °C and 1 ml of THF was added followed by 0.4 ml (2.4 mmol) of 6 N aqueous sodium hydroxide and a solution of 270 mg (1.1 mmol) of iodine in 2 ml of THF. The mixture was brought to room temperature over 30 min and stirred for 2.5 h. Workup as previously described gave 600 mg of colorless oil. Analysis by GLC with eicosane as an internal standard showed a 30% yield of olefin **31** and ~15% of a second product, identified as **35**, the product of competitive thexyl migration, by GLC–MS: *m/e* 326, 325, 311, 283, 269, 255.

1-(*trans*-2-Ethylcyclopentyl)-3-(*tert*-butyldimethylsiloxy)-(*Z*)-1-octene (31) from Boronic Ester 39. To a solution of 388 mg (1.05 mmol) of (*E*)-1-iodo-3-(*tert*-butyldimethylsiloxy)-1-octene[21] (**37a**) in 6 ml of dry THF, cooled to −78 °C under argon in a 25-ml pear-shaped flask, was added 3.18 ml (2.10 mmol) of a 0.66 *M* solution of *sec*-butyllithium in *n*-hexane. The reaction mixture was stirred for 1 h at −78 °C and then brought to 0 °C. Boronic ester **39** (0.204 ml, 1.05 mmol) was added to **37b** and the solution stirred for 10 min at 0 °C. To the reaction mixture was added a solution of 3.15 mmol of sodium methoxide in 1 ml of methanol, and a solution of 1.33 g (5.25 mmol) of iodine in 8 ml of methanol. The reaction mixture was stirred for 3 h at room temperature and diluted with 200 ml of ether. The solution was washed with 5% sodium thiosulfate solution, H_2O, 5% sodium hydroxide solution with ~10% hydrogen peroxide, 5% sodium thiosulfate solution, and brine. The ether layer was dried ($MgSO_4$) and filtered and solvent removed in vacuo to yield 549 mg of a pale yellow oil. Eicosane (40.9 mg) was added as an internal standard. Analysis by GLC (5% SE-52, 80–250 °C at 6 °C/min) showed a 75% yield of olefin **31** along with vinyl iodide **37a** (~15%) and olefin **37c** (~15%). The product was chromatographed on 100 g of silica gel with petroleum ether to give 373 mg of colorless oil. A portion of this material was purified by medium-pressure liquid chromatography on 100 g of preparative TLC grade silica gel, eluting with petroleum ether, to give pure olefin **31**.

1-(*trans*-2-Ethylcyclopentyl)-3-(tetrahydropyran-2-yloxy)-(*E*)-1-octene (30a). To a solution of 168 mg (0.497 mmol) of (*Z*)-1-iodo-3-(tetrahydropyran-2-yloxy)-1-octene (**38a**)[22] in 5 ml of ether cooled to −78 °C under argon in a 25-ml pear-shaped flask was added 0.89 ml (0.994 mmol) of a 1.12 M solution of sec-butyllithium in cyclohexane. The solution was stirred for 1 h at −78 °C and 0.096 ml (0.497 mmol) of boronic ester **39** was added. The reaction mixture was stirred for 10 min at −78 °C and 10 min at 0 °C. To the reaction mixture was added a solution of 1.49 mmol of sodium methoxide in 1 ml of methanol and a solution of 630 mg (2.48 mmol) of iodine in 15 ml of methanol. The reaction mixture was stirred for 3 h at room temperature and the bulk of the methanol was removed in vacuo. Ether (150 ml) was added and the solution was washed with 5% sodium thiosulfate, 5% sodium hydroxide solution, 5% sodium hydroxide solution containing ~10% hydrogen peroxide, 5% sodium thiosulfate, and brine. The ether layer was dried (Na_2SO_4) and filtered, and solvent removed in vacuo to yield 235 mg of product. Tetracosane (55.3 mg) was added, and analysis by GLC (5% SE-52, 100–250 °C at 6 °C/min) showed the presence of olefin **30a** (51%) and vinyl iodide **38a** (21%). Fractional molecular distillation at 120 °C (0.001 mm) gave an analytical sample: ir (neat) 1660, 1020, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.1–5.6 (m, 2, vinyl), 4.65 (m, 1, –OCHO–), 3.30–4.20 (m, 3, –CHO–), 0.60–2.20 (m, 30).

Anal. Calcd for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76. Found: C, 77.77; H, 11.82.

1-(*trans*-2-Ethylcyclopentyl)-(*Z*)-1-octen-3-ol (31b). To a solution of 100 mg (0.296 mmol) of silyl ether **31a** in 2 ml of dry THF stirred under nitrogen in a 25-ml round-bottomed flask was added a solution of 235 mg (0.90 mmol) of tetra-*n*-butylammonium fluoride in 8 ml of THF. The reaction mixture was stirred for 6 h at room temperature and diluted with 100 ml of hexane. The solution was washed with aqueous sodium bicarbonate and brine. The solution was dried ($MgSO_4$) and filtered and solvent removed in vacuo to yield 100 mg of yellow oil. Chromatography on 20 g of activity III neutral alumina (hexane/$CHCl_3$) followed by molecular distillation at 50 °C (0.1 mm) gave 50 mg (75%) of alcohol **31b**: ir (neat) 3350, 1650, 1450, 1370, 1015 cm^{-1}; NMR ($CDCl_3$) δ 5.28 (m, 2, vinyl), 4.35 (m, 1, –CHOH–), 0.5–2.8 (m, 25).

Analysis by GLC (6 ft of 5% Carbowax 20M, 160 °C) showed the product to be a mixture of diastereomers containing ~5% of the isomeric alcohol **30b**.

Anal. Calcd for $C_{15}H_{28}$: C, 80.29; H, 12.58. Found: C, 80.15; H, 12.66.

1-(*trans*-2-Ethylcyclopentyl)-(*E*)-1-octen-3-ol (30b). Tetrahydropyranyl ether **30a** was prepared exactly as described on a 0.762-mmol scale. The crude product (282 mg of brown oil) was dissolved in a mixture of 8 ml of 66% acetic acid and 4 ml of THF. The reaction mixture was heated at 55 °C for 3.5 h. The cooled reaction mixture was neutralized with cold 5% sodium hydroxide solution and extracted twice with ether. The combined ether layers were washed with water and brine and dried (Na_2SO_4) and solvent removed in vacuo to yield 198 mg of yellow oil. The material was chromatographed on 30 g of activity III neutral alumina (hexane/chloroform) to give 76 mg (0.34 mmol, 45%) of alcohol **30b**. Molecular distillation at 100 °C (0.001 mm) gave an analytical sample: ir (neat) 3340, 2960, 2930, 1660, 1275, 970 cm^{-1}; NMR ($CDCl_3$) δ 5.35–5.60 (m, 2, vinyl), 4.00 (m, 1, –CHOH–), 0.70–2.20 (m, 25).

Analysis by GLC indicated the product to be a diastereoisomeric mixture containing less than 1% of the isomeric alcohol **31b**.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.15; H, 12.66. Found: C, 80.24; H, 12.66.

Dimethyl *trans*-2-Ethylcyclopentylboronate (39). In a 250-ml, round-bottomed flask under nitrogen atmosphere was placed 67 ml (75 mmol) of 1.2 M borane in THF solution. The reaction mixture was cooled to 0 °C and 8.9 ml (75 mmol) of 2,3-dimethyl-2-butene was added slowly. After stirring for 1.5 h, the resulting solution of thexylborane was cooled to −30 °C and 9.1 ml (75 mmol) of 1-ethylcyclopentene was added dropwise over 10 min. The reaction mixture was stirred for 1.5 h at −30 °C and 41.7 ml (300 mmol) of dry triethylamine was added over 20 min. The reaction mixture was brought to room temperature and stirred for 2.5 h. Dry methanol (12.1 ml, 300 mmol) was slowly added (vigorous gas evolution) and the reaction mixture was stirred for 1 h at room temperature. The flask was fitted with a distillation head and the solvents were removed in vacuo (<45 °C at 70–110 mm) to ~20 ml volume. The material was transferred to a 50-ml flask and distilled (60 °C at ~2 mm) to give 9.4 g (55 mmol, 74%) of product. The product was redistilled at 40 °C (~1 mm) to give 6 g of boronic ester **39** as a colorless liquid: ir ($CHCl_3$) 2950, 2862, 1470, 1320, 1013 cm^{-1}; NMR ($CDCl_3$) δ 3.57 (s, 6, $-OCH_3$), 0.65–2.0 (m, 13).

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Registry No.—**20**, 1088-01-3; **21**, 60134-82-9; **23**, 60134-83-0; **24**, 60134-84-1; **25**, 60134-85-2; **26a**, 60134-86-3; **26b**, 60134-87-4; **28**, 60134-88-5; **29**, 60134-89-6; **30** (R = tetrahydropyran-2-yl), 60134-90-9; **30** (R = H), 60134-91-0; **31** (R = SiMe, Bu-*t*), 60134-92-1; **33**, 60134-93-2; **35**, 60134-94-3; **37b**, 39178-67-1; **38a**, 39647-92-2; **39**, 60134-95-4; 1-octyn-3-al, 818-72-4; *tert*-butyldimethylchlorosilane, 18162-48-6; tricyclopentylborane, 23985-40-2; tris(*trans*-2-ethylcyclopentyl)borane, 60134-96-5; (*trans*-2-ethylcyclopentyl)thexylborane, 60134-97-6; thexylborane, 3688-24-2; 1-ethylcyclopentene, 933-06-2.

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Total Synthesis of (±)-*cis*-Sativenediol

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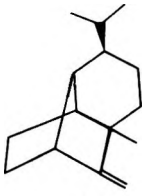
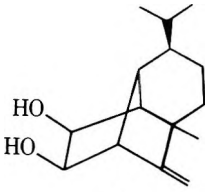
A total synthesis of the plant growth promoter *cis*-sativenediol (**2**) is reported. The key step involves internal alkylation to cyclopropane **7** followed by thermal rearrangement to tricyclic enone **6**. Cis hydroxylation of the double bond, followed by transformation of the carbonyl into a methylene group, completes the synthesis.

Some years ago we reported[1] a stereospecific total synthesis of the tricyclic sesquiterpene hydrocarbon sativene (**1**). More recently, our continuing interest in this skeletal class has also led to syntheses of copacamphene[2] and of longifolene.[3] When, therefore, Marumo[4] and Arigoni[5] independently assigned the *cis*-sativenediol structure (**2**) to a metabolite isolated from the fungus *Helminthosporium sativum*, we were drawn to attempt a synthesis of the molecule.[6] The Marumo report is particularly interesting because it appears that *cis*-sativenediol posesses gibberellin-like plant growth promoter activity.



1

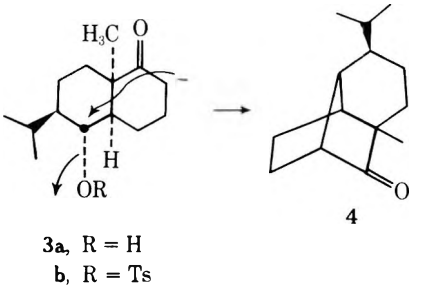


2

The key step in our sativene synthesis was the intramolecular alkylation of bicyclic keto tosylate **3b** to tricyclic ketone **4**. If one imagines that the cis diol functionality in the target **2** arises by less hindered exo hydroxylation of the proper olefinic ketone **6**, then this requires that we synthesize and cyclize the enone tosylate **5b**. One conceivable difficulty with this route is that **5b** might choose an alternate mode of cyclization leading to cyclopropane **7**, but only experiment can show which cyclization path is more favorable.

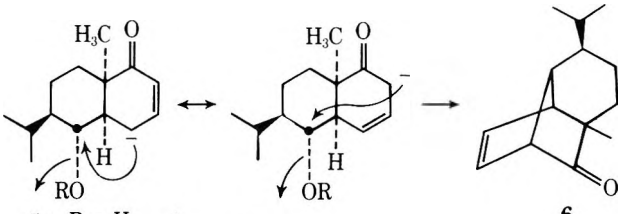
Enone **5b** was therefore synthesized in straightforward manner from **3a** whose synthesis we have previously reported[1] (Scheme I). One modification made in the present work, however, is the use of aqueous titanous ion[7] to cleave 2,4-DNP **14** to the corresponding ketone **3a**. The transformation occurred in 97% yield vs. the 70% reported earlier when ozonolytic cleavage was used. Ketone **3a** was readily transformed into enone **5a** in 82% yield by the Reich–Sharpless procedure,[8] and, after tosylation, we were ready to attempt intramolecular alkylation.

Treatment of keto tosylate **5b** with 1.2 equiv of dimsyl sodium in Me_2SO for 5 min at room temperature led to a 96% yield of pure cyclization product. Ir and NMR spectroscopy clearly showed, however, that the product was exclusively the undesired cyclopropane, **7** (ir 1670 cm^{-1}).



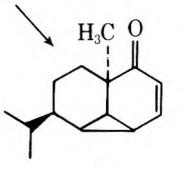
4

3a, R = H
b, R = Ts



5a, R = H
b, R = Ts

6



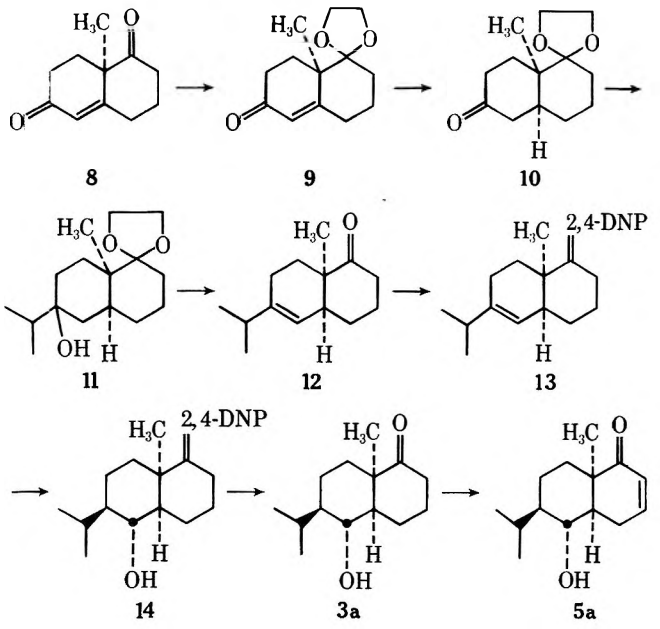
7

We had hoped, from inspection of molecular models, that geometric constraints imposed by the decalin system would hinder the development of orbital overlap necessary for three-membered ring formation, but this was clearly not the case.

Since the cause of the problem is the extended enolate system in **5b** one can devise potential solutions based on carrying out the cyclization with enone equivalents to **5** in which the double bond is somehow masked. The actual resolution of the problem turns out to be much simpler, however, when one realizes that the undesired product **7** and the desired product **6** are formally interconvertible by a vinylcyclopropane → cyclopentene rearrangement. Thus they should be in a thermal equilibrium, and one would expect the relatively unstrained **6** to predominate rather than cyclopropane **7**. When, in fact, **7** was heated to 450 °C in a nitrogen swept quartz pyrolysis system, **6** was isolated as the sole product in nearly quantitative yield.

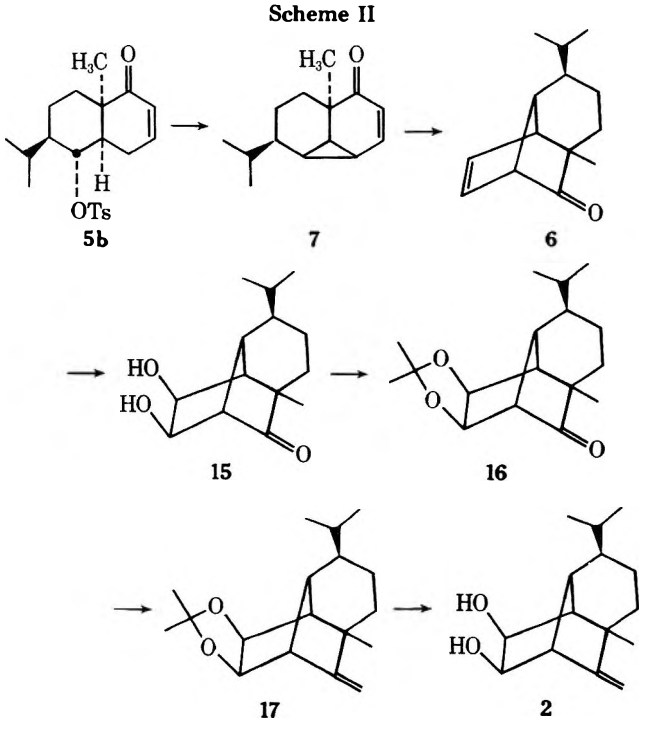
With this key rearrangement completed, **6** was then

Scheme I

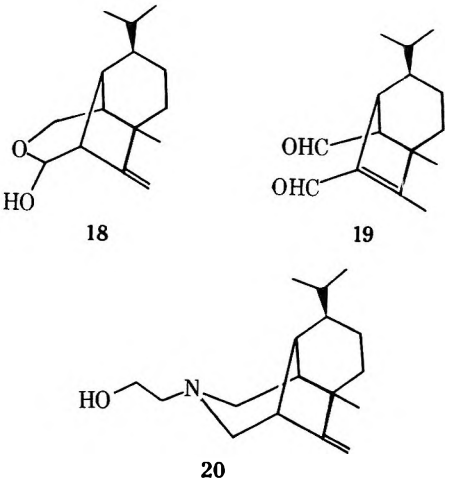


transformed into *cis*-sativenediol. Hydroxylation of **7** with OsO_4 took place exclusively from the less hindered exo direction to afford a keto diol (**15**) which was protected as the acetonide **16**. Addition of methyllithium to the carbonyl, followed by dehydration of the resultant alcohol with thionyl chloride in pyridine, led to (±)-*cis*-sativenediol acetonide (**17**). Removal of the protective group by treatment with dilute acid in methanolic THF gave synthetic **2**, identical in its ir and NMR characteristics with the natural product.[9] An alternative sequence, designed to avoid the two steps involved in diol protection and deprotection, might be to transform keto olefin **6** into a diolefin which could be selectively hydroxylated at the endocyclic double bond. This scheme failed, however, when **6** failed to react with methylenetriphenylphosphorane and when the tertiary alcohol from addition of methyllithium to **6** gave a mixture of rearrangement products on attempted dehydration with thionyl chloride in pyridine. The transformations leading to *cis*-sativenediol are summarized in Scheme II.

Scheme II



This synthesis of *cis*-sativenediol proceeds in an overall yield of nearly 17% for 16 steps from the Wieland–Miescher ketone (**8**) and should serve to make sufficient quantities available for biological testing. One further point is that since Marumo has reported[4] the periodate oxidation of **2** to prehelminthosporal[10] (**18**), this work constitutes a total synthesis of that material, of helminthosporal (**19**), and of the related



phytotoxin, victoxinine[11] (**20**). The entire class of sativene metabolites is therefore made available by synthesis.[12]

Experimental Section

NMR spectra were obtained in $CDCl_3$ solution (Me_4Si internal standard), except where indicated, on Varian A-56/60A and JEOL PS 100 instruments. Ir spectra were obtained on a Perkin-Elmer 337. Mass spectra were taken on a Hitachi Perkin-Elmer RMU6E and high-resolution mass spectra were obtained at the University of California, Berkeley. Melting points were determined on a Hoover-Thomas apparatus and are uncorrected.

1α-Hydroxy-2β-isopropyl-4aα-methyl-1,2,3,4,4a,7,8,8aα-octahydronaphthalen-5(6*H*)-one (3a). A buffered solution of titanium trichloride was prepared by the addition of NH_4OAc (25.7 g, 0.334 mmol) in nitrogen-purged water (100 ml) to an aqueous titanium trichloride solution (35 ml, 1.6 M) under N_2. The 2,4-DNP alcohol **14**[1] (1.5 g, 3.71 mmol) in dimethoxyethane (150 ml) was added and the resulting solution warmed to 85 °C for 10 min. The reaction mixture was cooled, diluted with H_2O, and extracted three times with ether. The combined ether extracts were washed with saturated $NaHCO_3$, H_2O, and saturated NaCl. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The crude oil was chromatographed on alumina (ether eluent) to give 0.80 g (97%) of the desired keto alcohol **3a** which crystallized on standing in the refrigerator: mp 66–67 °C; ir (neat) 3450 (OH) and 1705 cm^{-1} (C=O); NMR (CCl_4) δ 1.31 (s, 3 H) and 0.95 and 0.80 (two doublets, 6 H, J = 7 Hz).

1α-Hydroxy-2β-isopropyl-4aα-methyl-1,2,3,4,4a,8aα-hexahydronaphthal-6-en-5(8*H*)-one (5a). Keto alcohol **3a** (0.50 g, 2.23 mmol) in THF (25 ml) was added dropwise to a 0.2 M solution of lithium isopropylcyclohexylamide (25 ml) cooled at −78 °C under N_2. After 20 min, phenylselenyl chloride (0.51 g, 2.68 mmol) in THF (25 ml) was added dropwise to the cooled solution. The solution was stirred at −78 °C for 1 h and warmed to room temperature. The solution was quenched with cold saturated NH_4Cl solution and extracted three times with ether. The combined extracts were washed with 1 N HCl, $NaHCO_3$, H_2O, and saturated NaCl. The ether was dried ($MgSO_4$), filtered, and concentrated. The crude concentrate was dissolved in THF (50 ml), 30% H_2O_2 (0.70 ml) added, and the solution stirred for 1 h. Water was added and the mixture was extracted with ether. The ether extract was washed with saturated Na_2CO_3, H_2O, and saturated NaCl. The extract was dried ($MgSO_4$), filtered, and concentrated. Chromatography on neutral alumina (ether eluent) gave 0.41 g (82%) of the desired enone alcohol **5a** as a colorless oil: ir (neat) 3445 (OH) and 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.70 and 0.88 (two doublets, 6 H, J = 7 Hz), 1.15 (s, 3 H), 5.88 (d of m, 1 H, J = 10 Hz), and 6.75 (m, 1 H).

Anal. Calcd for $C_{14}H_{22}O_2$: m/e 222.1620. Found: m/e 222.1629.

2β-Isopropyl-4aα-methyl-1α-toluenesulfonyloxy-1,2,3,4,4a,-8aα-hexahydronaphthal-6-en-5(8*H*)-one (5b). The enone alcohol **5a** (0.30 g, 1.35 mmol) was dissolved in dry pyridine (6 ml) under N_2.

p-Toluenesulfonyl chloride (0.65 g, 3.26 mmol) was added and the solution allowed to stand for 3 days at room temperature. Water (10 ml) was added, and the solution was placed in the refrigerator for crystallization; 0.36 g (70%) of the desired keto tosylate **5b**, mp 142.5–143.5 °C, was collected.

9-Isopropyl-6-methyltricyclo[4.4.0.0^{2,10}]dec-3-en-5-one (7). A solution of dimethyl sulfinyl carbanion in Me_2SO (3.8 ml, 0.50 M) was added dropwise to a solution of keto tosylate **5b** (0.60 g, 1.59 mmol) in 9 ml of Me_2SO under N_2. After 5 min at room temperature the reaction mixture was quenched with water, saturated with NaCl, and extracted twice with ether. The ether extracts were washed with H_2O and with saturated NaCl, then dried ($MgSO_4$), filtered, and concentrated. The crude oil was chromatographed on Florisil (8% ethyl acetate–92% pentane eluent) to give 0.31 g (96%) of the cyclopropyl compound **7** as a colorless oil: ir (neat) 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.96 and 1.15 (two doublets, 6 H, J = 6 Hz), 1.40 (s, 3 H), 5.76 (d, 1 H, $J_{3,4}$ = 10 Hz), 7.00 (d of d, 1 H, $J_{3,4}$ = 10 and $J_{2,4}$ = 4 Hz); mass psectrum M$^+$ *m/e* 204.

3-Isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]dec-9-en-7-one (6). A quartz tube with quartz chip packing, which had been neutralized with bis(trimethylsilyl)acetamide, was heated to 450 °C with a N_2 flow rate of 50 ml/min passing through. Cyclopropyl compound **7** (0.60 g, 2.94 mmol) was dissolved in hexanes and added dropwise to the column over a period of 1 h. The pyrolysate was trapped in a dry ice cooled receiver and then concentrated. The crude oil was chromatographed on silica gel (5% ethyl acetate–95% pentane eluent) to give 0.54 g (90%) of the desired tricyclic ketone **6** as a colorless oil: ir (neat) 1745 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.87 and 0.91 (two doublets, 6 H, J = 6 Hz), 1.02 (s, 3 H), 2.37 (m, 1 H), 2.72 (m, 1 H), 2.98 (m, 1 H), 6.05 (broadened d of d, 1 H, $J_{9,10}$ = 6, $J_{1,10}$ = 3 Hz), 6.59 (d of d, 1 H, $J_{9,10}$ = 6, $J_{8,9}$ = 3 Hz).

Anal. Calcd for $C_{14}H_{20}O$: *m/e* 204.1514. Found: *m/e* 204.1528.

9,10-Dihydroxy-3-isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]-decan-7-one (15). Tricyclic ketone **6** (0.35 g, 1.71 mmol) was dissolved in pyridine (4.5 ml), and added to a solution of OsO_4 (4.6 ml, 0.39 M) in benzene. The resulting solution was stirred under N_2 for 18 h. After this time a solution consisting of $NaHSO_3$ (0.84 g), H_2O (14 ml), and pyridine (9 ml) was added and stirred for 40 min. The resulting orange solution was extracted with $CHCl_3$, washed with H_2O and saturated NaCl, and dried (Na_2SO_4). Filtration and concentration under vacuum gave 0.36 g (87%) of the desired diol **15** as a crystalline material: mp 119–120 °C; ir ($CHCl_3$) 3410 and 3325 (OH), 1745 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.81 and 4.11 (two doublets, 2 H, J = 6 Hz); mass spectrum M$^+$ *m/e* 238.

9,10-Dihydroxy-3-isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]-decan-7-one Acetonide (16). Diol **15** (0.34 g, 1.43 mmol) was dissolved in acetone (20 ml) and CH_2Cl_2 (60 ml). Toluenesulfonic acid H_2O (0.04 g) was added and the solution warmed to 75 °C under N_2. Water was removed using a Soxhlet extractor containing 4 Å molecular sieves. After 24 h, the reaction mixture was cooled, neutralized with saturated $NaHCO_3$, and extracted with ether. The ether was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated. The crude oil was chromatographed on Florisil (10% ethyl acetate–90% pentane eluent) to give 0.35 g (89%) of the desired acetonide **16**, which crystallized on standing in the refrigerator: mp 64–65 °C; ir ($CHCl_3$) 1750 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.49 (s, 3 H), 4.13 and 4.48 (two doublets, 6 H, J = 6 Hz).

Anal. Calcd for $C_{17}H_{26}O_3$: *m/e* 278.1882. Found: *m/e* 278.1870.

(±)-*cis*-Sativenediol Acetonide (17). Acetonide **16** (0.23 g, 0.827 mmol) was dissolved in ether (10 ml) and added to a solution of methyllithium (29 ml, 1.45 M) under N_2. The solution was warmed to reflux for 12 h and cooled. The mixture was poured into ice, extracted with ether, and washed with saturated NaCl. The ether was dried ($MgSO_4$), filtered, and concentrated. Ir showed complete absence of carbonyl absorption, and the presence of hydroxyl absorption at 3620 and 3480 cm^{-1}. This crude alcohol was dissolved in pyridine (13 ml) and cooled to 0 °C. Thionyl chloride (0.3 ml) was added and the reaction mixture stirred at 0 ° for 30 min. Water was added and the mixture extracted with ether. The ether extracts were washed with cold 6 N HCl and with saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The crude oil was chromatographed on silica gel (5% ethyl acetate–95% pentane eluent) to give 0.22 g (94%) of the desired exocyclic methylene compound **17** as a colorless oil which crystallized on standing in the refrigerator: mp 28–29 °C; ir (neat) 1670 and 885 cm^{-1} (C=CH_2); NMR ($CDCl_3$) δ 4.64 and 4.90 (two doublets, 2 H); mass spectrum M$^+$ *m/e* 276.

(±)-*cis*-Sativenediol (2). Acetonide **17** (51 mg, 0.186 mmol) was dissolved in THF (4 ml) and methanol (20 ml) with stirring under N_2. Hydrochloric acid (2 ml, 2 N) was added and the solution stirred at room temperature for 3 days. An excess of solid $NaHCO_3$ was added, and stirring continued for 1 h. The solution was filtered and concentrated. Ether was added, and the solution washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated. The crude reaction mixture was chromatographed on silica gel (5% ethyl acetate–95% pentane eluent) to give 18 mg of starting material **17**, and 28 mg (65%, 100% based on recovered starting material) of (±)-*cis*-sativenediol as a colorless oil which solidified on standing in the refrigerator. The diol was recrystallized from acetonitrile, mp 56–57 °C. The synthetic product was identical with the natural product by spectral comparison: ir (CCl_4) 3640, 3365, 885 cm^{-1}; NMR ($CDCl_3$) δ 0.88 and 0.94 (two doublets, 6 H, J = 7 Hz), 1.04 (s, 1 H), 1.57 (m, 1 H), 2.42 (m, 1 H), 2.65 (m, 1 H), 3.64 and 4.03 (two doublets, 2 H, J = 6 Hz), 4.60 and 4.91 (two doublets, 2 H).

Anal. Calcd for $C_{15}H_{24}O_2$: *m/e* 236.1776. Found: *m/e* 236.1773.

Registry No.—**2**, 60426-94-0; **3a**, 60410-80-2; **5a**, 60410-81-3; **5b**, 60410-82-4; **6**, 60410-83-5; **7**, 60410-84-6; **14**, 60410-85-7; **15**, 60410-86-8; **16**, 60410-87-9; **17**, 60410-88-0; *p*-toluenesulfonyl chloride, 98-59-9.

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Melampodinin, Leucanthinin, and Melampolidin, Three New Melampolides from *Melampodium* (Compositae)

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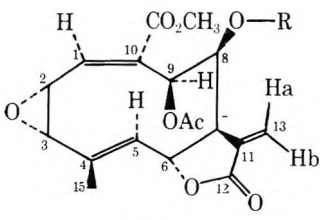
The isolation and structure elucidation of three melampolides from the genus *Melampodium* (Compositae, Heliantheae) is reported. Melampodinin (**2**) is typical of the yellow-rayed species, *M. americanum* L. Leucanthinin (**3a**) and melampolidin (**4**) are found in the white-rayed species, *M. leucanthum* Torr. and Gray. Compounds **2** and **4** represent the first sesquiterpene lactones with a 2-hydroxy-2-methyl 3-acetoxybutanoate side chain.

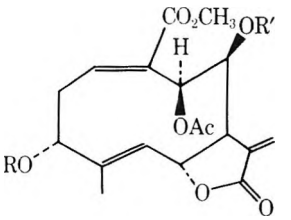
In our biochemical systematic study of the genus *Melampodium* (tribe Heliantheae, subtribe Melampodiinae),[2] we have previously reported the isolation and structural elucidation of several new sesquiterpene lactones[3,4] and dilactones.[5,6] In continuation of a detailed populational analysis of different species of *Melampodium* we now report on three new melampolides[7] from *M. leucanthum* Torr. and Gray and *M. americanum* L.

Results and Discussion

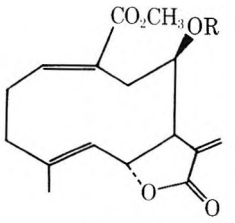
A. Melampodinin (2). Melampodinin (**2**), $C_{25}H_{30}O_{12}$, mp 208–210 °C, is the major constituent in a number of populations of the yellow-rayed species *M. americanum* from Mexico. The structure of **2** was mainly deduced on the basis of



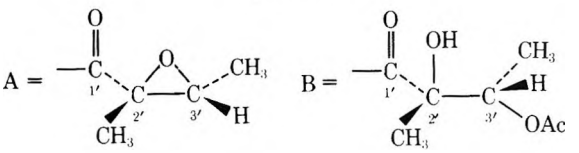
1, R = A
2, R = B



3a, R = H; R′ = A
b, R = Ac; R′ = A



4, R = B



correlations of physical parameters. The 100-MHz NMR spectrum of **2** exhibited two one-proton doublets at 5.79 (J = 3.0 Hz) and 6.19 ppm (J = 3.5 Hz) and a broad, featureless one-proton multiplet near 2.65 ppm that are characteristic of α,β-unsaturated γ-lactones, which was also indicated in the ir spectrum (1770 cm^{-1}). Melampodin A acetate (**1**)[3,4] and **2** exhibited gross NMR spectral similarities, except that the one-proton quartet at 3.05 ppm (J = 5.5 Hz), due to H-3′ in **1**, was replaced by a one-proton quartet at 5.18 ppm (J = 6.0 Hz) in **2**. In addition, **2** showed a sharp three-proton singlet at 1.89 ppm, typical for an acetate, and a one-proton singlet at 3.24 ppm, which must be due to a hydroxy hydrogen the presence of which was also evident from an OH absorption (3450 cm^{-1}) in the ir spectrum of **2**. The similarities of the NMR spectral parameters of the medium ring portions of **1** and **2** indicated that the structural differences between the two compounds must be situated in the side chain of the medium ring and most likely be due to a modification of the 2,3-epoxy-2-methylbutanoyl moiety (A) in **1** by the addition of acetic acid. This was corroborated by the appearance of mass spectral peaks at m/e 346 (M − $C_7H_{12}O_5$) and 159 (M − $C_7H_{11}O_4$) which indicated that seven carbon atoms have to be present in a single fragment in the side chain. Furthermore, the mass spectrum provided evidence for the presence of a side chain of type B in **2** by showing strong peaks at m/e 436 (M − 86, $C_4H_6O_2$) and 131 ($C_6H_{11}O_3$) which were attributed to the ions formed by fragmentations between C-2′ and C-3′ and C-1′ and C-2′ in B, respectively. The mass spectra of melampodin A acetate (**1**) and melampodinin (**2**) have very similar absorption patterns in the region due to the medium ring skeletal ions, which is further evidence for the structural similarity in the medium ring portions of **1** and **2**. Strong peaks at m/e 286 indicated sequential or simultaneous McLafferty rearrangements of the side chains from C-8 [epoxyangelic acid (116 mu) in **1** and 2-hydroxy-2-methyl 3-acetoxybutyric acid (176 mu) in **2**] and acetic acid (60 mu) from C-9 in **1** and **2**. Furthermore, in **1** and **2**, strong peaks appeared at m/e 227 which must be due to an additional loss of the carbomethoxy moiety from C-10 of the medium ring ions at 286. Peaks at m/e 198 indicated the loss of CO (28 mu), most likely from the lactonic portion of the ions due to m/e 226.

The proton resonances of **2** were assigned with the aid of double-resonance experiments. Irradiation at the center of the broad multiplet at 2.65 ppm (H-7) caused collapse of the doublets at 5.79 (H-13a) and 6.19 ppm (H-13b) plus collapse of the narrower spacing ($J_{7,8}$ = 1.2 Hz) of the doublet of doublets at 6.65 ppm (H-8), and a substantial narrowing in the structure of the upfield portion (H-6) of the H-5,6 pattern centered near 5.25 ppm. Irradiation of the narrow doublet at 2.19 ppm (J = 1.0 Hz, C-4 methyl group) sharpened the low-field portion of the H-5,6 multiplet. Saturation of the H-9 doublet at 5.37 ppm ($J_{8,9}$ = 9.0 Hz) removed the wide spacing (J = 9.0 Hz) from the H-8 signal at 6.65 ppm. Irradiation at the signal at 7.00 ppm (H-1) narrowed the broadened doublet (J = 1.0 Hz) at 3.73 ppm (H-3) to two sharp lines and collapsed the narrower spacing of the H-2 doublet of doublets at 3.62 ppm. Irradiation at the center of the C-3′ methyl doublet at 1.24 ppm (J = 6.0 Hz) caused collapse of the quartet at 5.18 ppm (H-3′). The striking downfield shift in the resonance position of the H-3′ quartet (3.05 ppm in **1**[3] and 5.18 ppm in **2**) and the presence of an additional acetate group in **2** suggested an attachment of the acetoxy group to C-3′ in **2**

Table I. ^{1}H NMR Parameters[a] of Melampodinin (2), Leucanthinin (3a), Its Acetate 3b, and Melampolidin (4)

Signal	2	3a	3b	4[e]	4
H-1	7.00 dd (1; 2.3)	7.03 dd (8.5; 8.5)	6.93 dd (8.0; 9.0)	6.63 m	6.85 brt (6.0)
H-2	3.62 dd (2.3; 3.6)	~2.7 m[f]	~2.85 m[f]	2.5–2.8[f]	(a) 2.0–2.4 m[f] (b) 2.8 m[f]
H-3	3.73 dd (1.0; 3.6)	4.55 m	5.31 m[f]	*f*	*f*
H-5	5.07–5.38 m	5.52 brd (10.0)	5.30 brd (10.0)	4.81 dd (1.0; 10.0)	5.03–5.12 m
H-6		5.18 dd (9.0, 10.0)	5.17 dd (10.0; 10.0)	5.09 dd (10.0; 10.0)	
H-7	2.65 m	2.85 m	~2.80 m[f]	2.48 m	2.6 m
H-8	6.65 dd (1.2; 9.0)	6.67 dd (1.5; 8.0)	6.68 dd (1.5; 8.2)	6.44 m	6.33 ddd (1.5; 7.5; 9.0)
H-9	5.37 d (9.0)	5.31 d (8.0)	5.32 d (8.2)	(a)[f] (b) 2.66 m	(a)[f] (b) 2.77 ddd (1.5; 7.5; 14.0)
H-13a	5.79 d (3.0)	5.73 d (3.0)	5.74 d (3.0)	5.49 d (3.0)	5.59 d (3.0)
H-13b	6.19 d (3.5)	6.23 d (3.5)	6.26 d (3.5)	6.14 d (3.5)	6.17 d (3.5)
H-3′	5.18 q (6.0)	3.00 q (5.5)	3.02 q (5.5)	5.15 q (6.5)	5.08 q (6.5)[f]
H-15	2.19 d (1.0)[c]	1.95 br[c]	2.03 d (1.0)[c]	1.62 d (1.2)[c]	1.93 d (1.0)[f]
C-2′-Me	1.25	1.45	1.46	1.24	1.35
C-2′-Me	1.24 d (6.0)	1.18 d (5.5)	1.19 d (5.5)	1.18 d (6.5)	1.23 d (6.5)
COO Me	3.82	3.77	3.82	3.51	3.77
Acetates	1.89; 1.99	1.98	2.00; 2.10	1.75	1.94
C-2′-OH	3.24				3.36

[a] Spectra were run in $CDCl_3$ at 100 MHz and Me_4Si was used as internal standard. Values are recorded in parts per million relative to Me_4Si. Singlets are unmarked, multiplets are designated as follows: d, doublet; t, triplet; q, quartet; m, multiplet whose center is given; br, broad. Figures in parentheses are coupling constants or line separations in hertz. [b] Intensity two protons. [c] Intensity three protons. [d] Intensity four protons. [e] Run in C_6D_6. [f] Obscured by other signals.

which is in full agreement with the above mass spectral assignments. Since **2** does not form an acetate with Ac_2O in pyridine the hydroxy group must be tertiary, and be located at C-2′ which is in accord with the above spectral data. Therefore, by NMR and mass spectral analogy with melampodin A acetate (**1**), all the atoms of melampodinin have been accounted for, and the tentative structure **2** is suggested for melampodinin.

On the basis of the extreme similarity of the NMR parameters of **1** and **2** it appears that melampodinin exhibits the same configurational and conformational relationships around the medium ring as melampodin A acetate (**1**),[3,4] except the side chain at C-8. The stereochemistry at C-2′ and C-3′ in **2** could not be determined by spectroscopic methods. The side chain at C-8 in **2** could be possibly formed in a nucleophilic attack of an acetate at the C-3′ epoxide function of the epoxyangelic acid moiety (A) in **1** under opening of the epoxide ring to give the 2-hydroxy-2-methyl-3-acetoxy butyrate (B). Attack of a nucleophile at C-3′ is in agreement with our findings derived from neutron diffraction studies of melampodin A[8] that the epoxide group on the epoxyangelate side chain (A) in melampodin A is not symmetric. In melampodin A and therefore also in its acetate (**1**) the C-3′–oxygen bond is longer than the C-2′–oxygen bond, which should favor breaking of the C-3′–oxygen bond. A nucleophilic attack at the epoxyangelate side chain (A) should therefore occur with inversion of configuration at C-3′ to give directly the C-8 side group (B) as shown in **2**. Since the chiral centers in the epoxyangelate moiety in melampodin A[7] and therefore in its acetate (**1**) had been found to be 2′(*R*),3′(*R*) and nucleophilic attack at an epoxide group (here C-3′) generally occurs with inversion of configuration, the chirality at C-2′ and C-3′ in **2** should be *R* and *S*, respectively.

B. Leucanthinin (3a). Collections of *M. leucanthum* from Motley County, Texas, contained a crystalline compound which we named leucanthinin (**3a**), $C_{23}H_{28}O_{10}$ (high-resolution mass spectrum), mp 163–164 °C. The ir spectrum of **3a** contained absorptions typical of an α,β-unsaturated γ-lactone (1760 cm^{-1}) and a hydroxyl group (3480 cm^{-1}). Since the ir spectrum of the acetate (**3b**), $C_{25}H_{30}O_{11}$, lacked an OH absorption, **3a** must contain only one OH group.

Further information which led to the structure of leucanthinin was deduced from correlations of 25.2-MHz ^{13}C NMR and ^{1}H NMR spectral data and mass spectral fragmentation patterns. The ^{13}C NMR data (see Experimental Section) obtained under proton noise decoupling and single-frequency off-center decoupled conditions[9] and the ^{13}C chemical shift considerations indicated that leucanthinin contains 23 carbon atoms and possesses the following skeletal systems: five of >CHO–, four of each of $-CH_3$ and –C(=O)O, three of >C=, two of –CH= and one each of $-CH_2-$, >CH, >CO–, $-OCH_3$, and H_2C=.

The ^{1}H NMR parameters of leucanthinin (**3a**) were similar in many respects to those of melampodin A and its acetate (**1**).[3] The major differences between the ^{1}H NMR spectra of **1** and **3a** were observed for the proton signals assigned to H-2 and H-3 (compare Table I and table in ref 3). Instead of the absorptions centered at 3.65 (H-2) and 3.75 ppm (H-3) in **1**, in **3a** multiplets at 2.7 (2 protons) and 4.55 ppm (1 proton) were observed. In **3a** the appearance of the signals at 7.03 ppm (H-1) as a broadened doublet of doublets indicated the presence of two protons at C-2. Indeed, double irradiation at the

multiplet at 2.7 ppm collapsed the H-1 signal at 7.03 ppm to a broadened singlet and also caused the multiplet at 4.55 ppm (H-3) to collapse. From chemical shift considerations, H-3 in **3a** must be attached to a carbon atom bearing an oxygen function, possibly an OH group. A downfield shift of the H-3 absorption from 4.55 ppm in **3a** to 5.31 ppm in acetate **3b** corroborated the above assignments. Since double irradiation experiments involving the signals of H-5, H-6, H-7, H-8, H-9, and the two H-13 of **3a** produced results as expected,[3,4] leucanthinin must be represented by formula **3a** exclusive of stereochemistry.

The high-resolution mass spectra of leucanthinin (**3a**) and the acetate **3b** exhibited peaks which verified the above NMR spectral arguments. Leucanthinin gave a weak parent peak at *m/e* 464.1687 and a peak at *m/e* 404.1488 ($M - C_2H_4O_2$) indicative of the loss of CH_3COOH from the parent ion. The peaks at *m/e* 348.1193 ($M - C_5H_8O_3$) and 116.0495 ($C_5H_8O_3$) are in accord with the loss of epoxyangelic acid from the medium ring skeleton of **3a**. The fragment corresponding to *m/e* 288.1012 ($C_{16}H_{16}O_5$) could be formed by sequential or simultaneous McLafferty rearrangements of the epoxyangelic acid ($C_5H_8O_3$) from C-8 and CH_3COOH from C-9. The peak at *m/e* 229.0858 ($C_{14}H_{13}O_3$) was assigned the radical ion derived from the ion *m/e* 288 by a loss of the carbomethoxy group (59 mu) from C-10 of the medium ring. Intense peaks at *m/e* 99.0463 ($C_5H_7O_2$) and 81.0360 (C_5H_5O) and the base peak at *m/e* 71.0519 (C_4H_7O) were in agreement with the acylium ion derived from the epoxyangelic acid moiety at C-8 in **3a** and the fragments derived from the latter acylium ion by the loss of H_2O (18 mu) and CO (28 mu), respectively. Besides the above assignments a number of other diagnostic mass spectral peaks were in accord with the skeletal arrangement derived for leucanthinin.

On the basis of the similarity of the ^1H NMR parameters of **1** and **3a**, it appears that leucanthinin exhibits the same configurational and conformational relationships as melampodin A acetate (**1**) except at C-3. The hydroxy group at C-3 in **3a** was assigned an α configuration on the basis of the torsional angles between H-3 and the two C-2 hydrogens. The observed J values ($J_{2a,3} = J_{2b,3} \simeq 4.0$ Hz) can only be explained if the C-3 hydrogen bisects the two hydrogens at C-2 with about 60° torsional angles. Stereomodels show that the only possible configuration which is in agreement with the experimental data must have a β proton at C-3. Therefore, the configurational structure **3a** is suggested for leucanthinin.

C. Melampolidin (4). Collections of young shoots of *M. leucanthum* from Presidio County, Texas, gave, after repeated chromatography, a gummy material that was pure by TLC. The ir spectrum of this noncrystalline compound which we named melampolidin, $C_{23}H_{30}O_9$ (high-resolution mass spectrum), indicated an OH group (3450 cm^{-1}) which resisted acetylation with pyridine–acetic anhydride suggesting the presence of tertiary hydroxyl group in **4**. The 100-MHz ^1H NMR spectrum of **4** in $CDCl_3$ showed doublets at 5.59 (J = 3.0 Hz) and 6.17 ppm (J = 3.5 Hz) as well as a broad multiplet at 2.6 ppm, that are characteristic of α,β-unsaturated γ-lactones. Further ^1H NMR spectral assignments were made by double irradiation experiments on **4** in C_6D_6. Strong irradiation at the center of the multiplet at 2.48 ppm (H-7) caused the doublets at 5.49 (H-13a) and 6.14 ppm (H-13b) to collapse and the multiplet at 6.44 ppm (H-8) to simplify by the loss of the small coupling to give a doublet of doublets (J = 7.0 and 9.5 Hz). In addition, the doublet of a doublet at 5.09 ppm (H-6) simplified to a doublet. In return, when H-6 was irradiated, the C-7 proton signal at 2.48 ppm and the doublet of doublets at 4.81 ppm (H-5) lost their wide spacing (J = 10.0 Hz). When the C-5 proton signal at 4.81 ppm was saturated, H-6 became a doublet (J = 10.0 Hz) and the C-4 methyl doublet at 1.62 ppm (J = 1.2 Hz) collapsed to a singlet. Irradiation of the C-3′ methyl doublet at 1.18 ppm (J = 6.5 Hz) caused collapse of the quartet at 5.15 ppm (H-3′). The positioning of the latter two signals together with the occurrence of a methyl singlet at 1.24 ppm strongly suggested the presence of a 2-methyl-2-hydroxy-3-acetoxybutyrate moiety (B) in **4**. This was corroborated by the appearance of strong mass spectral fragments at *m/e* 274.1213 ($M - C_7H_{12}O_5$) and 159.0663 ($C_7H_{11}O_4$) which indicated that seven carbon atoms are present in a single fragment. The base peak at *m/e* 131.0728 ($C_6H_{11}O_3$) must be due to fragmentation between C-1′ and C-2′ of the side chain B of compound **4** and peaks at *m/e* 117.0553 ($C_5H_9O_3$) and 99.0435 ($C_5H_7O_2$) indicated the loss of ketene (42 mu) and acetic acid (60 mu), respectively, from the side chain fragment $C_7H_{11}O_4$ (159 mu). Other MS peaks verified the presence of side chain B in **4**.

A strong mass spectral fragment at *m/e* 215.1059 ($C_{14}H_{15}O_2$) indicated the loss of $\cdot CO_2CH_3$ (59 mu) from the ion due to the medium ring skeleton (*m/e* 274.1213); the presence of a carbomethoxy moiety was corroborated by the appearance of a methyl singlet at 3.77 ppm ($-CO_2CH_3$) in the NMR spectrum. In addition, a broadened triplet at 6.85 ppm in the ^1H NMR spectrum ($CDCl_3$) of melampolidin suggested the presence of an α,β-unsaturated methyl ester, the absorption at 6.85 ppm being due to the β hydrogen (H-1) of the conjugated ester. In $CDCl_3$, irradiation of the broadened triplet at 6.85 ppm affected the envelope at 2.0–2.4 and the multiplet near 2.8 ppm indicating the presence of two protons at C-2 in **4**. When the center of the H-8 multiplet at 6.33 ppm ($J_{7,8}$ = 1.5, $J_{8,9b}$ = 7.5, $J_{8,9a}$ = 9.0 Hz) was saturated, the H-7 signal at 2.6 ppm sharpened and the one-proton multiplet (H-9) at 2.77 ppm ($J_{9,1}$ = 1.5, $J_{9,8}$ = 7.5, $J_{9a,9b}$ = 14.0 Hz) simplified to a broadened doublet (J = 14.0 Hz). The remaining wide spacing (J = 14.0 Hz) of the broadened H-9 doublet indicated a geminal coupling, suggesting the presence of two hydrogens at C-9, one of the two H-9 hydrogens very likely being a part of the envelope at 2.0–2.4 ppm.

The above NMR spectral assignments together with the high-resolution mass spectral fragmentation patterns, in particular the peaks at *m/e* 274 and 215, are in full agreement with a medium ring skeleton as shown in **4**. Furthermore, on the basis of biogenetic relationships and the similarity of the NMR parameters, melampolidin (**4**) should exhibit the same configurational and conformational relationships around the medium ring as the other melampolide sesquiterpene lactones (**1**, **2**, and **3a**). The stereochemical considerations related to the C-8 side chain B in **2** also apply to the side chain in **4**. Finally, it is noteworthy that melampolidin represents the first melampolide from *Melampodium* lacking a C-9 oxygen function.

Experimental Section[10]

Melampodin A acetate (1)[3,4] gave significant low-resolution mass spectral peaks (20 eV, 160 °C) at *m/e* (rel intensity) 462 (1.6), 420 (0.6), 402 (58), 347 (2.5), 306 (9.4), 287 (26.1), 286 (60.0), 272 (23.3), 271 (36.6), 258 (32.4), 227 (95.8), 226 (100.0), 211 (48.6), 200 (89.5), 190 (49.3), 176 (43.0), 171 (43.7), 159 (9.8), 95 (11.3), 71 (10.6), 43 (48.0).

Melampodinin (2). A collection of *Melampodium americanum* L. was made on Dec 6, 1974, 8.5 miles north of Palma Sola on route 180, Veracruz, Mexico (Stuessy and Roberts No. 3171). Dried leaves (1012 g) were extracted and worked up as previously described,[4] providing 2.5 g of crude, terpenoid-containing syrup which was chromatographed over 100 g of silica gel using CH_2Cl_2/EtOAc (9:1) as elutant; 15-ml fractions were taken and all fractions were monitored by TLC. Fractions 11–20 contained about 3 mg of artemetin which was identical with authentic material by melting point and mixture melting point.[6] Fractions 36–60 provided 75 mg of **2**: mp 203–205 °C; uv λ_{max} (MeOH) 213 nm (ϵ, 1.7×10^4); CD (c 3.8×10^{-5}, MeOH) $[\theta]_{213}$ -1.5×10^5, $[\theta]_{246}$ $+3.2 \times 10^4$; ir ν_{max} (Nujol) 3500 (OH), 1770 (γ-lactone), 1730 (ester), 1670 and 1650 cm^{-1} (double bonds); significant low-resolution mass spectral peaks (20 eV, 120 °C) at *m/e* (rel intensity) 522 (0.8), 504 (1.3), 478 (1.4), 462 (4.9), 436 (34.2), 346 (2.0),

304 (22.0), 286 (99.0), 272 (39.7), 271 (24.4), 258 (35.2), 227 (89.0), 226 (100.0), 211 (31.6), 200 (66.7), 190 (26.2), 176 (61.3), 171 (23.4), 159 (17.2), 131 (61.3), 95 (10.4), 71 (15.3), 43 (51.4).

Anal. Calcd for $C_{25}H_{30}O_{12}$: C, 57.47; H, 5.79; mol wt, 522. Found: C, 57.51; H, 5.80; mol wt (MS), 522.

Leucanthinin (3a). *Melampodium leucanthum* was collected in Motley County, Texas, 18 miles north of Dickens on Farm road 3203 on June 25, 1974 (Stuessy-Stuessy 3560). Dried leaves (570 g) were extracted with cold $CHCl_3$ and worked up as described before.[4] From the combined $CHCl_3$ extracts 2.8 g of crude material was obtained. The crude syrup (1.0 g) was chromatographed over 100 g of silica gel (Merck 0.05–0.2 mesh) using *n*-propyl acetate as eluent and taking 15-ml fractions. The progress of the chromatographic run was monitored by TLC. Fraction 15–25 contained a material which was homogeneous by TLC. The fractions were combined and evaporated in vacuo providing a crystalline material (40 mg). Recrystallization from $CHCl_3$–Et_2O gave pure **3a**: mp 163–164 °C; uv λ_{max} (MeOH) 226 nm (ϵ 5.6 × 10^3); CD (c 2.1 × 10^{-4}, MeOH) $[\theta]_{222}$ −62 × 10^3, $[\theta]_{243}$ +3 × 10^3; ir ν_{max} (neat) 3480, 1760, 1740, 1720, 1670, 1630 cm^{-1}; ^{13}C NMR ($CDCl_3$) 169.4, 167.9, 167.5, 164.8 (>C=O); 145.0 d (–CH=); 140.5, 133.7, 130.9 (=C<); 122.7 d (=CH–); 121.0 t ($=CH_2$); 74.6 d, 73.6 d, 70.9 d, 70.6 d, 59.6 d (HCO); 59.1 (>CO); 52.0 d (>CH); 50.6 q ($-OCH_3$); 32.0 t ($-CH_2-$); 20.8 q, 19.1 q, 15.8 q, 13.6 q ($-CH_3$). The mass spectrum showed significant peaks at *m/e* 464.1687 (M^+), 404.1488 (M − CH_3COOH), 348.1193 (M − $C_5H_8O_3$), 288.1012 (M − $C_5H_8O_3$ − CH_3COOH), 229.0858 (M − $C_5H_8O_3$ − CH_3COOH − $C_2H_3O_2$), 183.0814 ($C_{13}H_{11}O$), 131.0491 (C_9H_7O), 116.0495 ($C_5H_8O_3$), 99.0463 ($C_5H_7O_2$), 71.0519 (C_4H_7O, base peak).

Anal. Calcd for $C_{23}H_{28}O_{10}$: mol wt, 464.1632. Found: mol wt (MS), 464.1687.

The acetate **3b** [uv λ_{max} (MeOH) 211 nm (ϵ 7.2 × 10^3); ir ν_{max} (neat) 1770, 1738, 1720, 1680, 1235, 1140 and 990 cm^{-1}] showed no parent peak but exhibited significant mass spectral peaks at *m/e* 446.1647 (M − CH_3COOH), 288.1002 (M − $C_5H_8O_3$ − CH_3COOH − CH_2CO), 270.0889 (M − $C_5H_8O_3$ − $2CH_3COOH$), 229.0866 ($C_{14}H_{13}O_3$), 183.0825 ($C_{13}H_{11}O$), 131.0466 (C_9H_7O), 116.0493 ($C_5H_8O_3$), 99.0422 ($C_5H_7O_2$), 81.0343 (C_5H_5O), 71.0486 (C_4H_7O, base peak).

Melampolidin (4). Collections of young shoots of *M. leucanthum* were made in Presidio County, Texas, 2.3 miles south of Marfa on Highway 67 on July 24, 1973 (Stuessy-Fischer No. 2044). Dried plant material (95 g) yielded 420 mg of crude syrup which was worked up and chromatographed as described above. Fraction 7–12 gave 95 mg of melampolidin (**4**) as a gum: uv λ_{max} (MeOH) 222 nm (ϵ 1.2 × 10^4); CD (c 8.4 × 10^{-5}, MeOH) $[\theta]_{218}$ −58 × 10^3, $[\theta]_{249}$ −3 × 10^3, $[\theta]_{265}$ −7 × 10^3; ir ν_{max} (neat) 3450, 1760, 1740, 1710, 1670, 1630 cm^{-1}; significant mass spectral peaks at *m/e* 432.1798 (M − H_2O), 274.1213 (M − $C_7H_{12}O_5$), 242.0935 ($C_{15}H_{14}O_3$), 215.1059 ($C_{14}H_{15}O_2$), 159.0663 ($C_7H_{11}O_4$), 131.0728 ($C_6H_{11}O_3$, base peak), 117.0553 ($C_5H_9O_3$), 99.0435 ($C_5H_7O_2$), 91.0550 (C_7H_7), 71.0513 (C_4H_7O). Since in the mass spectrum no parent peak was obtained for **4** the M − H_2O data were used for the determination of the empirical formula.

Anal. Calcd for $C_{23}H_{30}O_9$: mol wt, 432.1798. Found: mol wt (MS), 432.1784.

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Registry No.—**1**, 35878-52-5; **2**, 60295-53-6; **3a**, 60295-54-7; **3b**, 60295-55-8; **4**, 60295-56-9.

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(10) Melting points were performed in capillaries on a Thomas-Hoover and are uncorrected. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer Model 621 spectrophotometer and ultraviolet spectra were obtained on a Cary Model 14 spectrophotometer. The CD spectra were determined on a Durram-Jasco J-20 spectrometer. Low-resolution mass spectra were obtained on a Hitachi Perkin-Elmer Model RMS-4 and the high-resolution mass spectra were run on a CEC 21-1108 instrument (70 eV ionizing voltage). The samples were introduced via the direct inlet tube. The ^{13}C NMR spectra were determined on a Varian XL-100-15 spectrometer operating Fourier transform mode with proton decoupling. Me_4Si was used as internal standard and the values are in parts per million relative to Me_4Si. The number of lines in the single-frequency off-center decoupled spectra are designated as follows: d, doublet; t, triplet; q, quartet. Unmarked signals are singlets. The voucher specimens are on deposit in the Louisiana State University Herbarium at Baton Rouge, La.

Mass Spectrometry of Cytokinin Metabolites. Per(trimethylsilyl) and Permethyl Derivatives of Glucosides of Zeatin and 6-Benzylaminopurine

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The mass spectra of the Me_3Si and permethylated derivatives of a comprehensive series of synthetic isomeric glucosides of the cytokinins zeatin and 6-benzylaminopurine (6-BAP) have been recorded by combined gas chromatography–mass spectrometry. Comparison of these spectra with those obtained for a number of glucosyl metabolites of zeatin and 6-BAP allows unambiguous structural assignments to be made. Detailed analysis of the mass spectral fragmentation patterns indicate that, a priori, it should be possible to assign the sugar ring size (furanose vs. pyranose) in such compounds on the basis of characteristic fragment ion intensities. Mass spectra of the Me_3Si derivatives show more significant isomer differences than the corresponding permethylated compounds and their method of preparation appears less prone to multiple product formation. A thermal 1,3 migration of the sugar moiety from N_3 to N_9 was observed in the GC–MS of the derivatives of the 3-β-D-glucopyranoside of 6-BAP.

Phytohormones, and in particular the adenine derived cytokinins, evoke their biological responses at extremely low concentrations and occur free in plants in minute amounts. For example, the natural cytokinin zeatin (**1**) induces growth of carrot phloem tissue at concentrations of less than 0.1 μg/l. (5 × 10^{-10} M).[1] Zeatin-related compounds, e.g., N^6-(3-methyl-2-butenyl)adenosine, are ubiquitous, although minor, components of *t*-RNA hydrolysates from animals, plants, and

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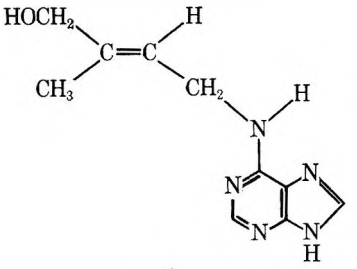
microorganisms. Because of the minute quantities of material involved, mass spectrometry has been and continues to be an essential means of providing information about the chemical nature of these compounds.[2,3]



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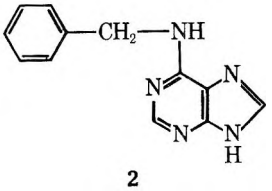

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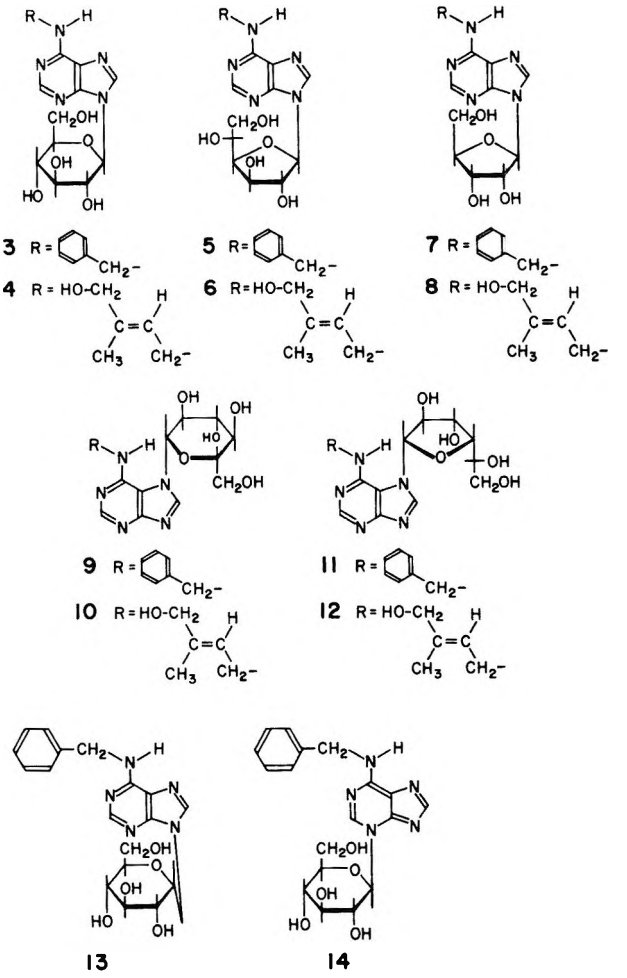
As part of a continuing study into the mechanism of action of cytokinins during plant growth, we have isolated a variety of metabolites from different plant systems following exogenous uptake of labeled zeatin and the synthetic cytokinin, 6-benzylaminopurine (6-BAP, **2**). As well as those metabolites of zeatin previously identified in plants such as its 9-riboside and 9-riboside 5′-phosphate plus adenosine and adenosine 5′-phosphate, several new stable metabolites of zeatin and 6-BAP have been isolated. In the main these have proved to be *N*-glucosides of the parent cytokinins,[3c-e] although an unusual amino acid conjugate of zeatin, lupinic acid, together with *O*-β-D-glucopyranosyl zeatin were isolated from lupin seedlings.[4] Preliminary identification and tentative assignments of structure have relied heavily on mass spectrometry, with unequivocal structural assignments being possible only after direct comparison with authentic synthetic samples. In the course of such comparisons, direct probe insertion of the underivatized compounds has often proved unreliable and on occasions given irreproducible mass spectra due to the instability of some of the more thermolabile glucosides. On the other hand, mass spectrometry of the volatile trimethylsilyl (Me_3Si), permethyl, acetyl, and trifluoroacetyl derivatives of nucleosides and related compounds has been utilized to obtain valuable structural information. A number of papers have been published analyzing the mass spectrometric fragmentation behavior of such derivatives using isotope labeling and high-resolution mass spectrometry.[5-11] As both the Me_3Si and permethyl derivatives of these compounds are amenable to gas chromatography, the GC–MS combination provides the additional comparison criteria of retention time and sample purity.

In this study the GC–MS spectra of Me_3Si and permethyl glucosyl metabolites of 6-BAP and zeatin have been compared with those recorded for the series of synthetic isomers **3, 5, 9, 11, 13, 14** and **4, 6, 10, 12,** respectively. It is also the purpose of this work to try to rationalize the characteristic fragmentations present in the mass spectra to determine whether structural assignments can be made from the GC–MS data without the necessity of reverting to direct comparisons with model compounds. That such an approach had previously been subject to uncertainty is illustrated by the incorrect assignment of a furanose structure to the sugar residue of the 7-glucosyl metabolite of 6-BAP based on a correlation of the mass spectral fragmentations of the Me_3Si derivative with previously published work on simple sugars (vide infra).

Results and Discussion

Derivatization and Gas Chromatography. Trimethylsilylation of the cytokinin glycosides **3–14** was carried out according to previously published methods for related compounds. Me_3Si ethers, as expected, were formed at all sugar hydroxyls and at the side-chain hydroxyl of the zeatin derivatives. No multiple derivatives were formed. Permethylation of the 9-glucosides by the Hakamori technique[11,12] gave good yields of homogeneous products, which eluted at slightly higher temperatures than the corresponding silylated compounds. N-Methylation at N_6 of the adenine moiety accounts for an extra site of derivatization in the permethylated derivatives. Poorer yields and multiple products were observed with the more labile 7-glucosides. If reaction times in excess of 5 or 10 min were used, only the products of hydrolysis of the glycosidic bond were obtained. With reaction times of 3 min or less, compounds of the expected molecular weight were mixed with the products of hydrolysis and partial methylation. In the particular case of the permethylation of 6-BAP-7-β-D-glucofuranoside (**11**) four products with the expected molecular ion at *m/e* 457 were formed in addition to those of hydrolysis and partial methylation. Of the components with molecular ion at *m/e* 457, one differed markedly from the rest in that the ion at *m/e* 210 was of very low intensity. This ion arises from loss of methylenimine from the b − H ion (see below) and is characteristic of a dialkylamino function at N_6. Its low intensity probably indicates methylation of an imino tautomer of **11**. Permethylation of the 7-β-D-glucopyranosides of 6-BAP (**9**) and zeatin (**10**) also gave low yields and mixtures of products, although only one derivative with molecular weight corresponding to the fully methylated, intact glucoside was formed. The fact that all cases of silylation of *N*-glucosides gave reproducible derivatization to a homogeneous product under the same reaction conditions suggests that this derivative has greater utility for the analysis of this group of compounds.



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Both the Me_3Si and permethylated derivatives of 6-BAP-3-β-D-glucopyranoside (**14**) underwent thermal rearrangement during gas chromatography. The gas chromatographs and the GC–MS total ion current traces both showed two

peaks, a broad one followed by a very sharp one which coeluted with the corresponding derivative of 6-BAP-9-β-D-glucopyranoside (**3**). The mass spectra under both peaks were identical with each other and with those of the respective derivative of **3**. This behavior would indicate a thermal rearrangement of the sugar moiety from N_3 to N_9 on the GC column, with rearrangement of any remaining N_3 derivative within the mass spectrometer ion source. The β configuration of the anomeric carbon of the sugar is retained during the rearrangement since the spectra of the products are easily distinguished from those of the corresponding derivatives of 6-BAP-9-α-D-glucopyranoside (**13**).

A similar migration has been reported for some 3-alkyladenine and 3-ribosyladenine derivatives and an intermolecular reaction mechanism has been proposed.[13] However, a necessary condition for those migrations was found to be the presence of an N_6 acyl substituent and a mercuric or hydrogen halide catalyst. A combination of inter- and intramolecular mechanisms, with the latter process predominating, has recently been found to be operating in the thermal rearrangement of 3-benzyladenine to 6-BAP.[14] The mechanism of the rearrangement in the 3-glucosyl derivatives of 6-BAP is under further investigation since 3-β-glucopyranosyl-6-BAP has been found as a metabolite of 6-BAP in radish seedlings and is itself highly active as a cytokinin.[3e]

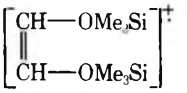
Mass Spectra. A. General. As expected, the fragmentation patterns of the derivatized zeatin and 6-BAP glucosides resembled those of previously published adenine ribosides except for those decompositions associated with the N_6 side chain or those characteristic of the sugar portion of the molecule. The assignments of structures to the major ions in the spectra (as in Table I) have been made on the basis of labeling studies carried out on other nucleosides[5,11] and derivatized carbohydrates[15] and have been supplemented by some high-resolution measurements. It must be emphasized that although structures have been assigned to certain ions throughout this paper, this does not imply that such structures are necessarily correct. Rather they are rationalizations based on available labeling data and chemical analogy.

Molecular ions were visible in all spectra, varying in intensity between 0.1% and 20% of the base peak. Spectra of Me_3Si derivatives were characterised by a base peak at *m/e* 73 and intense ions at *m/e* 75, 103, 129, 147, 169, 204, 217, 305, and 319 which are the well-documented ubiquitous species characteristic of Me_3Si carbohydrates and related compounds.[15] Permethylated derivatives showed a similar series of characteristic ions at *m/e* 71, 75, 88, 101, and 111.[18] The assignments in Table I have been grouped as far as possible according to the origin of the ionic species. The spectra of some of the silylated compounds are reproduced in full since our results indicate that this derivative has the most utility for structure assignment. The spectra of the successfully prepared permethylated compounds are in tabulated form, and available as supplementary material (see paragraph at end of paper).

Detailed examination of all spectra showed that apart from the obvious mass related assignments (e.g., hexose vs. pentose) the sugar ring size in glucosides could be established with certainty by the presence or absence of certain critical ions. Although a change of the position of substitution of the sugar moiety on the purine ring (e.g., 7 vs. 9) gave rise to markedly different spectra, it was not possible to assign the substitution pattern by inspection. The spectra of the derivatives of the 9-β- (**3**) and 9-α- (**13**) glucopyranosides of 6-BAP also showed major differences although there was no obvious structure–fragment ion relationship which could permit assignment of the configuration of the anomeric linkage with certainty.

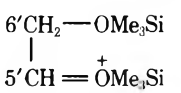
B. Me_3Si Derivatives of 6-BAP Glycosides. In this series we obtained spectra of the Me_3Si derivatives of **3**, and of its 9-α anomer (**13**), the 9-β-glucofuranoside (**5**), the 7-β-glucopyranoside (**9**), the 7-β-glucofuranoside (**11**), and the 9-β-riboside (**7**). The spectra of **3, 5, 9,** and **11** are shown in Figures 1–4, with the major ions of Table I signified, and exemplify the features which distinguish the glucopyranosides from glucofuranosides (see paragraph at end of paper regarding supplementary material).

In the spectra of the pyranosides (Figures 1 and 3) the ion at *m/e* 204 is more intense than *m/e* 205 while in the furanosides (Figures 2 and 4) the order is reversed. Our results indicate that this is the ion intensity data of greatest diagnostic value for assignment of sugar ring size. The ion at *m/e* 204 is a characteristic fragment ion of Me_3Si carbohydrates



m/e 204

and in hexose sugars has been shown to incorporate essentially the C2′–C3′ or C3′–C4′ pairs of sugar skeletal carbons.[16] The ion at *m/e* 205, apart from the isotope contribution of *m/e* 204,

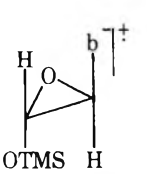


z, *m/e* 205

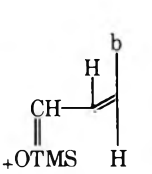
has been shown to arise in hexose sugars by cleavage of the C4′–C5′ bond with charge retention on the C5′–C6′ fragment to give ion z.[16] Analogous cleavages have been observed in the spectra of peracetyl[17] and permethyl[18] hexofuranosides. In the former derivative, however, ion z occurs at *m/e* 145 together with the ubiquitous triacetyloxonium species, thus limiting its use as a structural marker in this case.

The same C4′–C5′ bond cleavage, but with charge retention on the larger portion of the molecule, would give rise to an ion at *m/e* 470. Fox and co-workers[19] used the presence of the ion at this mass, together with the relative intensities of *m/e* 204 and *m/e* 217, to assign a furanose structure to the sugar moiety in 6-BAP-7-glucoside, the major stable metabolite of 6-BAP in soybean callus tissue. Examination of Figures 1–4, however, reveals that *m/e* 470 is most intense in Figure 3, the spectrum of the 7-glucopyranoside (**9**). Comparison of their published spectrum with Figure 4, the spectrum of Me_3Si-6-BAP-7-β-D-glucofuranoside, shows a number of dissimilarities, while it is almost identical with Figure 3, thus indicating that their metabolite is almost certainly the 7-glucopyranoside **9**. Compound **9** has also been isolated as the major metabolite of 6-BAP in radish seedlings and its identity recently confirmed by comparison with an authentic synthetic sample.[20]

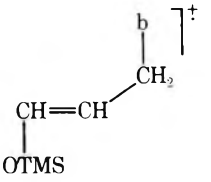
Other differences between the furanosides and pyranosides include the relative intensities of the ions at *m/e* 355 and 353. The ion at *m/e* 355 (q) is especially prominent in the spectrum



q, *m/e* 335



r, *m/e* 352



t, *m/e* 353

of Me_3Si **11** and its origin has previously been established.[11] The ion at *m/e* 353 (t) has an accurate mass corresponding to $C_{18}H_{23}N_5OSi$ (b + C_3H_4OR, R = Me_3Si). It thus appears to be the hydrogen rearranged analogue of the "ion m" (b + C_3H_3OR, R = CD_3) in the spectra of perdeuteriomethylated ribonucleosides[11] and the ion *m/e* 352 (r) (b + C_3H_3OR, R = Me_3Si) which is present but mostly at low intensity in all the

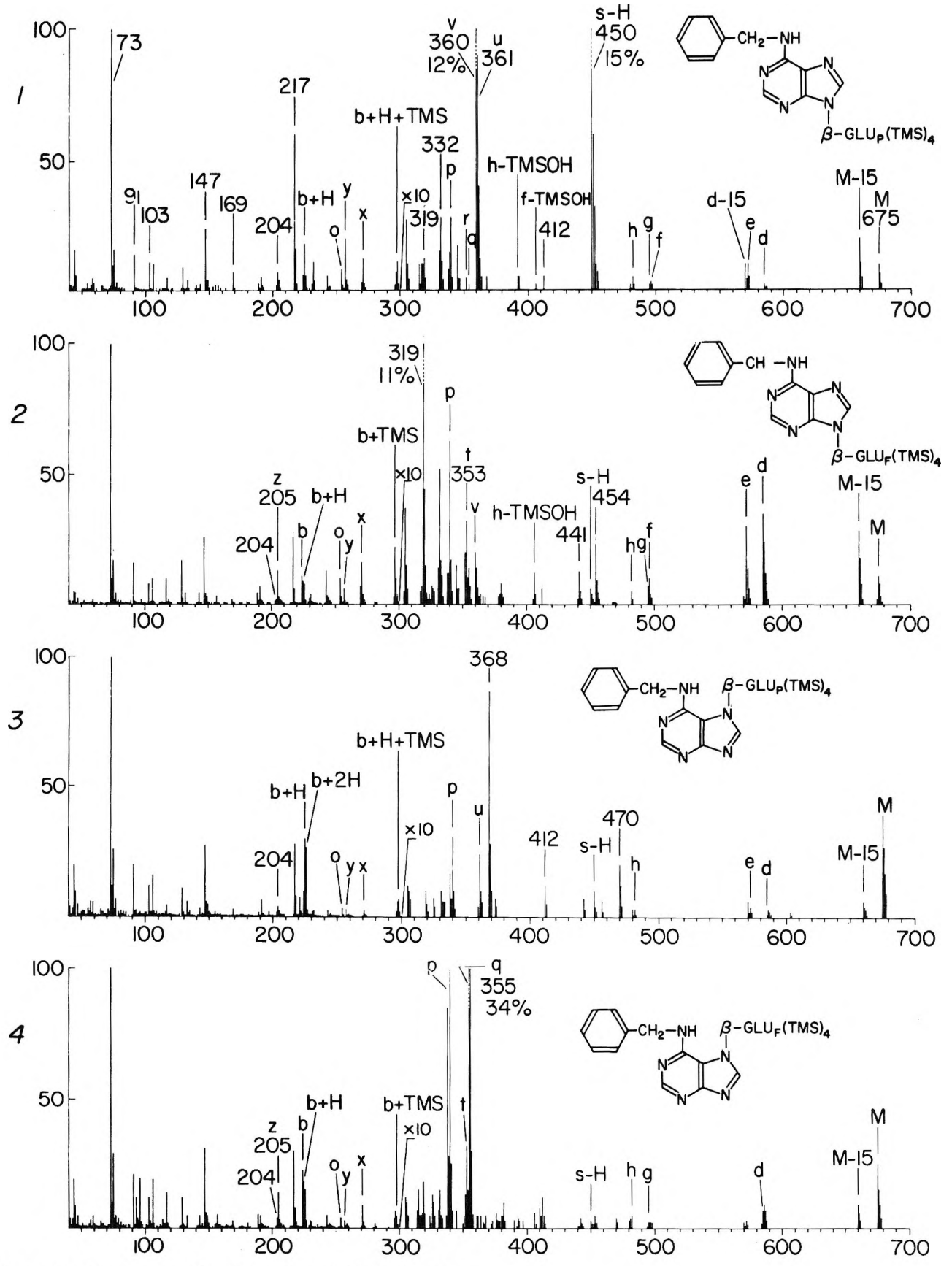
Table I. Summary of Major Decomposition Pathways of Permethyl and Pertrimethylsilyl Purine Glycosides

Symbol	Type	Description	Ref
		A. Ion Closely Related to the Molecular Ion	
M	$M\cdot^+$	Molecular ion	
M − 15	$M\cdot^+ - \cdot CH_3$	Methyl loss from Me_3Si derivatives	
a	$M\cdot^+ - \cdot R$	R = $Si(CH_3)_3$; R = CH_3 (permethyl)	
c	$M\cdot^+ - \cdot OR$		
d	$M\cdot^+ - ROH$		
e	$M\cdot^+ - \cdot CH_2OR$	Lost from sugar and/or zeatin side chain	
f	$M\cdot^+ - ROH - \cdot OR$		
g	$M\cdot^+ - 2ROH$		
h	$M\cdot^+ - \cdot CH_2OR - ROH$		
j	$d - CH_2NH$	Loss of methylenimine from ion d	
k	$M\cdot^+ - C_3H_8OR$	Cyclization ion of zeatin derivatives (M − 131, Me_3Si; M − 73, permethyl)	23–25
l	$M\cdot^+ - C_4H_6OR$	Cleavage β to N_6 in zeatin side chain (M − 143, Me_3Si; M − 85, permethyl)	
M − 29	$M\cdot^+ - CH_2NH$	Loss of methlenimine from N_6 methyl derivatives	26
M − 91	$M\cdot^+ - C_7H_7$	Loss of N_6 benzyl from 6-BAP derivatives	
		B. Ions Formed by Cleavage of Glycosidic Bond	
b	Base	Simple cleavage, charge retention on base	2, 7
b + H	Base + H	Cleavage with single hydrogen transfer	
b + 2H	Base + 2H	Cleavage with double hydrogen transfer	
b + Me_3Si	Base + Me_3Si	Cleavage with Me_3Si migration	
b + H + Me_3Si	Base + H + Me_3Si	Cleavage with Me_3Si and hydrogen migration	
s	Sugar	Simple cleavage, charge retention on sugar	
s − H	Sugar − H	Cleavage, H transfer to base, charge retention on sugar	
		C. Ions Derived from b or b + H	
n	$b + H - CH_2NH$	Loss of methylenimine from permethyl derivatives	
c′	$b - \cdot OR$	Loss of OR from zeatin side chain	
e′	$b + H - \cdot CH_2OR$	Loss of CH_2OR from zeatin side chain	
k′	$b + H - C_3H_8OR$	"Cyclization ion" in zeatin derivatives	
l′	$b + H - C_4H_6OR$	Cleavage β to N_6 in zeatin derivatives	
$C_6H_6N_5$	*m/e* 148	Cleavage of N_6 substituent from b + H in permethyl derivatives	11
		D. Ions Incorporating Base and Portion of Sugar	
o	$b + CH_2O$	b + H with C-1′ and ring oxygen of sugar (b + 30)	2, 28
p	$b + C_2H_3OR$	b + H with C-1′ and C-2′ − OR (b + 58 permethyl; b + 116, Me_3Si)[a]	7
q	$b + C_2H_2O_2R$	b with C-1′, C-2′ − OR, and ring oxygen (b + 131, Me_3Si)[a]	7
r	$b + C_3H_3OR$	b with C-1′, C-2′, and C-3′ − OR (b + 70, permethyl; b + 128, Me_3Si)[a]	11
t	$b + C_3H_4OR$	As above with one extra hydrogen (b + 129, Me_3Si)[a]	
		E. Ions Derived from s − H	
u	$s - ROH$		
v	$s - H - ROH$		
w	$s - \cdot CH_2OR$		
x	$s - 2ROH$		
y	$s - ROH - \cdot CH_2OR - H$		
z	$CH_2OR - CHOR\cdot$	Cleavage of C-4′–C-5′ bond of glucofuranosides with charge retention on "side chain"	16, 17
	m/e 144	Characteristic of adenosine derivatives	
		F. Ubiquitous Ions	
	m/e 73, 103, 129, 147, 169, 204, 217, 305, 319	Ions common to Me_3Si carbohydrates and related compounds	15, 16
	m/e 88, 75, 71, 101, 111	Ions common to permethyl sugar derivatives	18, 29
	m/e 91	Tropylium cation (6-BAP) derivatives	

[a] Formula established by high-resolution mass measurement.

spectra of Me_3Si 6-BAP-glycosides. The ion *m/e* 319, common to many Me_3Si carbohydrates, has been proposed as an indicator of furanosides.[16] It is an intense ion in the spectrum of Me_3Si **5** (Figure 2) but is as weak in the spectrum of Me_3Si **11** (Figure 4) as it is in the spectra of the pyranosides, indicating that use of such an indicator is incorrect in this series of compounds.

The cleavage of the glycosidic bond of nucleosides and the well-documented hydrogen transfers which accompany this process are also dependent on the nature of the sugar moiety. In Me_3Si derivatives the migrating hydrogens have been shown to arise from the sugar skeletal carbons[5] and while this is also true of permethyl derivatives, there is also some migration of the hydrogen atoms of the O-2′ methyl group.[11] In



Figures 1–4. Mass spectra of Me_3Si derivatives of 6-BAP glycosides.

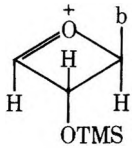
the Me_3Si 6-BAP glucosides, sugar ring size appears to influence this process quite significantly since in the pyranosides (Figures 1 and 3) b + H or b + 2H > b and in the furanosides (Figures 2 and 4) b > b + H > b + 2H. In the riboside (7) both b + H and b + 2H are larger than b. Migration of a Me_3Si group is also a favored process giving rise to intense ions at b + Me_3Si and b + H + Me_3Si at *m/e* 297 and 298 in all compounds.

Mass spectral features allowing assignment of the position of substitution of the sugar on the purine ring are more diffi-

cult to detect since differences present in the spectra of one pair of positional isomers are not always consistent for other pairs. In the case of the 3-β-glucosides, as mentioned above, the derivatized sugar undergoes migration from N_3 to N_9 and hence identical spectra result for these two positional isomers. The spectra of the 7- and 9-glucosides have obvious quantitative differences, for example in the ion abundance ratio M/(M − 15). However, these differences are probably the result of a number of interacting factors and any reliable decision as to the sugar position could only be made by direct comparison with reference spectra. A recent study has shown that, with reference compounds available, the differentiation between 7- and 9-substituted nucleosides by chemical ionization mass spectrometry appears feasible.[21]

The ions s − H, u, and v (as defined in Table I) at *m/e* 450, 361, and 360, respectively, are very intense in the Me_3Si 9-β-glucopyranosides of 6-BAP (**3**), zeatin (**4**), and adenine.[22] This indicates that particularly favorable conditions exist in this group of compounds for cleavage of the glycosidic bond, with charge retention on the sugar moiety. In all other spectra of the Me_3Si glucosides, s − H, u, and v are less than 5% rel intensity. In the spectrum of Me_3Si **5**, and in the corresponding zeatin derivative **6**, *m/e* 319 is a very intense ion (11% rel intensity), while it is only 1–2% rel intensity in the other spectra.

The ion at *m/e* 368 is present, but at low intensity in all spectra except that of Me_3Si **9**, where it is a characteristically intense peak. High-resolution mass measurement indicates

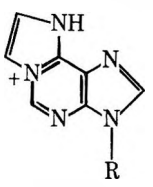


m/e 368

the formula for this ion of $C_{18}H_{22}N_5O_2Si$ or b + $C_3H_3O_2R$, R = Me_3Si. This ionic species most likely contains the first three skeletal carbons and ring oxygen of the sugar with a structure isomeric with that shown.

The ion at *m/e* 169, normally characteristic of Me_3Si ribonucleosides,[7] has 10% rel intensity in the spectrum of Me_3Si 6-BAP-9-β-D-ribofuranoside (**7**) and is also a reasonably significant ion in the spectra of the 9-glucopyranosides **3** and **13**. It is present but at lower abundance (2–3% rel intensity) in the remaining spectra.

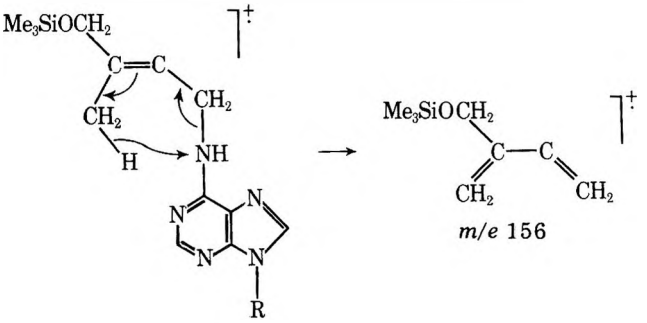
C. Me_3Si Derivatives of Zeatin Glycosides. In this series Figures 5–8 show the spectra of Me_3Si **4** and **10**, the 9-β- and 7-β-D-glucopyranosides, and Me_3Si **6** and **12**, the 9-β- and 7-β-D-glucofuranosides of zeatin. The spectrum of Me_3Si **8**, the 9-β-D-riboside of zeatin, is available as supplementary material. Some of the major ions are similar to those in the spectra of the Me_3Si derivatives of 6-BAP, but with additional peaks resulting from fragmentations of the zeatin side chain. The ions at *m/e* 610 (*m/e* 508 in the riboside), "cyclization ion" k, and at *m/e* 160 (k′) are analogous to the ion at *m/e* 160 in



k, R = glucosyl (Me_3Si)	*m/e* 610
R = ribosyl (Me_3Si)	*m/e* 508
k′, R = H	*m/e* 160

zeatin itself[23] and 6-*N*-(3-methyl-2-butenylamino)-9-β-ribofuranosylpurine.[24,25] In some cases this is accompanied by an intense hydrogen rearrangement ion at *m/e* 611 (e.g., Figure 7).

The intense ions at *m/e* 638, 201, and 202 result from loss of the Me_3SiOCH_2· radical from the side chain in M·+, b, and b + H, respectively, although there could be some contribution to *m/e* 638 from the same loss of the C-6′ portion of the sugar moiety. The ion at *m/e* 156 ($C_8H_{16}OSi$), which is prominent in all spectra, probably arises by the rearrangement process shown, with charge retention on the zeatin side chain.



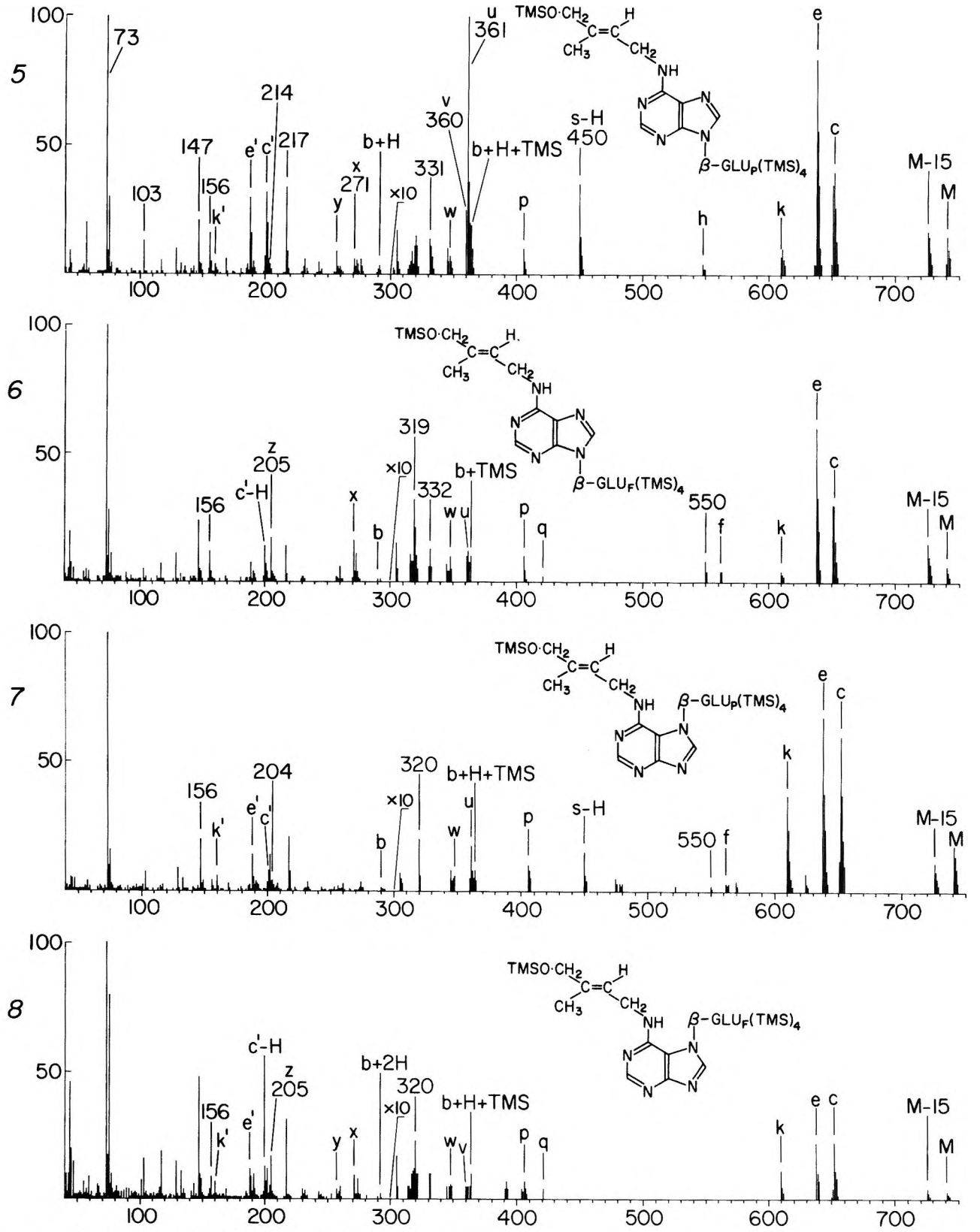
The indicators of sugar ring size evident in the 6-BAP spectra are also shown by the corresponding zeatin derivatives and include the relative intensities of the *m/e* 204 and 205 peaks, the latter being more intense in the spectra of Me_3Si **6** and **12** (Figures 6 and 8). Ion q (*m/e* 421) is also present in these spectra (0.2 and 0.4%, respectively), in accordance with the situation in the 6-BAP derivatives and the low intensity of this species is undoubtedly a reflection of how the decomposition pathways in zeatin are highly modified by the isopentenyl side chain.

The ion at *m/e* 319 is again of significant intensity in the spectrum of the 9-β-furanoside **6**, while the intense ions at *m/e* 450, 361 (u), and 360 (v) are characteristic of the 9-β-pyranoside **4** (Figure 5).

D. Permethylated Derivatives of 6-BAP Glycosides. The four 9-substituted glycosides (**3**, **5**, **7**, and **13**) methylated to afford homogeneous derivatives. The spectra of these compounds are available (see paragraph at end of paper regarding supplementary material). The 7-β-D-glucopyranoside (**9**), as mentioned before, methylated in low yield and this spectrum is included also. Results for the 7-β-D-glucofuranoside were ambiguous with respect to the spectrum of the desired product and are not included. A common feature of all the spectra is the strong molecular ion (10–20%). Taking into account the necessary mass shifts the major decomposition pathways are quite similar to those of the corresponding Me_3Si derivatives.

A striking feature of the spectrum of the glucofuranoside **5** is that *m/e* 89, the peak analogous to *m/e* 205 in the Me_3Si spectra, and corresponding to the glucose "side chain" cleavage, is in fact the base peak while there is an accompanying reduction in the intensity of *m/e* 88. Other features of the spectra similar to those seen in Me_3Si derivatives, are the presence of intense ions at *m/e* 218 (s − H) and 187 (u) in permethyl **3** (also seen in the spectrum of permethyl 9-β-D-glucopyranosyladenine)[22] and the relative intensity of *m/e* 155 (x) in permethyl **5**. The ion at *m/e* 111, analogous to *m/e* 169 in the Me_3Si spectra, mirrors the situation with those derivatives, being more intense in the 9-glucopyranosides and 9-β-riboside than in the glucofuranoside. The ion at *m/e* 114 appears to be characteristic of permethylated ribosides, having 24% rel intensity in the spectrum of permethyl **7**. McCloskey and co-workers have noted the characteristic presence of this ion in the spectrum of permethyladenosine.[11] In the specrum of permethyl **7** we have confirmed the formula $C_6H_{10}O_2$ for *m/e* 114 by a high-resolution mass measurement and the fact that it contains two methoxyl groups by its shift to *m/e* 120 in the MS of the perdeuteriomethylated analogue.

The permethylated 6-BAP derivatives also show similar behavior to the Me_3Si analogues with regard to the relative



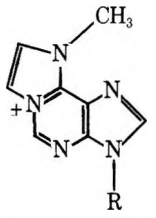
Figures 5–8. Mass spectra of Me_3Si derivatives of zeatin glycosides.

intensities of b, b + H, and b + 2H. The permethyl glucopyranosides **3**, **13**, and **9** have b + H > b, with b + H being the base peak. In the glucofuranoside **5**, the order of intensities is b > b + H > b + 2H.

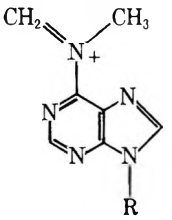
Expulsion of a methylenimine molecule, a process characteristic of methyl- and dimethylamino aromatics[26] and recently the subject of an isotope labeling study,[27] is a major process in the spectra of permethyl 6-BAP and zeatin glycosides. In the spectra of these derivatives of 6-BAP this process gives rise to an intense ion at *m/e* 210 where the expulsion is from the b + H ion at *m/e* 239, while in the 9-β-riboside the process also occurs from the molecular ion to give *m/e* 384. In the glucosides **5**, **9**, and **13** but not in **3**, methylenimine is expelled from the M − 15 ion to give an ion at *m/e* 413.

E. Permethylated Zeatin Glycosides. The spectra of permethylated zeatins **4**, **6**, **8**, and **10** are also available (see paragraph at end of paper regarding supplementary material).

The double bond of the isopentenyl side chain has a major directing influence on the fragmentation pattern, as it does in the corresponding Me_3Si derivatives. This factor gives rise to such characteristic features as the weak molecular ion, the intense ion at *m/e* 216 (base peak) corresponding to loss of methoxyl from b + H, and the "cyclization" and "side-chain cleavage" ions k and l.



k, R = glucosyl $(Me)_4$, *m/e* 392
R = ribosyl $(Me)_3$, *m/e* 348
k', R = H, *m/e* 194



l, R = glucosyl $(Me)_4$, *m/e* 380
R = ribosyl $(Me)_3$, *m/e* 336
l', R = H, *m/e* 162

As in the other methylated derivatives so far mentioned the distinction between glucofuranosides and glucopyranosides can be made on the basis of the relative intensities of *m/e* 88 and 89. In the spectrum of permethyl **6** the ions at *m/e* 434 ($M^{\cdot+} - OCH_3$) and 155 (s $- 2CH_3OH$) are also characteristically intense.

To summarize, the spectra of Me_3Si and permethyl derivatives of the individual isomeric glucosides of 6-BAP and zeatin are sufficiently diagnostic to allow structural assignments to be made. Metabolites of 6-BAP and zeatin extracted from various plant systems[3c-e] which have been unambiguously characterized by the GC–MS of their Me_3Si and permethyl derivatives are the 7- and 9-β-D-glucopyranosides **3, 4, 9,** and **10** and the 3-β-D-glucopyranoside of 6-BAP, i.e., **14.**

Experimental Section

Sources of Nucleosides. Zeatin-9-β-riboside was obtained from a commercial source. All other glycosides were synthesised as part of separate investigations into the structures of unusual cytokinin metabolites. For preliminary details of these syntheses see ref 3c–e and 20.

Derivatization Pertrimethylsilyl derivatives were prepared by dissolving a sample of the nucleoside (10–100 μg) in pyridine (10–20 μl), treating the mixture with BSTFA–TMCS, 99:1 (Regisil RC-2) (100 μl), and warming the solution at 60 °C for 30–60 min. Using this method all derivatizations were successful and gave essentially homogeneous products.

Permethyl derivatives were prepared according to the previously reported procedures for peptides[29] and nucleosides.[11] The nucleoside was treated with a 10-equiv excess of dimsyl anion solution for approximately 30 min, followed by the addition of a 10-equiv excess of methyl iodide. After a further 90 min the reaction was terminated by addition of water and the product was extracted, washed, and dried in the usual way. This procedure was not successful with the 7-substituted nucleosides, the only products being the permethylated fragments of hydrolysis of the glycosidic bond. In the case of the 7-glucopyranosides of zeatin and 6-BAP, using a 1-min contact with the anion solution and a 2-min contact with methyl iodide, the permethylated derivatives were prepared in slightly lower yield than for the corresponding 9-substituted derivatives. There were also some permethylated hydrolysis products present in the product. Multiple derivatives of the expected molecular weight and products of hydrolysis and incomplete methylation were formed in the attempted permethylation of the 7-glucofuranosides using the fast reaction sequence. The small quantity of material available precluded further experimentation.

Gas Chromatography. All samples were run under approximately the same conditions, using a Perkin-Elmer 900 gas chromatograph fitted with a 6 ft × 0.125 in. (i.d.) glass column packed with 2% OV-17 on 80–100 Gas-Chrom Q, using nitrogen carrier gas flowing at 20 ml/min and programmed from 200 to 300 °C at 4 °C/min. Elution temperatures ranged from 240 °C for the Me_3Si ribosides to 290 °C for the permethylglucosides.

Gas Chromatography–Mass Spectrometry. Mass spectra were recorded using a Varian MAT 111 instrument equipped with a slit separator using a similar GC column to that above but with helium as carrier gas. The separator and line were isothermal at 300 °C and the column programmed from 240 to 300 °C at 6 °C/min. The mass spectrometer was operated at 80 eV, source temperature ca. 250 °C, and spectra were recorded on an oscillograph chart.

Registry No.—**3** permethyl derivative, 60282-18-0; **3** Me_3Si derivative, 60282-19-1; **4** permethyl derivative, 60282-20-4; **4** Me_3Si derivative, 60282-21-5; **5** permethyl derivative, 60282-22-6; **5** Me_3Si derivative, 60282-23-7; **6** permethyl derivative, 60282-24-8; **6** Me_3Si derivative, 60282-25-9; **7** permethyl derivative, 60282-26-0; **7** Me_3Si derivative, 60282-27-1; **8** permethyl derivative, 60282-28-2; **8** Me_3Si derivative, 60282-29-3; **9** permethyl derivative, 60282-30-6; **9** Me_3Si derivative, 60282-31-7; **10** permethyl derivative, 60282-32-8; **10** Me_3Si derivative, 60282-33-9; **11** Me_3Si derivative, 60282-34-0; **12** Me_3Si derivative, 60282-35-1; **13** permethyl derivative, 60282-36-2; **13** Me_3Si derivative, 60282-37-3.

Supplementary Material Available. Plotted mass spectra of Me_3Si derivatives of compounds **7, 8,** and **13,** and mass spectra of permethylated 6-BAP glycosides **3, 5, 7, 9,** and **13** (Table II) and permethylated zeatin glycosides **4, 6, 8,** and **10** (Table III) (3 pages). Ordering information is given on any current masthead page.

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Electrochemical Reduction of 3-Cyano-1-methylpyridinium Iodide, a Nicotinamide Adenine Dinucleotide Model Compound

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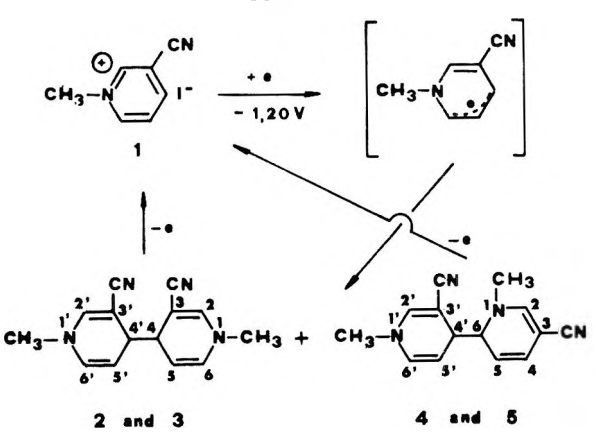
3-Cyano-1-methylpyridinium iodide (**1**) exhibits one polarographic wave at pH values below 11 ($E_{1/2}$ = −0.87 V vs. SCE). Electrolysis at the plateau potential of this wave, involving a one-electron uptake, leads to the formation of a mixture of four dimeric products, unambiguously identified as two diastereoisomer pairs: 3,3′-dicyano-1,1′-dimethyl-1,1′,4,4′-tetrahydro-4,4′-bipyridines **2** and **3**, and 3,3′-dicyano-1,1′-dimethyl-1,1′,6,4′-tetrahydro-6,4′-bipyridines **4** and **5**.

Dimeric products are known to arise from the one-electron reduction of nicotinamide adenine dinucleotide (NAD^+), and related compounds, by chemical,[1] electrochemical,[2] and photochemical[3] methods. While in a few cases these products could be isolated, their formation has been generally postulated on the ground of process stoichiometry and spectroscopic evidence. However, the literature on this subject lacks detailed evidence regarding the structure to be assigned to these dimeric compounds, and further research to obtain a deeper knowledge on the subject appears highly desirable. Accordingly, the electrochemical reduction of 3-cyano-1-methylpyridinium iodide (**1**), a NAD^+ model compound, was performed obtaining a mixture of four reduction products (Scheme I), that were isolated and unambiguously identified.

Scheme I



Results and Discussion

A. Polarographic Behavior. The reduction polarogram of **1**, recorded in the Britton–Robinson buffer solutions, exhibits one wave (A) from pH 2 up to pH 11. Another wave (B) appears at more negative potentials, at pH values greater than 11. Wave A is diffusion controlled (as ascertained from the limiting current variations with the mercury head height and temperature) over the investigated pH range. Its height is proportional to the concentration of **1**. The diffusion current constant, I, is 2.10 ± 0.05 $\mu A\ s^{1/2}\ (mM)^{-1}\ mg^{-2/3}$ for concentrations of **1** ranging from 0.05 to 5.0 mM, and this value corresponds to a one-electron Faradaic process. The half-wave potential, $E_{1/2}$, is pH independent for wave A (average value −0.87 V). The addition of surface active tetraethylammonium ions Et_4N^+ to a pH 9.5 buffered solution shifts $E_{1/2}$ toward more negative potentials (e.g., 25 mV when the concentration of Et_4N^+ was 0.1 M).

For the same pH 9.5 buffer, an increase of the ionic strength from 0.1 to 2.0 M, obtained by addition of KCl, causes $E_{1/2}$ to shift 40 mV toward more negative potentials. $E_{1/2}$ shifts also with the concentration of **1**: it is −0.86 V at 0.1 mM and -0.87_5 V at 1 mM.

From its slope over the pH range investigated, wave A seems related with a totally irreversible process ($E_{1/4} - E_{3/4}$ falls between 77 and 86 mV). The log $i/(i_d - i)$ vs. E plot is not always strictly linear over the whole rising portion of wave A: such deviations are probably due to the chemical reaction which follows the one-electron uptake (see subsequent discussion) and to the adsorption of the depolarizer and/or the one-electron reduction products.

The second wave (B) has a partially kinetic character, as ascertained from the limiting current variations with the mercury head height and the temperature. Its $E_{1/2}$ is virtually pH independent and has a value of −1.60 V in a pH 11.5 buffer with a 1.0 mM concentration of **1**, and its height is about ⅗ of the value of wave A. In the same buffer, addition of KCl, producing an increase in the ionic strength from 0.1 to 2.0 M, causes $E_{1/2}$ to shift 70 mV toward less negative potentials. The

Table I. NMR Data for Dimers 2, 3, 4, and 5

2			3		4			5	
δ, ppm	J, Hz	Protons	δ, ppm	J, Hz	δ, ppm	J, Hz	Protons	δ, ppm	J, Hz
6.62 (d)	1.8	$H_2 + H_{2'}$	6.64 (d)	1.8	6.81 (s broad)		H_2[a]	6.86 (s broad)	
5.89 (dd)	1.8	$H_6 + H_{6'}$	5.86 (dd)	1.8	6.65 (d)	1.8	$H_{2'}$	6.63 (d)	1.8
	8.0			8.0	6.08 (d broad)	10.0	H_4[a]	6.05 (d broad)	10.0
4.64 (dd)	4.0	$H_5 + H_{5'}$	4.72 (dd)	4.0	5.90 (dd broad)	8.0	$H_{6'}$	5.91 (dd broad)	8.0
	8.0			8.0		1.8			1.8
3.21 (d)	4.0	$H_4 + H_{4'}$	3.34 (d)	4.0	5.10 (dd)	5.0	H_5	4.95 (dd)	5.0
2.98 (s)		CH_3-1	2.96 (s)			10.0			10.0
		CH_3-1′			4.69 (dd)	4.0	$H_{5'}$	4.66 (dd)	4.5
						8.0			8.0
					4.12 (dd)	5.0	H_6	4.08 (dd)	5.0
						4.0			3.5
					3.54 (dd)	4.0	$H_{4'}$	3.36 (dd)	4.5
						4.0			3.5
					3.02 (s)		CH_3-1	3.12 (s)	
					2.96 (s)		CH_3-1′	2.99 (s)	

[a] H_2 and H_4 are coupled with J = 1.5 Hz.

slope of wave B suggests the occurrence of an irreversible electronic transfer.

B. Coulometric Behavior. Solutions of 1 in buffered media have been electrolyzed using potential values in the range corresponding to the plateau of wave A. The concentration of 1 varies from 0.2 to 20 mM; the pH of the buffer from 2 to 11.5. The Faradaic n value shows that the process corresponding to wave A is monoelectronic. The polarograms of the electrolyzed solutions do not show any reduction wave, indicating that the ultimate product of the reduction process at potential of wave A does not represent an intermediate in the formation of wave B and is not reduced further to different products. Furthermore, the polarograms show for pH ≥6 an anodic wave very close to the background anodic discharge; for example, after the electrolysis of a 2.0 mM solution of 1 at pH 9.0 the polarogram shows an anodic wave with $E_{1/2}$ = -0.27_5 V and limiting current (i_l) equal to 87% of the i_l value for the initial cathodic wave (A). The electrolytic reoxidation, performed at −0.20 V, consumed slightly less than one electron per molecule of 1. The solution so obtained shows a well-defined polarographic wave, with an $E_{1/2}$ value in good agreement with that of 1, and with the height consistent with the Faradaic n value just mentioned. The height of the anodic wave may be lower than that of the cathodic wave, owing to different diffusion coefficients between 1 and the reduction products; a 0.87 ratio for the anodic to cathodic wave heights corresponds to a 0.75 ratio for the diffusion coefficients.

In the uv spectra taken after electrolysis, the characteristic maximum of 1 disappears and a maximum appears at 345 nm for electrolyzed neutral or alkaline solutions and at 275 nm for acidic electrolyzed solutions. The same 275-nm maximum appears after acidification with 0.5 M HCl of the electrolyzed neutral or alkaline solutions. The uv spectra taken after reoxidation show the characteristic absorption band of 1.

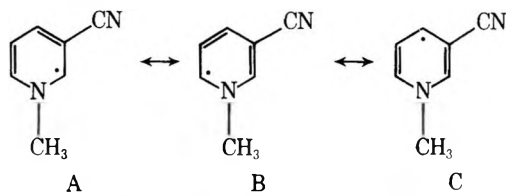
Therefore, the uv spectra and Faradaic properties of the solutions after electrolysis allow us to state that the nature of the electrolysis products is unaffected by variations in pH, concentration of 1, and potential within the range of values corresponding to the plateau of wave A.

C. Macroscale Electrolysis. Isolation and Characterization of the Dimers. After ascertaining that the reduction product of 1 does not depend on pH, potential, and depolarizer concentration, several electrolyses have been performed, at the potential values corresponding to the wave A plateau, on solutions whose concentration was suitable for the isolation and characterization of the reduction products. Ten samples of 1, ranging from 0.5 to 1.0 g, have been electrolyzed under the conditions described in the Experimental Section. During the electrolysis a yellow precipitate is formed. The reduction of 1 is practically completed within a period of about 3 h. Shortly after electrolysis completion, both solution and precipitate have been extracted with CH_2Cl_2 and the solvent evaporated to yield a gummy residue which solidifies upon water treatment (yield 65–88%). A chromatographic test (HPLC) allows us to detect four major compounds in the residue. All of them, on oxidation with an alcoholic I_2 solution, yield only salt 1.

The four compounds 2, 3, 4, and 5 could be separated owing to their different solubilities in ethanol. Their elemental analysis, together with molecular weight (238, from mass spectrum), suggest the same molecular formula $C_{14}H_{14}N_4$. The NMR spectrum of 2 (Table I) shows a signal at δ 2.98 ppm corresponding to two equivalent methyl groups, a signal at δ 3.21 ppm corresponding to two equivalent tertiary protons ($H_4 + H_{4'}$), three signals, each corresponding to two equivalent vinyl protons ($H_5 + H_{5'}$ at δ 4.64; $H_6 + H_{6'}$ at δ 5.89; $H_2 + H_{2'}$ at δ 6.62 ppm).

The NMR spectrum of 3 is almost the same as that of 2 with only minor changes of the chemical shifts of the various protons. Taking into account the molecular weight, these NMR data provide reasonable evidence for a symmetrical dimeric structure, namely 3,3′-dicyano-1,1′-dimethyl-1,1′,4,4′-tetrahydro-4,4′-bipyridine, for both products 2 and 3, which are therefore a diastereoisomeric pair with respect to the C_4–$C_{4'}$ stereochemistry. The ir and uv spectra of both 2 and 3 are consistent with these structures since they show the same typical absorption bands reported[4] for 3-cyano-1-methyl-1,4-dihydropyridine. The NMR spectrum of 4 shows two methyl signals (δ 2.96 and 3.02 ppm), a tertiary proton signal (H_4, at δ 3.54 ppm), a signal corresponding to a tertiary proton adjacent to the N atom (H_6 at δ 4.12 ppm), six signals corresponding to six vinyl protons ($H_{5'}$ at δ 4.69; H_5 at δ 5.10; $H_{6'}$ at δ 5.90; H_4 at δ 6.08; $H_{2'}$ at δ 6.65; H_2 at δ 6.81 ppm). The NMR spectrum of 5 is almost identical with that of 4, except for small differences in the chemical shifts for the various protons. These NMR data, together with the molecular weight, provide reasonable evidence for a dimeric asymmetric structure, namely 3,3′-dicyano-1,1′-dimethyl-1,1′,6,4′-tetrahydro-6,4′-bipyridine, for both products 4 and 5, which are therefore a diastereoisomeric pair with respect to the C_6–$C_{4'}$ stereochemistry. It should be noted that also in this case the ir and uv spectra of both 4 and 5 show the typical absorption bands reported[4] for 3-cyano-1-methyl-1,4- and -1,6-dihydropyridines.

D. Reaction Pattern. It is well known that the first step in the one-electron reduction of pyridinium salts yields pyridinyl radical species. The electron release to pyridinium ion should yield a mesomeric radical, stabilized in particular by resonance of the forms A, B, and C. The structure of the dimers isolated, where only 4,4′, and 6,4′ binding occur, supports the severe steric hindrance to dimerization through position 2, when positions 1 and 3 are substituted. In fact no 2,2′-linked dimers have been reported.[1-3,5] Furthermore, in our case, the absence of 6,6′-linked dimers as well can be traced to steric hindrance as is readily apparent from the molecular models.



Experimental Section

Compound **1** was prepared according to ref 4, mp 197–198 °C, uv max (H_2O) 268 nm. The melting points were taken on a Kofler apparatus, and are uncorrected.

The same apparatus described in a previous paper[6] was used for electrochemical measurements. Britton–Robinson and NH_3–NH_4Cl buffers were used; the solutions were deoxygenated with 99.99% pure nitrogen or argon, and the temperature was kept constant within ±0.1 °C. The potentials were measured against a saturated calomel electrode. The capillary characteristic was $m^{2/3}\,t^{1/6} = 1.57$ mg$^{2/3}$ s$^{-1/2}$ when measured at $E = -1.25$ V and $T = 21.5$ °C under a mercury head 80.2 cm in height in a pH 6.8 buffer solution containing **1** at 0.5 mM concentration. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian XL-100-15 spectrometer; the chemical shifts are reported as δ units relative to Me_4Si (δ 0) as internal standard. The *m/e* values were measured with an AEI MS-12 70 eV low-resolution mass spectrometer. The ir spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer, as Nujol mulls, and the uv spectra on a Perkin-Elmer 402 spectrophotometer. The chromatographic analyses were performed on a Du Pont 830 liquid chromatograph, using a 1 m × 2.1 mm i.d. stainless steel column packed with 1% BOP coated on Zipax; the eluent at 1400 psi was a mixture of isooctane–chloroform–ethanol (95:5:0.2 v/v). The column effluent was monitored at 247 nm using a Du Pont 837 spectrophotometer.

Electrochemical Reduction of 3-Cyano-1-methylpyridinium Iodide (1). In a typical run, 1.0 g of **1** was dissolved in 50 ml of 0.1 M NH_3–0.1 M NH_4Cl aqueous solution. This solution was then electrolyzed at −1.20 V using a round mercury pool (area 20 cm^2) as a working electrode with a saturated calomel electrode as reference, and a platinum gauze cylinder as a counterelectrode. The solution was magnetically stirred and blanketed by a continuous nitrogen flux over its surface.

Usually the electrolysis took about 3 h to get to completion, as inferred from the complete disappearance of the reduction wave (A) of compound **1**, and from the constant value of the current, equal to that obtained, at the same potential, on a solution containing only the supporting electrolyte.

After electrolysis, the mercury pool was covered by a yellow precipitate.

The whole content of the cell was repeatedly extracted with CH_2Cl_2. The gummy residue (0.5 g) recovered by evaporating the dried organic layer was washed with cold water till solidification and the solid (0.4 g) extracted three times with 10 ml of 95% ethanol at room temperature.

The residue from this extraction contained product **4** only. The slow evaporation of the ethanol, at room temperature, allowed compound **2** to precipitate together with its diastereoisomer **3** and **4** as impurities. The solution was treated under heating with small amounts of activated charcoal, filtered, and evaporated under vacuum. The residue, after recrystallization from ethanol yielded **3** while the solution contained practically only **5**. All the four dimers could be further purified by repeated crystallizations from ethanol. The pure products exhibited the physicochemical properties reported below.

2: mp 146–148 °C; uv max (MeOH) 342 nm (ϵ 7400), 235 (sh); ir 2190 (CN) 1675, 1580 (C=C), 745 cm^{-1}; HPLC retention time 23.1 min. Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51; mol wt, 238.28. Found: C, 70.62; H, 5.95; N, 23.00; *m/e* 238 (parent peak).

3: mp 143–145 °C; uv max (MeOH) 342 nm (ϵ 7450), 235 (sh); ir 2185 (CN), 1670, 1590 (C=C), 815, 790 cm^{-1}; HPLC retention time 13.1 min. Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51; mol wt, 238.28. Found: C, 70.66; H, 6.04; N, 23.30; *m/e* 238 (parent peak).

4: mp 161–163 °C; uv max (MeOH) 349 nm (ϵ 6400), 247 (11 000); ir 2195 (CN), 1670, 1645, 1595, 1580 (C=C), 780, 730, 710 cm^{-1}; HPLC retention time 21.0 min. Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51; mol wt, 238.28. Found: C, 70.85; H, 5.92; N, 23.77; *m/e* 238 (parent peak).

5: mp 127–129 °C; uv max (MeOH) 349 nm (ϵ 6500), 247 (11 300); ir 2185 (CN), 1675, 1650, 1585, 1575 (C=C), 770, 725 cm^{-1}; HPLC retention time 32.0 min. Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51; mol wt, 238.28. Found: C, 70.72; H, 6.10; N, 23.18; *m/e* 238 (parent peak).

Chemical Oxidation of the Dimers. Both crude reduction mixture and pure compounds **2**, **3**, **4**, and **5** on oxidation with iodine give the salt **1**. As example, 70 mg of I_2 was added to a solution containing 50 mg of **2** in 25 ml of ethanol, warming at 40 °C for 30 min. The solution was allowed to cool, then $Na_2S_2O_3$ was added until the iodine color disappeared. The ethanol was removed, the residue was extracted with $CHCl_3$, and the chloroform solution was evaporated. The residue, crystallized from acetone, gave the salt **1**.

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Registry No.—**1**, 1004-16-6; **2/3**, 60224-01-3; **3/2**, 60224-02-4; **4/5**, 60224-03-5; **5/4**, 60224-04-6.

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Heterocyclic *N*-Oxides as Synthetic Intermediates. 5. Synthesis of 5-Aminopyridazine 1-Oxides[1]

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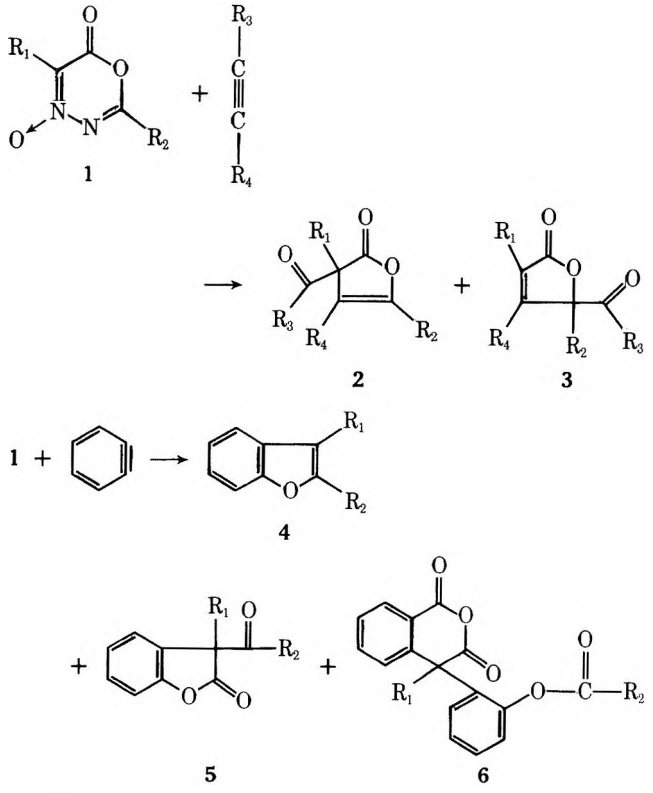
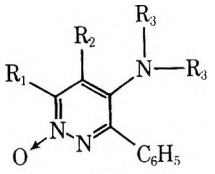
Condensation of 1,3,4-oxadiazin-6-one 4-oxides (**1**) with ynamines **7** produces 5-aminopyridazine 1-oxides **8** in good yields. The reaction is completely regiospecific and no 4-amino isomer is produced. Deoxygenation with phosphorus trichloride provides the parent 4-aminopyridazines **10**. Mechanisms involving a concerted [2 + 4] cycloaddition or a two-step process initiated by attack of the ynamine at the imidate carbon of **1** are considered. In one case a pyrazole derivative, 1-dimethylcarbamyl-3,4,5-triphenylpyrazole, was isolated along with the 5-aminopyridazine 1-oxide **8c** suggesting competition between 1,3 and 1,4 cycloaddition pathways.

We have recently reported the cycloadditions of 1,3,4-oxadiazin-6-one 4-oxides (**1**) with acetylenes[3] and benzyne.[4] The acetylene cycloadditions yielded acylbutenolides **2** and **3**, while the benzyne cycloadditions produced benzofurans **4**, benzofuranones **5**, and homophthalic anhydrides **6**.



These products (**2–6**) result from deep-seated rearrangements which could be rationalized on the basis of first-formed 1,3-dipolar cycloadducts. These transformations are analogous to those proposed in the cycloaddition of 3,4-diazacyclopentadienone oxides with acetylenes.[5]

In continuation of our interest in this area, we now have investigated the cycloaddition of **1** with ynamines (**7**). Under very mild conditions an exothermic reaction accompanied by the evolution of carbon dioxide produced pyridazine oxides (**8**) in high yields (Table I). This transformation is analogous to the Diels–Alder reaction of α-pyrones with acetylenes[6] and occurs in a highly regioselective manner, since the isomeric pyridazine oxide (**9**) was not detected in any case (^{1}H NMR



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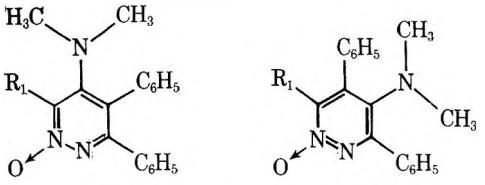
analysis). The structure of these pyridazine oxides (**8**) is based on elemental analysis, spectral information, chemical evidence, and mechanistic considerations.

Structure Proof. The molecular formulas of these derivatives were easily determined from the combustion analyses and the parent peaks in the mass spectra (see Table I for principal peaks). The infrared spectra, though compatible with the structural assignment, were of little use in distinguishing between structures **8** and **9**. The ^{1}H NMR spectra, on the other hand, uncovered the first clue in support of structure **8**. The chemical shifts of the *N*-methyl protons in the ^{1}H NMR spectra of **8c–e** varied depending on the nature of R_1 as shown below. The shielding of the *N*-methyl protons



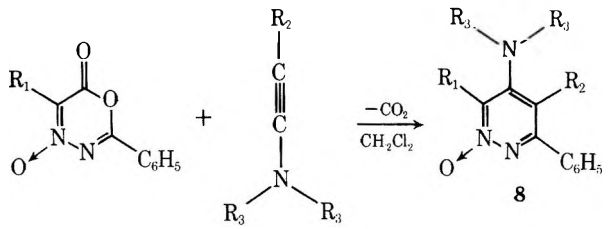
8 **9**

	N-CH_3, δ
8c, $R_1 = C_6H_5$	2.16
d, $R_1 = CH_3$	2.53
e, $R_1 = C_2H_5$	2.53

when R_1 is a phenyl group is consistent with structure **8c**, since these protons may be situated in the shielding cones of the two adjacent phenyl rings. In the spectra of **9c–e** the chemical shifts of the *N*-methyl protons should not change, since they are always flanked by the same substituents.

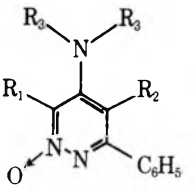
The chemical evidence accumulated firmly established **8** as the structure of these derivatives. Deoxygenation of **8** with phosphorus trichloride yielded pyridazines (**10**) in high yields (Table II). The physical properties of **10a** ($R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = C_2H_5$) were in excellent agreement with those reported by Roffey and Verge[7] and thus substantiated the presence of the pyridazine ring system in **8**.

Most aminopyridazine syntheses are quite tedious but it



1a, C_6H_5 **7a**, $R_2 = CH_3$; $R_3 = C_2H_5$
b, CH_3 **b**, $R_2 = C_6H_5$; $R_3 = CH_3$
c, C_2H_5 **c**, $R_2 = H$; $R_3 = CH_3$, C_6H_5

Table I. 5-Aminopyridazine 1-Oxides



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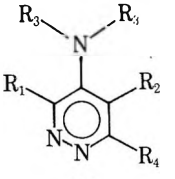
Compd	R_1	R_2	R_3	Procedure[a] and recrystn solvent[b]	Yield %	Mp, °C	Mass spectra, *m/e* (rel intensity)
8a	C_6H_5	CH_3	C_2H_5	I-A	94	153–156	333 (9), 317 (56), 316 (19), 302 (69), 160 (100)
8b	CH_3	CH_3	C_2H_5	I	88[c]		
8c	C_6H_5	C_6H_5	CH_3	II-B	57	241–243	367 (96), 351 (51), 350 (100)
8d	CH_3	C_6H_5	CH_3	II-C	71	173–174	305 (42), 289 (63), 288 (100)
8e	C_2H_5	C_6H_5	CH_3	II-C	74	147–148	319 (17), 303 (33), 302 (100)
8f	C_6H_5	H	C_6H_5, CH_3	II-B	84	166–168	353 (10), 337 (100), 336 (56)
8g	CH_3	H	C_6H_5, CH_3	II-C	95	151–153	291 (36), 275 (100), 274 (79)

[a] Procedure I requires stirring at room temperature for 0.5 h. Procedure II requires heating at reflux for 20 h. [b] A = cyclohexane, B = 95% ethanol, and C = benzene–hexane mixtures. [c] **8b** was isolated as a pale yellow oil after chromatography on alumina; melting point of hydrochloride salt, 135–137 °C

Table II. 4-Aminopyridazines



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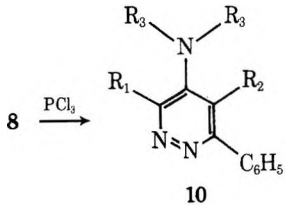
Compd	R_1	R_2	R_3	R_4	Yield, %	Mp (solvent),[b] °C	Partial NMR[c] R_1	R_2	R_3	R_4
10a	C_6H_5	CH_3	C_2H_5	C_6H_5	72	120–122[a] (A)		2.23	0.98 (t, 7 Hz) 2.93 (q, 7 Hz)	
10c	C_6H_5	C_6H_5	CH_3	C_6H_5	93	163–165 (B)			2.28	
10d	CH_3	C_6H_5	CH_3	C_6H_5	92	153–154 (B)	2.73		2.50	
10g	CH_3	H	CH_3, C_6H_5	C_6H_5	86	82–83 (B)	2.21	7.36	3.36	
12	C_6H_5	C_6H_5	CH_3	CH_3		127–128 (C)			2.23	2.42

[a] Lit.[7] mp 120–121 °C. [b] A = 2-propanol, B = cyclohexane, and C = hexane. [c] Measured in $CDCl_3$, Me_4Si standard, 60 MHz.



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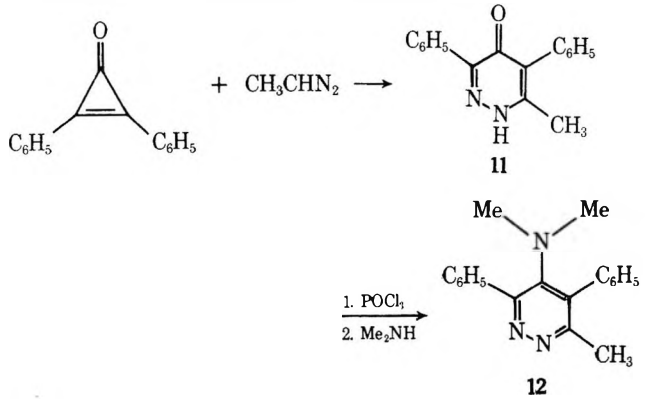
was possible to synthesize the alternative isomer of **10d** (R_1 = C_6H_5; R_2 = R_3 = CH_3), compound **12**, and show that it was not identical with the deoxygenation product of **8d**. This result indirectly proves the correctness of the structural assignments of **8**. Treatment of diphenylcyclopropenone with diazoethane according to the procedure of Breslow and co-workers[8] yielded the appropriate pyridazinone **11**. Successive treatment of **11** with phosphorus oxychloride and dimethylamine yielded **12**. The physical properties of **12** showed that it was not **10d** and confirmed the isomeric structural assignment for the latter. In addition, the *N*-methyl protons in the spectra of **10c,d** and **12** varied consistently in the manner described earlier for the *N*-oxides (Table II).



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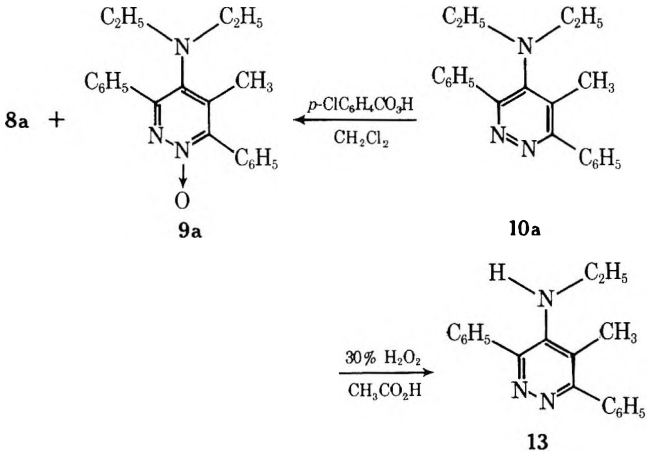
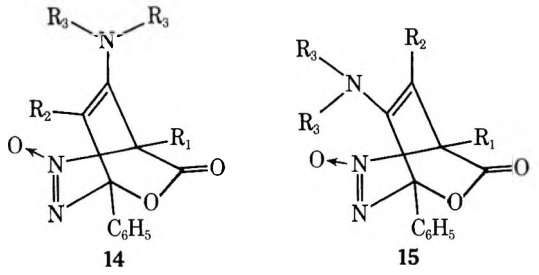
12

Attempts to oxidize pyridazine **10a** back to **8a** led to some interesting results. Peracetic acid treatment of **10a** yielded the dealkylated pyridazine **13** as the major product. The structure of **13** was deduced from spectral information and elemental analysis (Experimental Section), but its origin is uncertain. However, oxidation of **10a** with *m*-chloroperbenzoic acid yielded a yellow solid in high yield. The ^1H NMR spectrum of this solid suggested that it was a 1:1 mixture of **8a** and **9a**. Oxidation of the exocyclic nitrogen was ruled out, since there was no aliphatic N–O stretching band (950–970 cm^{-1}) in the infrared spectrum.[9] Attempts to separate the two isomers by fractional recrystallization or thin layer chromatography were unsuccessful.



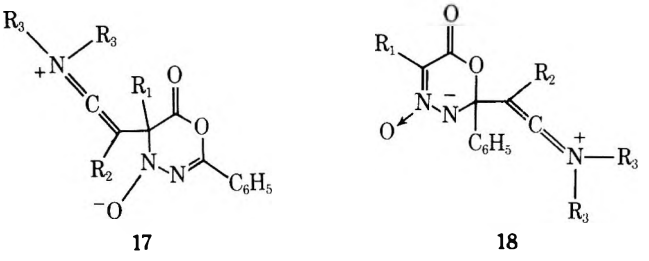
Mechanism. The [4 + 2] cycloaddition of **1** and **7** in principle can yield two cycloadducts, **14** and **15.**

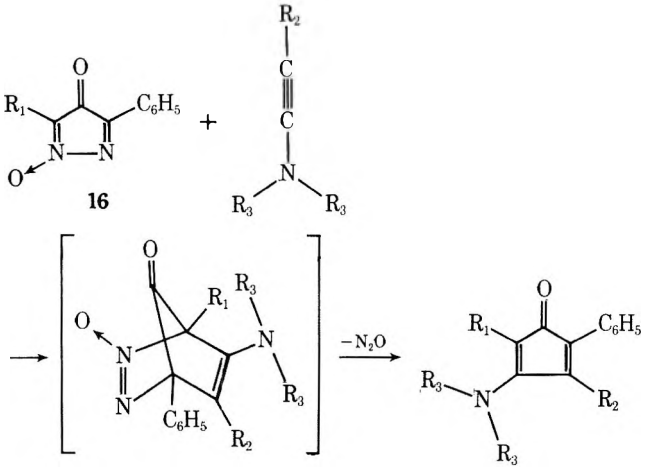


The preference for regioisomer **14,** the precursor of **8,** is analogous to that reported for the cycloadditions of oxazinones[10] and benzoxazinones[11] with ynamines. However, a more pertinent analogy is the cycloaddition of 3,4-diazacyclopentadienone 3-oxides (**16**) with ynamines, since the same mode of addition to the azine oxide moiety occurs there.[12]

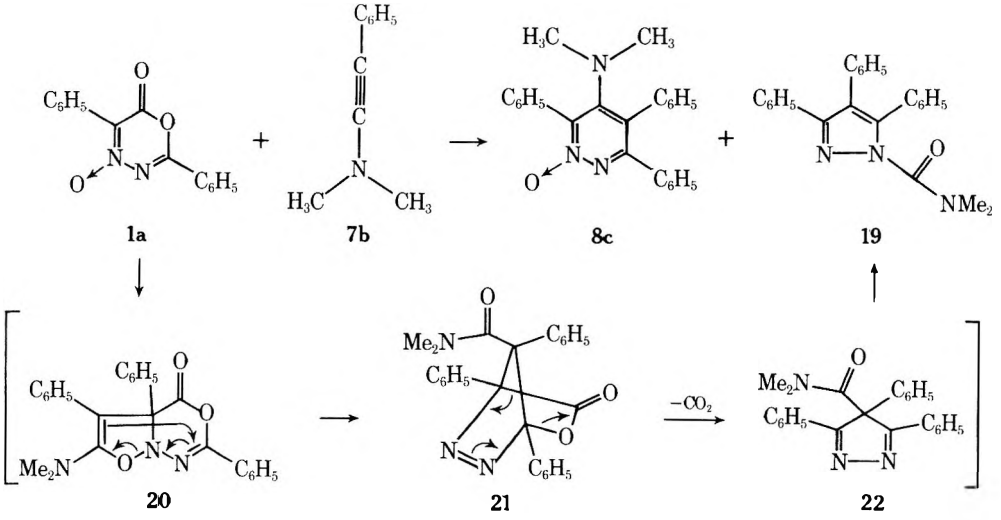
These inverse Diels–Alder cycloadditions might involve a concerted [$_\pi 4_s$ + $_\pi 2_s$] mechanism and the regiospecificity therefore explained on the basis of coulombic interactions between the heterocycle and the ynamine.

An attractive alternative is a two-step process involving an intermediate which could partition between a 1,3 cycloadduct, which is formed with most acetylenes, and a 1,4 cycloadduct. This would then help to explain the periselectivity of the ynamine cycloaddition. The regioisomer characterized from the 1,3-dipolar cycloaddition of simple nitrones and ynamines[13] suggests that the partitioning intermediate would have structure **17.** However, collapse of **17** to the 1,4 cycloadduct would yield the wrong regioisomer (**15**). Therefore nucleophilic attack of the ynamine (**7**) must occur at the imidate carbon, since cyclization of **18** would yield the correct regioisomer (**14**).





Although a 1,3 cycloaddition and a 1,4 cycloaddition must involve different interactions, competition between these two paths is still conceivable. Thus the reaction of oxidiazinone **1a** with ynamine **7b** yielded pyrazole **19** in addition to pyridazine **8c.** The structure of **19** was surmised from spectral information and by its hydrolysis to 3,4,5-triphenylpyrazole. This reaction may be an example of competing cycloadditions, since the formation of pyrazole **19** can be rationalized from a first-formed 1,3 cycloadduct **20.** Rearrangement of 4-isoxazoline **20** to intermediate **21** follows the path that has been suggested for the acetylene cycloadditions.[3] Loss of carbon dioxide from **21** would then yield isopyrazole **22,** although this step varies from that observed earlier[3] and violates the general trend reported for extrusion reactions ($N_2 > CO_2$).[14] Migration of the amido group in **22** to nitrogen would then yield **19.** Rearrangements of this type are known in the isopyrazole system,[15,16] but the migratory preference of the amido group over a phenyl group is interesting. The migratory preference of an ester group over a phenyl group has been noted.[15]



Experimental Section

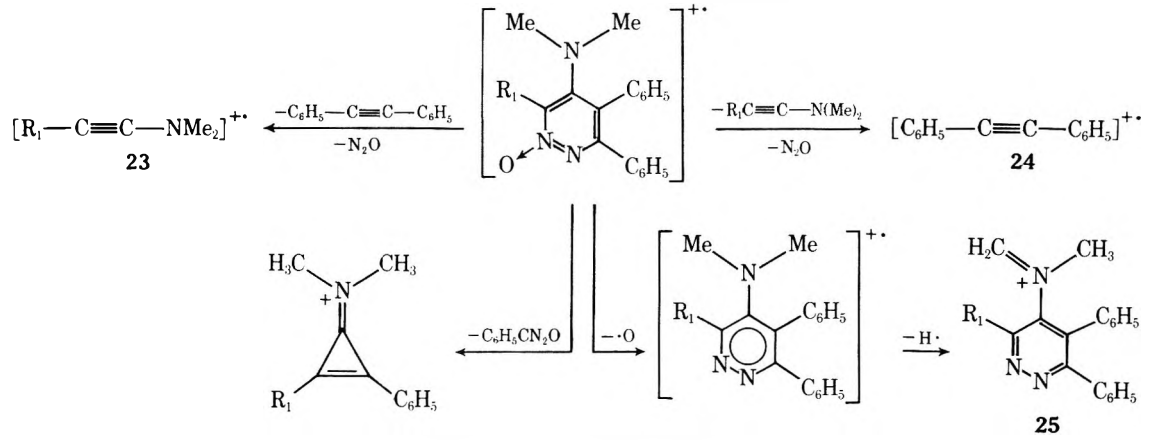
General. Infrared spectra were recorded on a Perkin-Elmer Model 137-A Infracord or a Perkin-Elmer 457. NMR spectra were measured on a Varian A-60A spectrometer; mass spectra were measured with an A. C. I. MS 902 mass spectrometer at 70 eV. We are indebted to Mr. Donald Schifferl for these measurements. The elemental analyses were done by Midwest Microlab.

1-Diethylamino-1-propyne (**7a**) was purchased from Fluka Chemicals. Phenyldimethylaminoacetylene (**7b**) was prepared from phenylchloroacetylene[17] and lithium dimethylamide according to the procedure of Viehe.[18] *N*-Methylanilinoacetylene (**7c**) was prepared from *N*-methyl-*N*-phenyl-1,2,2-trichlorovinylamine[19] according to the method of Ficini and Barbara.[20]

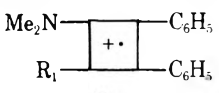
General Procedure for Ynamine Cycloadditions. A magnetically stirred solution of the oxadiazinone oxide (1, 4 mmol) in 20–30 ml of CH_2Cl_2 was treated with a solution of the ynamine **7** (4.4 mmol) in 5 ml of CH_2Cl_2. The reaction mixture was then subjected to the reaction conditions outlined in Table I and concentrated in vacuo, and the pyridazine oxide (**8**) was crystallized from the resulting residue with the appropriate solvent (Table I). Only pyridazine oxide **8b** could not be obtained crystalline by this method. Its isolation is described below.

Spectral Properties of Pyridazine Oxides, 8. The infrared spectra of these compounds possessed no special characteristics except a strong band in the region of 1350–1370 cm^{-1}, which is probably due to the N–O stretching vibration. The NMR spectra also were routine except as noted in the discussion.

The mass spectra of the pyridazine oxides were more useful and the cracking patterns for **8c–e** are representative of these derivatives and are illustrated below.



These spectra exhibited abundant parent ions, while the base ions were cations resulting from the loss of 17 mass units; they were assigned structure **25**. Formation of radical cations **23** and **24** might result from a common intermediate (**26**) analogous to that detected in the cracking pattern for simple pyridazines.[21]



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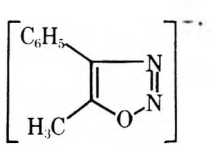
The mass spectrum of **8a** was analogous to those of **8c–e**, except for the base ion which was observed at 160 mass units; it may be assigned structure **27**.



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5-Diethylamino-4,6-dimethyl-3-phenylpyridazine 1-Oxide Hydrochloride. The oily residue obtained from oxadiazinone **1b** and ynamine **7a** was purified on a neutral alumina column with $CHCl_3$ as the eluant. **5-Diethylamino-4,6-dimethyl-3-phenylpyridazine 1-oxide (8b)** was isolated as a yellow, viscous oil (88% yield): ^1H NMR ($CDCl_3/Me_4Si$) δ 1.09 (t, J = 7 Hz, 6 H), 2.18 (s, 3 H), 2.53 (s, 3 H), 3.24 (q, J = 7 Hz, 4 H), 7.25–7.7 (m, 5 H).

The oil was dissolved in anhydrous Et_2O and anhydrous HCl was bubbled through the solution. Suction filtration yielded a yellow solid which was recrystallized from benzene to yield the hydrochloride salt as yellow needles: ir (Nujol) 2330, 1555, 1330 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 1.16 (t, J = 7 Hz, 6 H), 2.34 (s, 3 H), 2.79 (s, 3 H), 3.38 (q, J = 7 Hz, 4 H), 7.4–7.75 (m, 5 H), 15.3 (s, 1 H).

Anal. Calcd for $C_{16}H_{22}ClN_3O$: C, 62.45; H, 7.16; Cl, 11.53; N, 13.66. Found: C, 62.52; H, 7.20; Cl, 11.36; N, 13.62.

1-Dimethylcarbamyl-3,4,5-triphenylpyrazole (19). The ethanolic filtrate from the crystallization of **8c** was concentrated to one-half its original volume and treated with ether at 0 °C to precipitate a pale yellow solid, mp 205–240 °C.[16] Several fractional recrystallizations from absolute ethanol yielded 150 mg (4% yield) of **19** as colorless plates: mp 210–212 °C; ir (KBr) 1655, 1510, 1490, 1445, 1370, 773, 763, 695 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 2.71 [broad singlet, $(CH_3)_2NCO$]; MS *m/e* (rel intensity) 367 (43), 296 (100), 295 (19), 72 (75), 31 (18), 28 (20).

Anal. Calcd for $C_{24}H_{21}N_3O$: C, 78.47; H, 5.72; N, 11.44. Found: C, 77.92; H, 5.84; N, 11.72.

A stirred suspension of **19** (100 mg, 27 mmol) in 2 ml of 30% H_2SO_4 was heated under reflux for 6.5 h. After cooling, suction filtration yielded a white powder which was washed with H_2O. Recrystallization from 95% ethanol yielded **3,4,5-triphenylpyrazole** (62 mg, 78% yield) as long, feathery needles, mp 268–269 °C (lit.[22] mp 265 °C).

General Procedure of Deoxygenation. Formation of Pyridazines 10. A mixture of pyridazine oxide **8** (3 mmol) and 1 ml of phosphorus trichloride in 20 ml of $CHCl_3$ was stirred at room temperature overnight under a $CaSO_4$ drying tube. This mixture was then treated with 10% Na_2CO_3 until it was basic. The layers were separated and the aqueous phase was extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed with H_2O and then with brine. The dried (K_2CO_3) $CHCl_3$ solution was concentrated in vacuo and the pyridizines **10** were obtained by crystallization with the solvents listed in Table II.

Peracetic Acid Oxidation of Pyridazine 10a. A solution of pyridazine **10a** (319 mg, 1 mmol) in 5 ml of glacial acetic acid was treated with a solution of 30% H_2O_2 (670 mg, 9.83 mmol) in 1 ml of acetic acid. This mixture was then heated at 72–74 °C for 15 h. Acetic acid was removed by distillation at aspirator pressures and the resulting residue was diluted with H_2O. The pH was adjusted to 10 with 10% Na_2CO_3 and the mixture was extracted with ether (3 × 10 ml). The ether solutions were washed with H_2O and then with brine. The dried (Na_2SO_4) ether solution was concentrated in vacuo and the residue was purified on a neutral alumina column (2 × 16 cm) with ethyl acetate as the eluent. The major component was recrystallized from benzene–hexane mixures to yield **5-ethylamino-3,6-diphenyl-4-methylpyridazine (13)** as biege prisms: 85 mg, 29% yield; ir (KBr) 3350, 1530, 1440, 1375, 1345, 1175, 1070, 768, 699 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 1.05 (t, J = 7 Hz, 3 H), 2,22 (s, 3 H), 3.04 (broad quintet, 2 H), 3.92 (broad singlet, 1 H), 7.3–7.8 (m, 10 H); MS *m/e* (rel intensity) 289 (92), 288 (100), 274 (11), 260 (10), 245 (10), 231 (15), 78 (25).

Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.89; H, 6.57; N, 14.53. Found: C, 78.61; H, 6.58; N, 14.48.

***m*-Chloroperbenzoic Acid Oxidation of Pyridazine 10a.** A stirred, ice-cold solution of pyridazine **10a** (275 mg, 0.87 mmol) in 10 ml of CH_2Cl_2 was treated dropwise with an ice-cold solution of *m*-chloroperbenzoic acid (1.26 mmol) in 10 ml of CH_2Cl_2. The mixture was allowed to equilibrate to ambient temperatures overnight. The solution was then washed with saturated $NaHCO_3$ (2 × 10 ml), H_2O (2 × 10 ml), and brine (2 × 10 ml). The dried ($MgSO_4$) CH_2Cl_2 solution was evaporated in vacuo and the yellow oil was passed through a short alumina column with ethyl acetate. Recrystallization from

benzene–hexane mixtures yielded yellow needles in two crops (255 mg, 88% yield), mp 143–144 °C. The ^{1}H NMR spectrum of this solid suggested that it was a 1:1 mixture of **8a** and **9a**: δ C(CH_3) 2.06 (**9a**), δ C(CH_3) 2.18 (**8a**).

3,5-Diphenyl-6-methyl-4-pyridazinone (11). Diazoethane was prepared according to the procedure of Wilds and Meader[23] with slight modification.

A 500-ml flask was fitted with an addition funnel and a distilling head set for simple distillation; a 500-ml receiver, immersed in an ice water bath, contained a small amount of anhydrous Et_2O.

A stirred solution of KOH (12.5 g, 0.22 mmol) in 50 ml of 1-propanol and 50 ml of anhydrous Et_2O was heated to 50 °C with a H_2O bath. When the Et_2O started to distill, *N*-nitroso-*N*-ethylurethane[23] (12.5 g, 85.6 mmol) in 40 ml of anhydrous Et_2O was added rapidly from the addition funnel. The bath was maintained at 50 °C and Et_2O was added portionwise until the distillate was colorless. Total volume of the ethereal diazoethane solution was 300 ml.

The diazoethane solution was treated in one portion with a solution of diphenylcyclopropenone[8a] (6.2 g, 30 mmol) in 150 ml of benzene. Precipitation occurred within a few minutes and the mixture was stirred overnight at ambient temperature. Suction filtration yielded a white powder which was recrystallized from methanol to yield **11** as small white needles in several crops (6.18 g, 79% yield): mp 304–305 °C; ir (KBr) 3300, 3080, 3000, 1525, 1290, 803, 756, 732, 695 cm^{-1}; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 2.18 (s, 3 H), 7.39 (broad singlet, 8 H), 8.0–8.2 (m, 2 H), 13.65 (broad singlet, 1 H).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.34; N, 10.69. Found: C, 77.78; H, 5.32; N, 10.80.

4-Dimethylamino-3,5-diphenyl-6-methylpyridazine (12). A stirred mixture of pyridazinone **11** (2.62 g, 10 mmol) in 20 ml of $POCl_3$ was heated on a steam bath for 30 min. After cooling, the mixture was slowly added to a mixture of ice (100 g) and $CHCl_3$ (100 ml). Na_2CO_3 (≈40 g) was added in small portions until the mixture was basic. The layers were separated and the aqueous phase was extracted with $CHCl_3$ (50 ml). The $CHCl_3$ solutions were washed with brine (3 × 25 ml), dried (K_2CO_3), and concentrated in vacuo. Crystallization from cyclohexane yielded **4-chloro-3,5-diphenyl-6-methylpyridazine** as biege plates in two crops (1.98 g, 71% yield): mp 127–128 °C; ir (KBr) 1475, 1425, 1380, 900, 762, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 2.53 (s, 3 H), 7.1–7.6 (m, 8 H), 7.7–7.9 (m, 2 H).

A mixture of the chloropyridazine (281 mg, 1 mmol) and anhydrous dimethylamine (1 g, 22.2 mmol) in 10 ml of Me_2SO was heated in a Fischer-Porter sealed tube for 5 days at 110–120 °C. The mixture was then added to 75 ml of H_2O and extracted with $CHCl_3$ (3 × 25 ml). The $CHCl_3$ solutions were washed with H_2O, then with brine, dried (K_2CO_3), and concentrated in vacuo to leave a pale yellow oil. Chromatography of this oil on alumina (1 × 29 cm) with CH_2Cl_2 yielded unchanged chloropyridazine as the first component. After a small amount of an unidentified material, pyridazine **12** was collected. Recrystallization from hexane yielded 65 mg of pale yellow plates (Table II).

Registry No.—**1a**, 28969-37-1; **1b**, 28969-38-2; **1c**, 28969-39-3; **7a**, 4231-35-0; **7b**, 4604-65-3; **7c**, 4231-31-6; **8a**, 60325-92-0; **8b**, 60325-93-1; **8b** HCl, 60325-94-2; **8c**, 60325-95-3; **8d**, 60325-96-4; **8e**, 60325-97-5; **8f**, 60325-98-6; **8g**, 60325-99-7; **9a**, 60326-00-3; **10a**, 23900-47-2; **10c**, 60326-01-4; **10d**, 60326-02-5; **10g**, 60326-03-6; **11**, 60326-04-7; **12**, 60326-05-8; **13**, 60326-06-9; **19**, 60326-07-0; 4-chloro-3,5-diphenyl-6-methylpyridazine, 60326-08-1.

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Stereoselective Syntheses of *cis*- and *trans*-2-Substituted 1,3-Dithiane 1-Oxides

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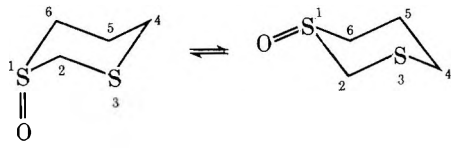
Stereoselective syntheses of *cis*-2-deuterio- (**7b**), *cis*-2-methyl- (**4b**), *cis*-2-phenyl- (**4c**), and *trans*-2-deuterio- (**7a**), *trans*-2-methyl- (**3b**), and *trans*-2-phenyl-1,3-dithiane 1-oxide (**3c**) are described. Oxidation of 2-methyl-1,3-dithiane and 2-phenyl-1,3-dithiane with either sodium metaperiodate or *m*-chloroperoxybenzoic acid is consistently 92% stereoselective and gives pure **3b** and **3c** in good yield after recrystallization. The cis isomers **4b** and **4c**, as well as the specifically deuterated compounds **7a** and **7b**, were prepared by a reaction sequence involving *stereospecific* trimethylsilyl cleavage from C(2) of a 1,3-dithiane 1-oxide as a key step. Oxidation of 2-deuterio-2-trimethylsilyl-1,3-dithiane (**5b**) occurred trans to the trimethylsilyl substituent (cis to deuterium). Cleavage of the trimethylsilyl group with methanol–sodium methoxide occurred with retention of configuration at C(2) to give **7b**. An analogous process starting with 2-trimethylsilyl-1,3-dithiane (**5a**) and using CH_3OD in the cleavage step gave **7a**. The trimethylsilyl group was used as a stereospecifically removable substituent capable of influencing the stereoselectivity of oxidation in a similar manner in the synthesis of **4b** and **4c**. It is suggested that NMR provides a simple indicator of sulfoxide stereochemistry in 1,3-dithiane 1-oxides in certain circumstances. The chemical shift of the C(6) equatorial proton is in the range δ 3.2–3.5 ppm for *trans*-2-monosubstituted 1,3-dithiane 1-oxides. The applicability of the method is illustrated for the diastereomeric 2-(diphenylhydroxymethyl)-1,3-dithiane 1-oxides **3d** and **4d**.

Reactions involving carbanionic species stabilized by adjacent sulfur, sulfoxide, and sulfone have been the subject of numerous stereochemical investigations.[1] Recent emphasis on synthetic applications has served to stimulate interest in compounds containing two sulfur atoms.[2] In particular, the lithiation and subsequent reactions of 1,3-dithiane,[3] 1,3-dithiane 1-oxide (**1**),[4] methyl methylthiomethyl sulfoxide,[5] and related $-SCH_2S(O)-$ species[6] offer certain advantages in synthetic operations which require a nucleophilic carbonyl equivalent. The conformational properties of **1** have also attracted attention from a number of investigators interested in the interactions between polar groups in heterocyclic molecules.[7] The conformer having the sulfoxide oxygen equatorial is 0.63 kcal/mol more stable than the sulfoxide oxygen-axial conformer at −81 °C.

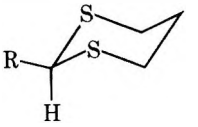


16% **1** 84%

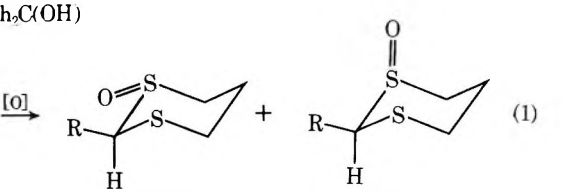
The metalation of **1** and subsequent reactions of its 2-lithio derivative with several electrophiles have been reported.[4] It was not possible, on the basis of the information available at the time, to determine the stereochemical courses of these reactions. The present work seeks to answer these questions. The approach which was employed is described in two parts. The first part is the subject of this paper and concerns the stereochemical relationships and stereoselective syntheses of the starting materials and products central to the study. The second paper[8a] reports the stereochemical course followed in the metalation of **1** and reactions of 2-lithio-1,3-dithiane 1-oxide with electrophiles. A subsequent paper will present a complete x-ray crystallographic study of the 1,3-dithiane 1-oxide system and will include several of the compounds described in this paper.[8b]

Results and Discussion

The preparation of *trans*-2-alkyl- and *trans*-2-aryl-1,3-dithiane 1-oxides presents no difficulties because oxidation of 2-substituted 1,3-dithianes is highly stereoselective (eq 1). Sodium metaperiodate oxidation of 2-*tert*-butyl-1,3-dithiane (**2a**) has been reported to afford a 9:1 trans/cis mixture of sulfoxides.[7a,c] When 2-methyl-1,3-dithiane (**2b**) was oxidized with either sodium metaperiodate in methanol–water or *m*-chloroperoxybenzoic acid in dichloromethane, a 92:8 mixture of diastereomers was obtained (analysis by liquid chromatography using authentic samples to calibrate the detector). The assignment of trans stereochemistry (**3b**) to the major isomer follows by analogy to the oxidation of **2a** to **3a**, and by the NMR spectra to be discussed later. An identical 92:8 trans/cis ratio was obtained on oxidation of 2-phenyl-1,3-dithiane (**2c**) with *m*-chloroperoxybenzoic acid. The configurational assignments to **3c** and **4c** were made on the same basis as those of **3b** and **4b** and are further supported by single crystal x-ray diffraction studies on each diastereomer.[8b] A single recrystallization usually suffices to give **3b**, mp 93–94 °C, and **3c**, mp 145–147 °C, in good yield.



2a, R = $(CH_3)_3C$
b, R = CH_3
c, R = C_6H_5
d, R = $Ph_2C(OH)$



(1)

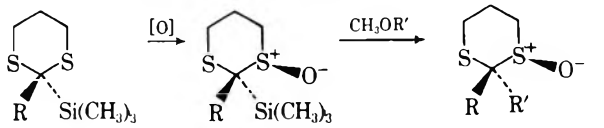
trans: **3a**, R = $(CH_3)_3C$; **b**, R = CH_3; **c**, R = C_6H_5; **d**, R = $Ph_2C(OH)$

cis: **4a**, R = $(CH_3)_3C$; **b**, R = CH_3; **c**, R = C_6H_5; **d**, R = $Ph_2C(OH)$

The identical direction and degree of stereoselectivity in oxidation of 1,3-dithianes with sodium metaperiodate and *m*-chloroperoxybenzoic acid contrasts markedly with that observed in thianes.[9] In thiane oxidation, sodium metaperiodate gives primarily the more stable axial sulfoxide. Peroxy acids give primarily equatorial thiane oxide, presumably corresponding to oxygen transfer from the less hindered direction.

It was reasoned that entry could be gained to the cis series of diastereomers (**4b** and **4c**) if C(2) bore a substituent which

was sufficiently sterically demanding to direct oxidation trans to itself, and which could be replaced by hydrogen stereospecifically with retention of configuration. A trimethylsilyl substituent appeared a good candidate to meet both criteria,[10,11] and the scheme described by eq 2 was applied to the synthesis of *cis*-2-methyl- (**4b**) and *cis*-2-phenyl-1,3-dithiane 1-oxide (**4c**), as well as to the stereospecifically labeled *cis*- and *trans*-2-deuterio-1,3-dithiane 1-oxides **7a** and **7b**.



(2)

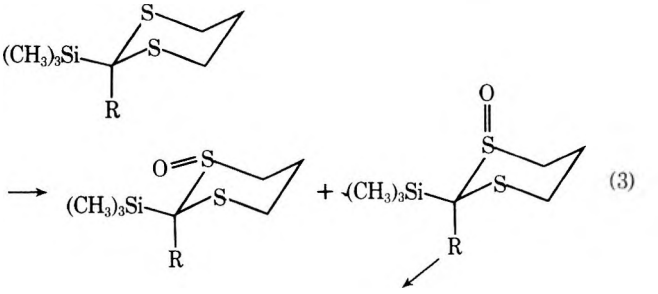
5a, R = H	**6a**, R = H	**7a**, R = H; R' = D
5b, R = D	**6b**, R = D	**7b**, R = D; R' = H
8, R = CH_3	**9**, R = CH_3	**4b**, R = CH_3; R' = H
10, R = C_6H_5	**11**, R = C_6H_5	**4c**, R = C_6H_5; R' = H

Oxidation of 2-trimethylsilyl-1,3-dithiane (**5a**) with sodium metaperiodate in methanol-water (4 h, 5 °C) is highly stereoselective, affording *trans*-2-trimethylsilyl-1,3-dithiane 1-oxide (**6a**) as a clear syrup in 92% yield. The stereoselectivity of this reaction has been confirmed by x-ray diffraction techniques using the corresponding 2-triphenylsilyl derivative which is crystalline.[8,12] Cleavage of the trimethylsilyl group occurred readily on treatment of **6a** with methanol-*O*-*d* in the presence of sodium methoxide (0.05 equiv, room temperature, 24 h) *with complete retention of configuration at C(2)* to give *trans*-2-deuterio-1,3-dithiane 1-oxide (**7a**) cleanly in 71% yield. The stereochemistry of deuterium incorporation can be determined readily by NMR analysis.[7] The proton at C(2) which is trans to oxygen, i.e., equatorial in the dominant conformation, appears at lower field than the proton at C(2) which is cis to oxygen (δ 4.02 and 3.64 ppm, respectively). This assignment can be made with confidence because it is the low-field signal which is further split by long-range coupling, and the required W orientation is met only when the proton is equatorial. The product obtained exhibited a one-proton signal (triplet, J = 1.8 Hz, due to geminal H–D coupling) at 3.6 ppm indicative of the C(2)-axial proton and showed no signal for the C(2)-equatorial proton.

The analogous sequence beginning with 2-deuterio-2-trimethylsilyl-1,3-dithiane (**5b**) and using CH_3OH in the cleavage step gave *cis*-2-deuterio-1,3-dithiane 1-oxide (**7b**) in 93% yield. NMR analysis confirmed its stereochemical integrity. Mass spectral analysis of **7a** and **7b** indicated that each was >93% monodeuterated.

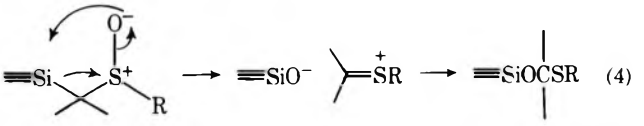
Application of the sequence to the synthesis of *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**) proceeded smoothly. Reaction of 2-methyl-2-trimethylsilyl-1,3-dithiane (**8**) with sodium metaperiodate in methanol–water gave the sulfoxide **9** as a colorless oil in 85% yield. Analysis by NMR indicated that **9** was a single diastereomer. Treatment with methanol containing ammonium hydroxide (8:1) at room temperature for 12 h gave **4b**, mp 60–62 °C, in 77% yield.

The conversion of 2-phenyl-2-trimethylsilyl-1,3-dithiane (**10**) to *cis*-2-phenyl-1,3-dithiane 1-oxide (**4c**), mp 163.5–165.5 °C, proceeds in substantially lower overall yield (39%), presumably because the oxidation step is both more difficult and less stereoselective. The phenyl and trimethylsilyl substituents are comparable in their preference for the equatorial orientation.[10] It is reasonable to expect oxidation to produce comparable amounts of sulfoxide **11** and its diastereomer. The trimethylsilyl group in **11** is, however, very labile and the best conditions found (sodium metaperiodate in methanol–acetonitrile–water, 20 °C, 40 h) also led to cleavage of the trimethylsilyl group after oxidation. It should be mentioned that, in spite of the low absolute yield of **4c** isolated, the crude product contained only about 2% of the trans isomer. We believe that the high apparent stereoselectivity, as evidenced by product isolation, is a consequence of a rapid decomposition which takes place when a 2-trimethylsilyl group is cis to sulfoxide oxygen in a 1,3-dithiane 1-oxide (eq 3).



(3)

The thermal rearrangement of trimethylsilylmethyl sulfoxides has been observed several times and is presumed to involve fragmentation of a four-center intermediate or transition state (eq 4).[13] A marked stereochemical dependence has



(4)

been demonstrated, with one diastereomer of 1-trimethylsilylethyl phenyl sulfoxide being quantitatively converted to rearranged product after 1 h at 60 °C, and the other to the extent of only 7%.[13c] It is possible that the *cis*-2-trimethylsilyl-1,3-dithiane 1-oxide series shown in eq 3 rapidly undergoes this rearrangement reaction to Pummerer or other products which are, as yet, unidentified. The *cis*-2-substituted 1,3-dithiane 1-oxides which are isolated are derived from the more thermally stable *trans*-2-trimethylsilyl series of 1,3-dithiane oxides. It is noteworthy that the lability of silylmethyl sulfoxides is such that **6a** (and **6b**) and **9** are the first examples of such compounds reported to have been prepared by direct oxidation of silylmethyl thioethers.

As mentioned earlier, the stereochemical assignments have been made by analogy to the reported stereoselective formation of **3a** on oxidation of **2a**.[7a,c] In addition, the structures of **3c** and **4c** have been rigorously confirmed by single crystal x-ray diffraction techniques.[8] It would be desirable to have available a simple physical method for distinguishing *cis*- and *trans*-2-substituted 1,3-dithiane 1-oxides. Nuclear magnetic resonance spectroscopy can be applied to stereochemical assignments of *cis*- and *trans*-2-substituted 1,3-dithiane 1-oxides on the basis of previous observations[7] and the present results. The trans compounds **3a, 3b, 3c,** and **6a** (as well as the 2-triphenylsilyl analogue of **6a**), as well as **1,** all exhibit a one-proton multiplet centered between δ 3.2 and 3.5 ppm. This signal has been assigned to the C(6)-equatorial proton in **1** (δ 3.32)[7c] and in **3a** (δ 3.38).[7c] The corresponding signal appears at higher field in the cis series and is usually not clearly defined but overlaps with the other ring protons. The observation of a signal at 3.2–3.6 ppm, then may be taken as indicative of a *trans*-2-substituted 1,3-dithiane 1-oxide. The chemical shift of the C(6)-equatorial proton is sensitive to the torsional relationship between the proton and the sulfoxide oxygen, and the addition of a second substituent at C(2) apparently produces sufficient distortion of the ring to cause a shift of the signal to higher field. The generalization is therefore limited to monosubstituted derivatives. As an example of the application of the relationship, the case of the oxidation of 2-(diphenylhydroxymethyl)-1,3-dithiane (**2d**) is informative. Participation of neighboring hydroxyl in influencing the stereoselectivity of peroxy acid oxidations is well known, so while predominant equatorial oxidation is likely it is not assured.[14] Indeed, the ratio of diastereomers produced on oxi-

dation with *m*-chloroperoxybenzoic acid was 3:1 by NMR analysis. Oxidation with sodium metaperiodate gave a 4:1 ratio of diastereomers. The NMR spectrum of the major diastereomer was well resolved in the region δ 2.7–4 ppm. A one-proton signal appeared as a doublet of triplets (J_{gem} = 13, J_{gauche} = 3.5 Hz) centered at 3.4 ppm, allowing the trans stereochemistry (**3d**) to be assigned to the major diastereomer. The corresponding multiplet is centered at 3.0 ppm in the minor diastereomer, which is accordingly assigned the cis stereochemistry **4d**.

Experimental Section

Nuclear magnetic resonance (NMR) spectra were recorded on Hitachi Perkin-Elmer R-20, Varian HA-100, and JEOL PS-FT spectrometers in $CDCl_3$, and chemical shifts are reported in parts per million (δ) from internal tetramethylsilane. Infrared spectra (ir) were obtained on a Perkin-Elmer 337 grating spectrometer as KBr disks and were calibrated with either the 1601-cm^{-1} or the 1028-cm^{-1} band of polystyrene. Melting points are corrected and were measured on a Thomas-Hoover apparatus. Boiling points are uncorrected. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing potential of 70 eV (15 eV for isotope analyses). Liquid chromatography (LC) analyses were performed on a Waters Associates ALC-100 liquid chromatograph with a differential uv detector (254 nm). In all experiments a microporasil column was used, the solvent was 5% 2-propanol/methylene chloride, and the flow rate was 1.0 ml/min. Relative peak areas were determined by weighing of peaks cut from photostatic copies. The detector was calibrated using authentic samples of pure isomers prepared as described in this paper. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Ga., and by Alfred Bernhardt, Engelskirchen, West Germany.

Oxidation of 2-Methyl-1,3-dithiane (2b). A. Sodium Metaperiodate. A solution of 5.615 g (26.3 mmol) of sodium metaperiodate in 52 ml of water was added dropwise to a solution of 3.3565 g (25.0 mmol) of 2-methyl-1,3-dithiane[15] in 200 ml of methanol at −7 to 0 °C. The resulting white slurry was stirred at −5 °C for 1 h, then refrigerated at 0 °C overnight. The precipitated sodium iodate was removed by filtration and washed with chloroform, the chloroform being combined with the filtrate. The solvent was removed in vacuo, and the residue extracted with chloroform (2 × 100 ml). The combined organic layers were washed with brine (2 × 100 ml) and dried over potassium carbonate. A yellow-hued solid, 3.25 g, mp 81–88.5 °C, was isolated. LC analysis of the material showed it to contain 92% *trans*- (**3b**) and 8% *cis*- (**4b**) 2-methyl-1,3-dithiane 1-oxide.

Recrystallization from dichloromethane–ether gave 2.44 g (65%) of **3b**: mp 92–94 °C (lit. mp 93–94 °C);[4] ir (KBr) 3400, 2910, 1430, 1410, 1294, 1270, 1236, 1190, 1170, 1116, 1050, 1010 (vs), 914, 870, 830, 750, 715, 688, and 650 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 3.55 (q, 1, J = 7 Hz, $HCCH_3$), 3.2–3.5 [m, 1, eq H at C(6)], 2.2–2.9 (m, 5, ring protons), 1.60 (d, 3, J = 7 Hz, CH_3).

B. *m*-Chloroperoxybenzoic Acid. A solution of 1.34 g (10 mmol) of **2b** in 50 ml of dichloromethane was cooled in an ice bath while 2.03 g (10 mmol) of *m*-chloroperoxybenzoic acid in 75 ml of dichloromethane was slowly added. After standing for 12 h, the solution was washed with two 50-ml portions of 10% sodium carbonate solution and dried over magnesium sulfate. Evaporation of the solvent left 1.25 g of white solid, mp 77–88 °C, which on recrystallization from hexane–dichloromethane gave 790 mg (53%) of *trans*-2-methyl-1,3-dithiane 1-oxide (**3b**) as white needles, mp 91–95 °C.

In a separate experiment, carried out at −15 to −20 °C, analysis of the crude product by liquid chromatography showed a composition of 92% **3b** and 8% **4b**.

Oxidation of 2-Phenyl-1,3-dithiane (2c). A. Sodium Metaperiodate. The procedure used was similar to that employed for the oxidation of **2b** described above. The reaction was carried out on a 10-mmol scale and the solvent used was 100 ml of methanol–dioxane (9:1). The crude product (2.0 g), mp 139–142 °C, was recrystallized from dichloromethane–cyclohexane to give 1.98 g (94%) of **3c**: mp 140.5–142.5 °C; ir (KBr) 3400, 2900, 1490, 1440, 1420, 1290, 1270, 1175, 1060, 1030 (S=O), 750, 695, and 495 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (s, 5, aromatic), 4.5 (s, 1, C-2 H), 3.7–3.3 (m, 1, C-6 eq H), and 3.0–2.2 ppm (m, 5, ring H); mass spectrum (70 eV) *m/e* (rel intensity) 212 (M^+, 100), 196 (7), 163 (14), 135 (24), 122 (35), 121 (70), 106 (17), 91 (23), 90 (77).

The analytical sample, mp 145–147 °C, was obtained by recrystallization from dichloromethane–cyclohexane.

Anal. Calcd for $C_{10}H_{12}OS_2$: C, 56.57; H, 5.70; O, 7.52; S, 30.20. Found: C, 56.52; H, 5.66; O, 7.37; S, 30.22.

B. *m*-Chloroperoxybenzoic Acid. A similar procedure to that employed for **2b** was followed, using 4.91 g (25 mmol) of **2c**[15] and 5.08 g (25 mmol) of *m*-chloroperoxybenzoic acid in 210 ml of dichloromethane at −15 to −25 °C overnight. The crude product (5.56 g) was a white solid, mp 123.5–134 °C. Liquid chromatographic analysis showed it to consist of 92% *trans*- (**3c**) and 8% *cis*-2-phenyl-1,3-dithiane 1-oxide (**4c**). After recrystallizing from dichloromethane–cyclohexane, 3.37 g (63%) of **3c**, mp 143.5–145 °C, was obtained.

Oxidation of 2-(Diphenylhydroxymethyl)-1,3-dithiane (2d). These oxidations were performed on a 2-mmol scale.

A. Sodium Metaperiodate. The sodium metaperiodate was added as a solution in 45 ml of water to a solution of **2d** in 90 ml of 3:1 methanol–dioxane at 5 °C. Workup was as described for previous periodate oxidations to give 661 mg of crude product, mp 141–144 °C dec which appeared from its NMR spectrum to be a 4:1 mixture of **3d** and **4d**. After recrystallizing from chloroform–cyclohexane, 537 mg (84%) of white crystals, mp 131–133.5 °C, was obtained. This material was dissolved in warm acetonitrile, allowed to cool, and applied to four preparative TLC plates (silica gel). After allowing the acetonitrile to evaporate overnight, the plates were developed twice with 9:1 carbon tetrachloride–2-propanol to yield **3d** (289 mg), mp 150–155 °C dec, and **4d** (127 mg), mp 159–160 °C dec. The melting points are highly variable, and decomposition to a deep blue melt occurs for both diastereomers.

The major diastereomer, *trans*-2-(diphenylhydroxymethyl)-1,3-dithiane 1-oxide (**3d**), was recrystallized from chloroform–cyclohexane to afford 250 mg of pure material: mp 123–125 °C dec; ir (KBr) 3360, 3050, 2940, 2910, 1500, 1450, 1425, 1390, 1290, 1270, 1230 1185, 1030 (vs), 1120 (vs), 1000, 930, 905, 820, 790, 760, 740, 700, 685, and 635 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 7.9–7.5 (m, 2), 7.5–7.1 (m, 8), 5.85 (s, 1, OH), 4.38 (s, 1, C-2 H), 3.6–3.1 (dt, 1, J = 13, 3 Hz, C-6 eq H), 3.1–2.7 (td, 1, J = 3.5, 13 Hz, C-6 ax H), 2.7–2.2 (m, 4, C-4, 5 ring H).

Anal. Calcd for $C_{17}H_{18}O_2S_2$: C, 64.12; H, 5.70; S, 20.14. Found: C, 63.94; H, 5.55; S, 20.26.

The minor diastereomer assigned cis stereochemistry **4d** had ir and NMR spectra identical with those of the compound reported previously by Carlson:[4,16] ir (KBr) 3400, 2920, 1500, 1450, 1050 (s), 1020, 990 (s), 970, 900, 780, 750, 735, 700, and 650 cm^{-1}; NMR ($CDCl_3$) δ 7.7–7.1 (m, 10, aromatic), 4.80 and 4.68 [each a one-proton singlet, C(2) H and OH], and 3.2–1.5 ppm (m, 6, CH_2).

B. *m*-Chloroperoxybenzoic Acid. The oxidation was carried out at −15 to −25 °C in 75 ml of dichloromethane. The crude product (450 mg), mp 123–129 °C, was a 3:1 mixture of **3d** and **4d**. Recrystallization from ethanol gave 104 mg of white crystals, mp 134–136 °C dec, which were at least 85% **3d** by NMR.

Oxidation of 2-Trimethylsilyl-1,3-dithiane (5a) with Sodium Metaperiodate. To 1.92 g (10 mmol) of 2-trimethylsilyl-1,3-dithiane (**5a**)[17] in 90 ml of methanol was added a solution of 2.14 g (10 mmol) of sodium metaperiodate in 20 ml of water while maintaining the temperature below 10 °C. After 4 h at 4–6 °C the solution was allowed to warm to room temperature and filtered. The methanol was removed by evaporation and the residue partitioned between brine and chloroform. Drying (sodium sulfate) and evaporation gave 1.91 g (92%) of *trans*-2-trimethylsilyl-1,3-dithiane 1-oxide (**6a**) as a light yellow oil: ir (neat) 2970, 2910, 1430, 1250, 1172, 1040 (S=O), 880, 850, 770, 730, 700, and 650 cm^{-1}; NMR ($CDCl_3$) δ 3.4–3.2 (m, 1, C-6 eq H), 3.19 (s, 1, C-2 H), 2.6–2.2 (m, 5, ring H), and 2.8 ppm (s 9, Me_3Si); mass spectrum (70 eV) *m/e* (rel intensity) 208 (5), 193 (14), 165 (11), 199 (66), 87 (34), 83 (18), 75 (100), and 73 (59).

The analytical sample was obtained by preparative TLC on silica gel using chloroform–ethanol (95:5) as the developing solvent.

Anal. Calcd for $C_7H_{16}OS_2Si$: C, 40.34; H, 7.74; S, 30.77. Found: C, 40.17; H, 7.51, S, 30.72.

Cleavage of 2-Trimethylsilyl-1,3-dithiane 1-Oxide (6a) in Methanol-*O*-*d*. A solution of 390 mg (1.87 mmol) of purified **6a** in 25 ml of CH_3OD (Diaprep, 99%) containing sodium methoxide (5 mg, 0.09 mmol) was stirred under nitrogen at 25 °C for 24 h. The solvent was removed and the residue was dissolved in chloroform (50 ml), washed with water and brine, and dried with sodium sulfate. The crude product was purified by preparative TLC on silica gel using chloroform–ethanol (95:5) to afford 182 mg (71%) of material, mp 88–89 °C. NMR analysis showed the product to be *trans*-2-deuterio-1,3-dithiane 1-oxide (**7a**). The NMR spectrum was consistent with all the deuterium being at the C-2 equatorial position. Recrystallization from dichloromethane–cyclohexane gave 160 mg of white crystals: mp 89–90.5 °C; ir (KBr) 2175 cm^{-1} (C–D); mass spectral analysis (15 eV) indicated 93.5% d_1, 6% d_0, and 0.5% d_2 material.

Preparation of *cis*-2-Deuterio-1,3-dithiane 1-Oxide (7b). A solution of 1.0 g (5.2 mmol) of 2-trimethylsilyl-1,3-dithiane (**5a**) in

20 ml of tetrahydrofuran was cooled to −25 °C and metalated with 2.7 ml (5.8 mmol) of *n*-butyllithium (2.2 M in *n*-hexane). After 45 min D_2O was added, the solvent evaporated, and the residue taken up in 50 ml of ether and washed with water. The aqueous extracts were washed with ether and the combined ether extracts dried over sodium sulfate. The ether was evaporated to leave 855 mg of 2-deuterio-2-trimethylsilyl-1,3-dithiane (**5b**) as a colorless oil. NMR analysis indicated complete exchange of protium by deuterium at C(2).

Oxidation of **5b** with sodium metaperiodate in methanol–water was carried out as described for the conversion of **5a** to **6a**, and the resulting sulfoxide dissolved in methanol and allowed to stand overnight. The solvent and volatile products were removed under vacuum to leave 563 mg (93%) of **7b**, mp 84–86 °C. The product was recrystallized from dichloromethane–cyclohexane to give 465 mg (76%) of material, mp 89–90 °C. The NMR spectrum of **7b** indicated exclusive and complete deuterium incorporation at C(2) cis to the sulfoxide oxygen. Mass spectral analysis (15 eV) gave an isotopic composition of 1.6% d_0, 98.3% d_1, and 0.4% d_2.

A similar reaction using 2-triphenylsilyl-2-deuterio-1,3-dithiane 1-oxide (319 mg, 0.79 mmol) afforded 95 mg (88%) of *cis*-2-deuterio-1,3-dithiane 1-oxide (**7b**), mp 89–90 °C; mass spectral analysis indicated 94% d_1 and 6% d_0 material.

Synthesis of *cis*-2-Methyl-1,3-dithiane 1-Oxide (4b). A. Oxidation of 2-Methyl-2-trimethylsilyl-1,3-dithiane (8) with Sodium Metaperiodate. Sodium metaperiodate (2.25 g, 10.5 mmol) was dissolved in 22 ml of water and added to a solution of 2.06 g (10 mmol) of 2-methyl-2-trimethylsilyl-1,3-dithiane[17] (**8**) in 90 ml of methanol while maintaining the temperature at −6 to −8 °C. A heavy white precipitate formed rapidly. After stirring overnight at 10 °C, the solution was allowed to warm to room temperature and filtered and the methanol removed by evaporation. The residue was partitioned between brine and dichloromethane, dried (Na_2SO_4), and evaporated to leave the sulfoxide **9** as a colorless oil (1.89 g, 85%): ir ($CHCl_3$, 5%) 3000, 1420, 1250, 1030 (s), 1020 (s), 880, and 850 cm^{-1} (s); NMR ($CDCl_3$) δ 3.0–2.0 (m, 6, ring CH_2), 1.70 (s, 3, CH_3), 0.25 (s, 9, $SiMe_3$).

The analytical sample was obtained by preparative TLC on silica gel using 95:5 chloroform–ethanol.

Anal. Calcd for $C_8H_{18}OS_2Si$: C, 43.20; H, 8.16; S, 28.83. Found: C, 43.05; H, 7.96; S, 28.63.

B. Methanol Cleavage of 9. After standing for 12 h, a solution of **9** (2.60 g, 11.7 mmol) in 40 ml of methanol containing 5 ml of concentrated ammonium hydroxide was evaporated and the volatile materials removed by vacuum pump to leave 1.78 g of soft, yellowish-white solid. The crude product was recrystallized from ether containing a trace of dichloromethane to give 1.36 g (77%) of *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**): mp 60–63 °C; ir (KBr) 3400, 2910, 1450, 1410, 1280, 1260, 1250, 1200, 1170, 1125, 1060, 1030 (vs), 1000, 900, 865, 830, 670, and 630 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 3.86 (q, 1, J = 7 Hz, $HCCH_3$), 1.9–3.0 (m, 6, ring protons), and 1.63 ppm (d, 3, J = 7 Hz, CH_3).

The analytical sample, mp 60–62 °C, was obtained by recrystallization from ether.

Anal. Calcd for $C_5H_{10}OS_2$: C, 39.97; H, 6.71; S, 42.68. Found: C, 39.84; H, 6.77; S, 42.72.

Synthesis of *cis*-2-Phenyl-1,3-Dithiane 1-Oxide (4c). 2-Phenyl-2-trimethylsilyl-1,3-dithiane[17] (**10**, 10.0 g, 37 mmol) was dissolved in a mixture of 200 ml of acetonitrile and 200 ml of methanol. It was necessary to heat on the steam bath to effect complete dissolution. A solution of sodium periodate (8.4 g, 39 mmol) in 100 ml of water was added dropwise at ca. 40 °C over a 10-min period. Midway through the addition, a white precipitate ($NaIO_3$) formed. After stirring at room temperature for 40 h, the reaction mixture was filtered, and the white precipitate washed with chloroform. The chloroform washings were combined with the yellow filtrate and the solvent removed in vacuo. The residue was partitioned between 150 ml of brine and 150 ml of chloroform. The layers were separated, and the aqueous layer extracted with 100- and 50-ml portions of chloroform. The combined organic extracts were dried over sodium sulfate; evaporation of solvent yielded 7.75 g of yellow solid, which was chromatographed on a column containing 90 g of silica gel 60. Elution with *n*-pentane and carbon tetrachloride gave 2.46 g of starting material. Further elution with 5% 2-propanol/carbon tetrachloride afforded 727 mg of a cloudy, pale yellow oil believed to be polymeric propylene disulfide[18] on the basis of its NMR spectrum. Elution with 8% 2-propanol/carbon tetrachloride gave 3.46 g (44%, 58% based upon recovered starting material) of crude **4c** as a white solid, mp 154–157.5 °C. The NMR spectrum indicated the presence of approximately 2% *trans*-2-phenyl-1,3-dithiane 1-oxide. Recrystallization from dichloromethane–cyclohexane afforded 3.06 g (39%, 51% based on recovered starting material) of pure **4c**: mp 163.5–165.5 °C; ir (KBr) 3400, 3030, 2900, 1500, 1450, 1420, 1050, 1040 (s), 1005, 910, 760, and 695 cm^{-1}; NMR ($CDCl_3$) δ 2.2–3.4 (m, 5, ring H), 4.72 (s, 1, PhCH), and 7.2–7.5 ppm (broad s, 5 aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 212 (77), 173 (14), 146 (14), 145 (24), 132 (40), 131 (79), 101 (40), and 100 (100).

Anal. Calcd for $C_{10}H_{12}OS_2$: C, 56.57; H, 5.70; S, 30.20. Found: C, 56.66; H, 5.78; S, 30.20.

The same product was obtained in 24% yield when the oxidation was carried out with *m*-chloroperoxybenzoic acid in ether at reflux.

Registry No.—**2b**, 6007-26-7; **2c**, 5425-44-5; **2d**, 5849-23-0; **3b**, 60349-75-9; **3c**, 60349-76-0; **3d**, 60349-77-1; **4b**, 60349-78-2; **4c**, 60349-79-3; **4d**, 60349-80-6; **5a**, 13411-42-2; **5b**, 60349-81-7; **6a**, 60349-82-8; **6b**, 60349-83-9; **7a**, 60349-84-0; **7b**, 60349-85-1; **8**, 13411-43-3; **9**, 60349-86-2; **10**, 13411-45-5; sodium metaperiodate, 7790-28-5; *m*-chloroperoxybenzoic acid, 937-14-4; 2-triphenylsilyl-2-deuterio-1,3-dithiane 1-oxide, 60349-87-3.

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The Stereoselectivity of Reactions of Electrophilic Species with 2-Lithio-1,3-dithiane 1-Oxide

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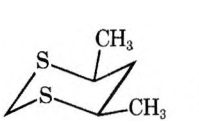
The stereoselectivity of the reactions of 2-lithio-1,3-dithiane 1-oxide (**12**) and its 2-methyl (**19**) and 2-phenyl (**20**) analogues with electrophilic reagents was determined. Reaction of **12** with DCl and with benzophenone occurs preferentially cis to the sulfoxide oxygen by a factor of 3–4:1. Reaction of **12** with methyl iodide yields almost equal amounts of *trans*- (**3b**) and *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**). Lithio derivatives **19** and **20** exhibit a more pronounced tendency for protonation from the axial direction; the ratios are 8–10:1 and >20:1, respectively. Methylation of **20** with CH_3I occurs predominantly from the axial direction (84:16). Metalation of 1,3-dithiane 1-oxide (**1**) with lithium diisopropylamide in tetrahydrofuran occurs by preferential abstraction of the C(2)-equatorial proton (k_{eq}/k_{ax} = 2.7). The stereochemical courses observed for protonation of **19** and methylation of **20** were independent of the stereochemistry of the substrates which were metalated. A steric model is proposed to account for the trends in stereoselectivity between **12**, **19**, and **20** and between electrophiles. The stereoselectivity is based on an intrinsic preference for axial attack and developing van der Waals repulsions in the transition state between the C(4) and C(6) axial protons and either the C(2) substituent (favoring axial attack) or the incoming group (favoring equatorial attack).

The preceding paper[1] reported syntheses of stereochemically homogeneous samples of *trans*-2-deuterio- (**7a**), *cis*-2-deuterio- (**7b**), *trans*-2-methyl- (**3b**), *cis*-2-methyl- (**4b**), *trans*-2-phenyl- (**3c**), and *cis*-2-phenyl-1,3-dithiane 1-oxide (**4c**). Additionally, NMR criteria were proposed which, together with the method of their synthesis, allowed stereochemical assignments to be made to *trans*- and *cis*-2-(diphenylhydroxymethyl)-1,3-dithiane 1-oxides (**3d** and **4d**, respectively). This group of compounds forms the basis of the study to be described in this paper. The study is concerned with the stereochemistry of metalation of 1,3-dithiane 1-oxide (**1**) and the stereoselectivity of the reactions of its 2-lithio derivative (**12**) with electrophilic species. The generation and some reactions of **12** had been reported, but the sterochemical details could not be defined on the basis of the information previously available.[2] Since **12** may be useful as a nucleophilic carbonyl equivalent in synthetic transformations, it was considered of interest to examine in more detail the stereochemical aspects of its formation and reactions. Such a study might be relevant, as well, to previous investigations in other systems. Metalation of the anancomeric 1,3-dithiane derivative **13** (with *n*-butyllithium) proceeds with a slight preference for abstraction of the equatorial proton at C(2) (k_{eq}/k_{ax} = 8.6 ± 1.3). The reactions of the lithio derivative are highly stereoselective, proceeding with >99% equatorial attack by DCl, methyl iodide, and carbonyl compounds.[3] With the cyclic sulfoxides *cis*- (**14**) and *trans*-4-*tert*-butylthiane 1-oxide (**15**),



13

14, R = $(CH_3)_3C$
16, R = C_6H_5

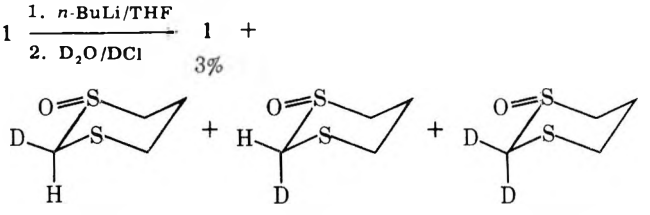
15, R = $(CH_3)_3C$
17, R = C_6H_5

the stereoselectivity of anion reactions is influenced by the configuration of the sulfoxide group. Methylation of the 2-lithio derivative of **14** occurs from the axial direction, and that of **15** from the equatorial direction; i.e., both reactions introduce a methyl group trans to the sulfoxide oxygen.[4] The rates of hydrogen-deuterium exchange have been determined for *cis*- (**16**) and *trans*-4-phenylthiane 1-oxide (**17**).[5] In **16**, the C(2) axial proton exchanges eight times faster than the C(2) equatorial proton in methanol or water. In **17**, the C(2) equatorial proton exchanges about 60 times faster than the C(2) axial proton.

In acyclic sulfoxides, such as benzyl methyl sulfoxide ($PhCH_2S(O)CH_3$), the diastereotopic methylene protons exchange at different rates.[6,7] The lithio derivative prepared by metalation exhibits different stereochemical courses on reaction with DCl (retention) and with methyl iodide (inversion).[8]

Results

Preliminary studies indicated that metalation of **1** with *n*-butyllithium in tetrahydrofuran was complete within 15 min at −50 to −70 °C. Direct quenching of the lithio derivative with DCl in D_2O was apparently accompanied by intermolecular exchange processes since the isolated product contained about 20% of dideuterated material under these conditions. Accordingly, the results given in eq 1 are for "inverse

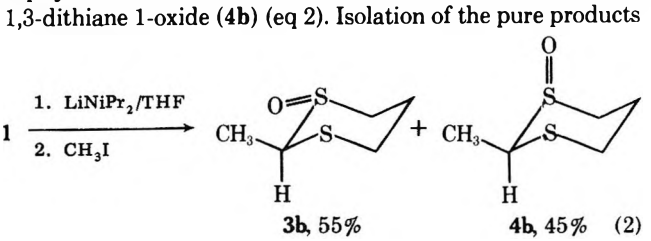


7a, 19% **7b**, 77% **18**, 1% (1)

quenching" wherein a solution of **12** was added to a cooled solution of D_2O–DCl in tetrahydrofuran. Isotopic compositions were determined by mass spectrometry[9] and the stereoselectivity determined by NMR analysis of the signals corresponding to the C(2) axial and equatorial protons at 3.64 and 4.02 ppm, respectively.[10] The ratio of axial to equatorial deuterium incorporation was 4:1.

When the hydrogen–deuterium exchange of **1** was carried out in methanol-O-*d* containing 0.08 M sodium methoxide, no selectivity was observed. A mixture containing 26% **1**, 28% **7a**, 28% **7b**, and 18% **18** resulted.

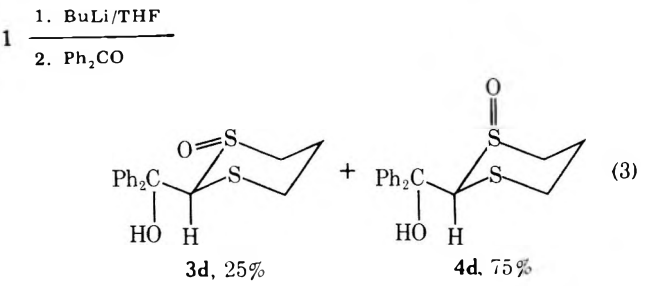
Methylation of **12** (generated by metalation of **1** with lithium diisopropylamide in tetrahydrofuran) with methyl iodide at −60 °C gave a mixture determined by liquid chromatography[11] to consist of 55% *trans*- (**3b**) and 45% *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**) (eq 2). Isolation of the pure products



3b, 55% **4b**, 45% (2)

by preparative TLC gave **3b** in 50% yield and **4b** in 40% yield, confirming the ratio obtained by LC analysis and demonstrating >90% conversion.[12]

Reaction of **12** with benzophenone afforded a mixture of the diastereomeric tertiary alcohols **3d** and **4d** (eq 3). The ratio



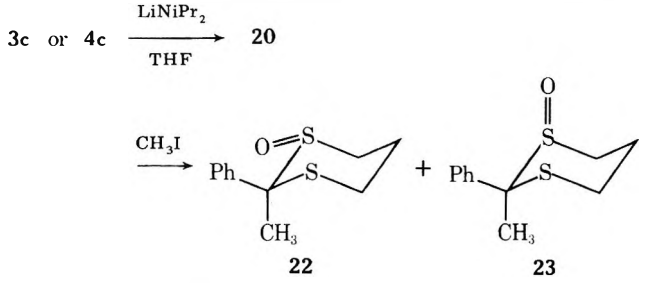
3d, 25% **4d**, 75%

was temperature dependent, with the cis compound **4d** dominating by 3:1 at −70 °C (NMR analysis). If the reaction mixture was allowed to stand at 25 °C for 1 h prior to workup, then the **4d**:**3d** ratio decreased to 1:1.

Metalation of 2-substituted 1,3-dithiane 1-oxides is more efficient with lithium diisopropylamide than with *n*-butyllithium. When the lithio derivatives of *trans*- (**3b**) or *cis*-2-methyl-1,3-dithiane 1-oxides were prepared in this way and quenched with HCl, identical (within experimental error) mixtures of **3b** and **4b** were produced. LC analysis indicated a **3b**:**4b** ratio of 88:12 from **3b** and 91:9 from **4b.** Thus, it appears that **3b** and **4b** produce the same lithio derivative (**19**) on metalation. Protonation of this lithio derivative occurs preferentially cis to the sulfoxide oxygen, as was the case with **12,** but with slightly greater stereoselectivity.

Highly stereoselective protonation of 2-lithio-2-phenyl-1,3-dithiane 1-oxide (**20**) was observed. Metalation of *trans*-2-phenyl-*cis*-2-deuterio-1,3-dithiane 1-oxide (**21**) with lithium diisopropylamide in tetrahydrofuran at −68 °C, followed by addition of aqueous HCl, gave **3c** as the exclusive product in quantitative yield. Under equilibrium conditions (0.008 M sodium methoxide in refluxing methanol), and starting with either pure **3c** or its cis diastereomer **4c,** the **3c**/**4c** ratio as determined by LC was 89:11.

The ready metalation of 2-substituted 1,3-dithiane 1-oxides, indicated by these experiments, suggested the possibility of preparing 2,2-disubstituted 1,3-dithiane 1-oxides in spite of a previous brief report that dialkylation of **1** was not efficient.[13] Indeed, reaction of the lithio derivative of **3b** with methyl iodide afforded 2,2-dimethyl-1,3-dithiane 1-oxide in 74% yield after distillation. A mixture of diastereomeric 2-phenyl-2-methyl-1,3-dithiane 1-oxides was isolated in 84% overall yield from the reaction of the lithio derivative of **3c** with methyl iodide. The major diastereomer, mp 129–130 °C, isolated in 76% yield by preparative TLC, is identical with the major product obtained on oxidation of 2-phenyl-2-methyl-1,3-dithiane with *m*-chloroperoxybenzoic acid and is therefore *trans*-2-phenyl-*cis*-2-methyl-1,3-dithiane 1-oxide (**22**).[1a] The



22 **23**

minor product, *cis*-2-phenyl-*trans*-2-methyl-1,3-dithiane 1-oxide (**23,** mp 89–90.5 °C), was isolated in 8% yield. In a separate methylation experiment, LC analysis of the crude reaction mixture gave a **22**:**23** ratio of 84:16. An almost identical **22**:**23** ratio of 86:14 was obtained on metalation–methylation of **4c,** but the conversion was low (41%).

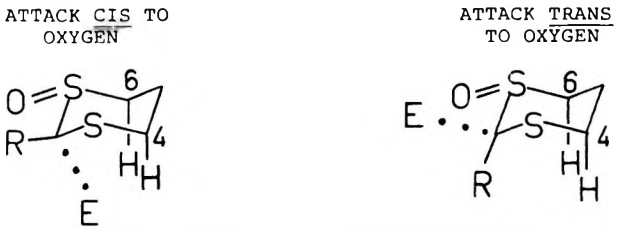


Figure 1. Representations of transition state geometries for electrophilic attack on anionic species derived from 1,3-dithiane 1-oxide.

The stereoselectivity of the metalation step was also considered. The kinetic preference for abstraction of the C(2) equatorial vs. C(2) axial proton in **1** can readily be determined through the use of the stereospecifically deuterated substrates **7a** and **7b.**[3,14] Metalation of **7a** and **7b,** in separate experiments, followed by reaction with methyl iodide and mass spectrometric analysis of the extent of deuterium retention in the methylated product, permits the selectivity factor (k_{eq}/k_{ax}) and the isotope effect (k_H/k_D) to be calculated[3] (see Experimental Section for details). The selectivity factor favoring equatorial proton abstraction was determined to be 2.7 and the isotope effect k_H/k_D to be 1.1.

Discussion

As measured by their relative ease of abstraction by lithium diisopropylamide, the diastereotopic protons at C(2) in **1** do not differ greatly in kinetic acidity. An apparent selectivity factor k_{eq}/k_{ax} = 2.7 was determined. This measurement is subject to the reservation that **1** exists as an 86:14 mixture of two conformations which may exhibit different selectivities for a pair of diastereotopic protons in two different environments. The low apparent selectivity may reflect a leveling effect associated with the enhanced acidity of this system relative to systems in which the anion is stabilized to a lesser degree, e.g., **13–17.**

The stereoselectivity of the reactions of lithiated 1,3-dithiane 1-oxides is dependent upon the attacking electrophile and the substituent already present at C(2). The reactions are not stereospecific. The same product mixtures are obtained irrespective of which diastereomer of a 2-substituted 1,3-dithiane 1-oxide is used. Reactive electrophiles (DCl, benzophenone) attack 2-lithio-1,3-dithiane 1-oxide (**12**) cis, in preference to trans, to the sulfoxide oxygen by a factor of 3–4:1. The preference for protonation (or deuteration) increases to 8–10:1 when a methyl group is present at C(2) as in the lithio derivatives of **3b** and **4b,** and to >20:1 in the lithio derivative of **3c.**

The ground-state geometry at C(2) in **12** and related lithio derivatives,[15] as well as the extent of ion pairing and aggregation, is not known. These factors clearly play a role in determining the intrinsic preference for attack cis to sulfoxide oxygen. A steric model such as outlined in Figure 1, however, suffices quite well to rationalize the observed *trends* in stereoselectivity. The geometry at C(2) in the transition state must be more congested than in the ground state, and so both the attacking electrophile and the substituent at C(2) will alter the "normal" preference for attack cis to oxygen. A C(2) substituent will increase the tendency toward attack cis to oxygen because the energy of the transition state for attack trans to oxygen is raised to the extent that the substituent approaches an axial orientation. The increased stereoselectivities observed when R = CH_3 and R = Ph are in accord with this analysis. When the electrophilic reagent is less reactive, such as methyl iodide, the transition state is reached later and requires a more highly developed covalent interaction between

C(2) and the electrophile. The interactions between an attacking methyl iodide molecule and the syn-axial hydrogens at C(4) and C(6) oppose the "normal" mode of attack and increase the fraction of product in which the incoming group (methyl) is trans to oxygen. When R = H, the ratio of cis/trans attack is 45:55 (vs. 4:1 for deuteration). When R = Ph, it is 84:16 (vs. >20:1 for protonation).

For simplicity, only the conformation of the lithio derivatives having the sulfoxide oxygen equatorial was considered in the preceding analysis and the transition state models represented in Figure 1. The alternative conformation of the lithio derivatives in which the sulfoxide oxygen is axial could be significant if (a) the conformational equilibrium between the lithio derivatives deviated significantly from that of the precursors, or (b) the sulfoxide oxygen-axial conformation is attacked by electrophilic reagents much faster than the sulfoxide oxygen-equatorial conformation. The internal consistency of the results indicates that neither of these possibilities is very likely. For example, if the "reacting conformation" had the sulfoxide oxygen axial (or approximately axial) it is difficult to understand why the tendency for methylation cis to oxygen would *increase* from 45% in **12** (R = H) to 84% in **20** (R = Ph) where a phenyl group moves toward an axial site in the transition state. Similarly, the fact that protonation of the lithio derivative **20** gives a **3c**:**4c** ratio significantly in excess of that at equilibrium (>20:1 vs. 89:11) argues against the importance of conformations of the lithio derivative in which the oxygen-axial:oxygen-equatorial energy relationship is reversed from that of **3c** itself.

In conclusion, the stereoselectivity of the reactions of 2-lithio-1,3-dithiane 1-oxide and its analogues with electrophilic reagents can be understood as a combination of an intrinsic preference for attack cis to the sulfoxide oxygen and steric effects of a conventional type. These include syn-axial repulsions between the C(2) substituent and the C(4) and C(6) axial protons in the transition state and van der Waals repulsions between the electrophile and the C(4) and C(6) axial protons. The intrinsic preference for attack cis to sulfoxide oxygen is not high and provides little in the way of an answer to the continuing question of the preferred geometry of sulfinyl carbanions.

Experimental Section

The general experimental information and listing of the instruments used is identical with that of the preceding paper. All reactions involving organolithium reagents were carried out in an atmosphere of dry nitrogen. Tetrahydrofuran and diisopropylamine were distilled from calcium hydride. *n*-Butyllithium in *n*-hexane was purchased from Alfa Inorganics and its concentration determined by the double titration method of Gilman using 1,2-dibromoethane.[16] Deuterium oxide (99.7%) and 20% DCl in D_2O (99$^+$ atom % D) were purchased from Diaprep.

1,3-Dithiane 1-Oxide (1). The procedure of Carlson[2] involving sodium metaperiodate oxidation of 1,3-dithiane was followed to afford **1** in yields corresponding to those reported. For larger scale preparations it is more economical to use hydrogen peroxide in acetic anhydride. To 12.4 g (0.1 mol of 97% pure material) of 1,3-dithiane in 200 ml of acetic anhydride cooled to −15 °C was slowly added 8.6 ml (0.1 mol) of 30% hydrogen peroxide. The solution was stirred for 1 h at −15 °C, allowed to stand at room temperature for 36 h, and evaporated at 25 °C under vacuum, and the residue recrystallized from dichloromethane–cyclohexane to afford 8.3 g (61%) of **1**, mp 88–89.5 °C (reported[2] 87–88 °C). Mass spectrometric analysis indicated that no sulfone or disulfoxide was present.

General Procedure for Metalation of 1,3-Dithiane 1-Oxide (1). A. With n-Butyllithium. A solution of **1** in purified tetrahydrofuran (7 ml/mmol of **1**) was cooled to −70 °C and a solution of *n*-butyllithium in *n*-hexane (1 equiv) added. The resulting yellow solution was stirred at −70 °C for 15 min to ensure complete metalation.

B. With Lithium Diisopropylamide. Lithium diisopropylamide was prepared by adding *n*-butyllithium (1.1 equiv) in *n*-hexane to a cooled (−30 to −40 °C) solution of diisopropylamine (1.5 equiv) in tetrahydrofuran (7 ml/mmol of **1**). The reaction mixture was permitted to warm to ca. 0 °C, then cooled to −60 °C and a solution of **1** in tetrahydrofuran (5 ml/mmol) added rapidly. The pale yellow solution was stirred at −60 °C for 20 min to complete the metalation. This metalation procedure was found to be cleaner and more generally useful than that using *n*-butyllithium.[17]

Deuteration of 2-Lithio-1,3-dithiane 1-Oxide (12). The metalation of 136 mg (1 mmol) of 1,3-dithiane 1-oxide (**1**) was performed as described in A. The solution of the lithio derivative was then added, using a syringe, to a cooled (bath temperature −70 °C) mixture of 0.85 ml of 20% DCl in D_2O and 2–3 ml of tetrahydrofuran. After stirring for ca. 3 min, solid sodium carbonate was added and the mixture allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (30 ml), washed with water, brine, and dried with potassium carbonate. The residue after evaporation (74 mg, 54%) was purified by preparative TLC to afford 38 mg of 1,3-dithiane-1-oxide (mp 83–87 °C). Mass spectral analysis at 15 eV and an inlet temperature of 100 °C gave an isotopic composition of 3% d_0, 96% d_1, and 1% d_2. The stereoselectivity of deuteration was determined by NMR analysis at 100 MHz in $CDCl_3$ and found, from the 4:1 ratio of the integrated intensity of the equatorial proton at C-2 to the axial proton at C(2), to be 80% axial deuterium to 20% equatorial deuterium.

Hydrogen–Deuterium Exchange of 1 in CH_3OD. A solution of 50 mg (0.37 mmol) of **1** in 0.5 ml of methanol-*O*-*d* containing 2 mg (0.04 mmol) of sodium methoxide was allowed to stand at 25 °C for 47 h, then diluted with D_2O, brine added, and extracted with dichloromethane. The organic extracts were dried over sodium sulfate and evaporated to leave 38 mg (76%) of white solid, mp 88.5–89.5 °C. NMR and mass spectral analysis established the composition as 26% **1**, 28% **7a**, 28% **7b**, and 18% **18**.

Methylation of 1. Metalation of 272 mg (2.0 mmol) of **1** was effected using procedure B. Iodomethane (0.65 ml, 10 mmol) was added, and the solution stirred for 20 min at −60 °C and allowed to warm to room temperature. Water was added and the tetrahydrofuran removed by evaporation. Brine was added to the residue, and the product extracted with chloroform (2 × 25 ml). The organic phase was dried and the solvent evaporated. The crude product (307 mg) was examined by liquid chromatography, using standard solutions of **4b**, **3b**, and **1** fo calibration. These materials had retention times of 9.8, 11.5, and 10.9 min, respectively. The product mixture was found to consist of 55% *trans*-2-methyl-1,3-dithiane 1-oxide (**3b**) and 45% *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**). No starting material was detected.

In order to confirm the above analytical results, the components of the reaction mixture were isolated by preparative TLC on silica gel using carbon tetrachloride–2-propanol (3:1) as developing solvent. The higher R_f band afforded 149.2 mg (50%) of **3b**, mp 91–92.5 °C. Recrystallization from ether and a trace of dichloromethane gave fine white needles melting at 94–95 °C (lit.[2] mp 93–94 °C). From the lower R_f band was obtained 121.7 mg (40%) of crude **4b**, mp 41–51 °C. Recrystallization from ether and a trace of dichloromethane gave white crystals, mp 58–60.5 °C. The trans/cis ratio of isolated materials was 55:45, in excellent agreement with the analytical result.

Reaction of 2-Lithio-1,3-dithiane 1-Oxide with Benzophenone. Lithiation of 272 mg (2.0 mmol) of **1** was effected using procedure A. The solution of **12** was treated with 364 mg (2.0 mmol) of benzophenone and stirred at −70 °C for 0.5 h. A solution of hydrochloric acid (1 ml, 20%) in 2 ml of tetrahydrofuran was added. Solid sodium carbonate was then added and the solution allowed to warm to room temperature and worked up in the usual manner. The crude product was a white solid (668 mg), mp 154–164 °C, which appeared from its NMR spectrum to be a 3:1 mixture of *cis*-2-(diphenylhydroxymethyl)-1,3-dithiane 1-oxide (**4d**) and *trans*-2-(diphenylhydroxmethyl)-1,3-dithiane 1-oxide (**3d**).

Recrystallization from dichloromethane–ether afforded 333 mg (54%) of **4d**, mp 155–157 °C dec (reported[2] mp 155–156 °C dec). The NMR and ir spectra were identical with those of the adduct of undefined stereochemistry reported previously.[2] Assay by NMR indicated that **4d** was the only isomer present.

Determination of Stereoselectivity of Metalation Step. The methylation of *trans*-2-deuterio- (**7a**) and *cis*-2-deuterio-1,3-dithiane 1-oxide (**7b**) was carried out on a 1.5-mmol scale using procedure B.[18] The mixture of **3b** and **4b** obtained was analyzed for deuterium content by mass spectrometry at 15 eV. The deuterium incorporation data are presented in Table I. The selectivity factor (k_{eq}/k_{ax}) and isotope effect (k_H/k_D) are related by the equations below.

For the product from **7b**

$$\frac{d_1}{d_0} = (k_{eq}/k_{ax})(k_H/k_D)$$

Table I. Deuterium Retention in Methylated Products Obtained from *cis*- and *trans*-2-Deuterio-1,3-dithiane 1-Oxides

Run	Starting material	Isotopic composition of product, %[a] d_0	d_1
1	Cis (**7b**)[b]	32.3	67.7
2	Cis (**7b**)[b]	17.6	82.4
	Av	25.0	75.0
3	Trans (**7a**)[c]	67.8	32.2
4	Trans (**7a**)[d]	74.4	25.6
	Av	71.1	28.9

[a] Corrected for d_0, d_1, d_2 composition of starting material. [b] 1.34% d_0, 98.3% d_1, 0.4% d_2. [c] 6.12% d_0, 93.4% d_1, 0.4% d_2. [d] 12.67% d_0, 87.33% d_1.

For the product from **7a**

$$\frac{d_1}{d_0} = \frac{(k_H/k_D)}{(k_{eq}/k_{ax})}$$

then

$$\frac{75.0}{25.0} = (k_{eq}/k_{ax})(k_H/k_D)$$

and

$$\frac{28.9}{71.1} = \frac{(k_H/k_D)}{(k_{eq}/k_{ax})}$$

which gives

$$k_{eq}/k_{ax} = 2.7$$

$$k_H/k_D = 1.1$$

In runs 2 and 4, the cis- and trans-methylated products **4b** and **3b** were separated and analyzed for deuterium content independently. For run 2, the **4b** obtained was 15.9% d_0, 84.1% d_1; the **3b** was 22.3% d_0 and 77.7% d_1. For run 4, the **4b** obtained was 71.9% d_0, 28.1% d_1; the **3b** was 72.1% d_0 and 27.9% d_1.

Generation and Protonation of 2-Lithio-2-methyl-1,3-dithiane 1-Oxide (19). The metalation was carried out as described in procedure B, the reaction mixture stirred at −45 to −65 °C for 7 h and quenched at −60 °C with 20% hydrochloric acid. After workup in the usual way, the reaction mixture was analyzed by liquid chromatography. The product from *trans*-2-methyl-1,3-dithiane 1-oxide (**3b**) was an 89:11 mixture of **3b** and *cis*-2-methyl-1,3-dithiane 1-oxide (**4b**). The product from **4b** was a 91:9 mixture of **3b** and **4b**.

Methylation of *trans*-2-Methyl-1,3-dithiane 1-Oxide (3b). Metalation of 1.00 g (6.67 mmol) of **3b** was carried out using procedure B and the resulting solution treated with 1.0 ml (16.1 mmol) of iodomethane at −55 °C. The solution was warmed to room temperature and quenched with water and the solvent removed by evaporation. The residue was partitioned between brine and chloroform, and the chloroform removed to leave a yellow oil which was then distilled. The 2,2-dimethyl-1,3-dithiane 1-oxide was collected as a colorless liquid (808 mg, 74%) at 90–91 °C (0.09 Torr) [lit.[10] bp 98–100 °C (0.15 Torr)]. The NMR spectrum corresponded to that reported,[10] with methyl signals at δ 1.62 and 1.56 ppm.

Equilibration of *trans*- (3c) and *cis*-2-Phenyl-1,3-dithiane 1-Oxide (4c). A methanol (25 ml) solution containing 99.6 mg (0.47 mmol) of **3c** and 0.106 mmol of sodium methoxide was stirred at room temperature for 21 h. No appreciable change had occurred; so an additional 0.104 mmol of sodium methoxide was added and the solution refluxed for 5 h. The reaction mixture was allowed to cool, methanol removed in vacuo, and the residue partitioned between 10 ml of saturated ammonium chloride and 10 ml of dichloromethane. Layers were separated and the aqueous layer extracted with a second 10-ml portion of dichloromethane. Combined dichloromethane solutions were dried over sodium sulfate. Removal of solvent gave 95.1 mg of white solid, mp 136.5–139.5 °C, which was analyzed by LC. The material was found to consist of 89.6% **3c** and 10.4% **4c**.

In a similar fashion, 57.5 mg (0.271 mmol) of **4c** was treated with sodium methoxide in methanol. The equilibrium mixture was determined to consist of 89.0% **3c** and 11.0% **4c**.

Metalation and Protonation of *trans*-2-Phenyl-*cis*-2-deuterio-1,3-dithiane 1-Oxide (21). Lithiation of 320 mg (1.5 mmol) of **21** was carried out according to procedure B. The reaction mixture was quenched with 20% hydrochloric acid, and after 5 min, solid sodium carbonate (398 mg) was added, and the mixture allowed to warm to room temperature. The reaction mixture was worked up as usual, and 319 mg of yellowish-white solid (mp 142–145 °C) was isolated. The NMR spectrum of this material confirmed a quantitative yield of **3c**.

Methylation of *trans*-2-Phenyl-1,3-dithiane 1-Oxide (3c). Lithiation of 637 mg (3.0 mmol) of **3c** by procedure B followed by treatment with 0.75 ml (12 mmol) of methyl iodide gave a solution which, after warming from −60 °C to room temperature, was quenched with 10 ml of water. The tetrahydrofuran was removed under vacuum. To the residue were added 50 ml of brine and 50 ml of chloroform. The layers were separated, and the aqueous layer extracted with an additional 50 ml of chloroform. The combined chloroform layers were dried over sodium sulfate. Evaporation of the solvent gave 672 mg of crude product. Recrystallization from 2-propanol and preparative TLC (silica gel; 20% 2-propanol/carbon tetrachloride) of material remaining in the mother liquor yielded 516.4 mg (76%) of *trans*-2-phenyl-*cis*-2-methyl-1,3-dithiane 1-oxide (**22**), mp 126.5–129 °C, and 53.4 mg (7.9%) of *cis*-2-phenyl-*trans*-2-methyl-1,3-dithiane 1-oxide (**23**), mp 86.5–88 °C. Recrystallization of crude **22** from dichloromethane–ether gave the analytical sample as long, white needles: mp 129–130 °C; NMR ($CDCl_3$) δ 1.87 (s, 3, CH_3), 2.0–2.9 (m, 6, dithiane ring protons), 7.2–7.45 (m, 3, meta and para aromatic protons), 7.45–7.7 (m, 2, ortho protons); mass spectrum *m/e* (rel intensity) 226 (27), 121 (100), 193 (65), 77 (73).

Anal. Calcd for $C_{11}H_{14}S_2O$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.31; H, 6.26; S, 28.22.

Recrystallization of crude **23** from cyclohexane gave the analytical sample: mp 89–90.5 °C; NMR ($CDCl_3$) δ 1.88 (s, 3, CH_3), 2.1–3.0 (m, 6, dithiane ring protons), 7.27 (apparent t, 3, meta and para aromatic protons), 7.87 (doublet of doublets, 2, ortho protons); mass spectrum *m/e* (rel intensity) 226 (20), 121 (100), 103 (64), 77 (80).

Anal. Calcd for $C_{11}H_{14}S_2O$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.23; H, 6.29; S, 28.28.

Following the same procedure, 202 mg (0.95 mmol) of **3c** was converted to 223 mg of crude product. Analysis by LC gave the composition as 84% **22** and 16% **23**. The retention times were 8.0 min for **22** and 5.7 min for **23**. Isolation of the products by preparative TLC on silica gel using 4:1 carbon tetrachloride/2-propanol gave 24 mg (11%) of **23**, mp 84–86 °C, and 138 mg (64%) of **22**, mp 129.5–130.5 °C.

Methylation of *cis*-2-Phenyl-1,3-dithiane 1-Oxide (4c). The procedure was identical with that of the above experiment and afforded, from 105 mg (0.5 mmol) of **4c**, 107 mg of whit solid. The NMR spectrum of this material indicated that the alkylation was only about 41% complete. The product was determined to consist of 86% **22** and 14% **23** (LC analysis).

Oxidation of 2-Phenyl-2-methyl-1,3-dithiane (24). The oxidation of **24**[18] (3.16 g, 15 mmol) with *m*-chloroperoxybenzoic acid was carried out as described in the accompanying paper.[1a] The crude product (3.40 g, 97%), mp 124–132 °C, had an NMR spectrum virtually identical with that of the product mixture obtained on methylation of **3c**. Analysis by liquid chromatography indicated a composition of 89% **22** and 11% **23**.

Attempted oxidation of **24** with sodium metaperiodate in aqueous methanol was accompanied by extensive hydrolysis to acetophenone as indicated by the NMR spectrum of the crude product.

Registry No.—**1**, 16487-10-8; **3b**, 60349-75-9; **3c**, 60349-76-0; **3d**, 60349-77-1; **4b**, 60349-78-2; **4c**, 60349-79-3; **4d**, 60349-80-6; **7a**, 60349-84-0; **7b**, 60349-85-1; **12**, 60349-88-4; **18**, 60349-89-5; **19**, 60349-90-8; **21**, 60349-91-9; **22**, 60349-92-0; **23**, 60349-93-1; **24**, 6331-22-2; butyllithium, 109-72-8; lithium diisopropylamide, 4111-54-0; benzophenone, 119-61-9; 2,2-dimethyl-1,3-dithiane 1-oxide, 41893-06-5.

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A Synthesis of Mixed Dialkyl Peroxides via Reaction of an Alkyl Hydroperoxide with Alkyl Trifluoromethanesulfonates

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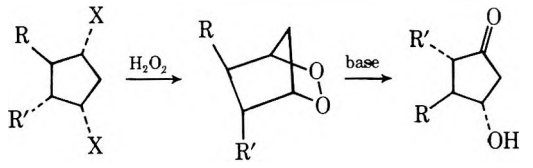
Mixed peroxides containing the *tert*-butyl group and secondary or primary alkyl groups are easily prepared under exceptionally mild conditions by reaction of primary or secondary trifluoromethanesulfonates with either potassium *tert*-butyl peroxide (method I) or with *tert*-butyl hydroperoxide in the presence of sodium bicarbonate (method II). Method I gives high yields of primary tertiary peroxides and moderate yields of secondary tertiary peroxides. The preparation of 1,3-cyclopentane bis triflates in good yields from 1,3-cyclopentanediols, models of the prostaglandin F nucleus, and conversion to 1,3-cyclopentane bis-*tert*-butyl peroxides are readily achieved. Loss of stereochemistry occurs with either method in the *cis*- and *trans*-cyclopentane-1,3-diol system, but method II is preferred in this system as it gives complete bisalkylation with no accompanying elimination.

In connection with studies on the synthesis of prostaglandin endoperoxides[1] (e.g., **2a**), we are seeking a mild, high-yield method for the synthesis of secondary alkyl peroxides. The prostaglandin endoperoxide nucleus is a strained bicyclic secondary peroxide which is extremely sensitive to base-catalyzed decomposition in comparison with common secondary peroxides. Thus, the usual harsh, alkaline method for preparation of bis secondary alkyl peroxides by reaction of secondary alkyl methanesulfonates with hydrogen peroxide in the presence of potassium hydroxide[2a,9] is incompatible with the survival of the prostaglandin endoperoxide nucleus. The ultimate goal of these studies is the synthesis of prostaglandin endoperoxides by treating suitably substituted 1,3-cyclopentane bis alkylating agents (e.g., **1a**) with hydrogen peroxide



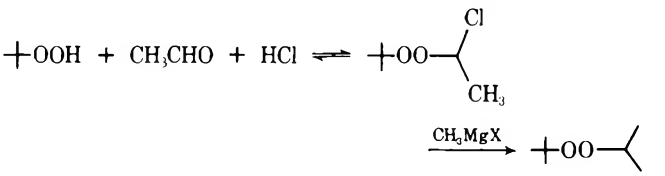
1 **2**

a, R = CH=CHCH(OH)C_5H_{11}; R′ = $(CH_2)_6COOH$; X = OH
b, R = R′ = H; X = OTf

or related peroxy nucleophiles. Thus, preparation of appropriately substituted cyclopentane derivatives must be feasible in any new method.

We report here development of new methods for synthesis of secondary or primary alkyl *tert*-butyl mixed peroxides by alkylation of either *tert*-butyl hydroperoxide in the presence of sodium bicarbonate or potassium *tert*-butyl peroxide with secondary or primary alkyl trifluoromethanesulfonates (triflates). These reactions give fair to good yields (30–60%) in secondary cases and an excellent yield with a primary triflate (83%). Furthermore, we report preparation of 1,3-bis(*tert*-butyl)peroxycyclopentane by these methods. Hence, further extensions of these reagents and procedures may be useful for the synthesis of prostaglandin endoperoxides.

In order to evaluate and develop various methods for synthesis of secondary peroxides, we chose preparation of the simple peroxide isopropyl *tert*-butyl peroxide as a model. Several methods have been employed to prepare this and related dialkyl peroxides. The most widely used synthesis involves reaction of alkyl bromides with sodium or potassium *tert*-butyl hydroperoxide.[3] The yields are low (33% for isopropyl bromide) and the purification somewhat tedious. Reaction of *tert*-butyl hydroperoxide with dialkyl sulfates and potassium hydroxide succeeds quite well in the methyl and ethyl cases,[1] but is only fair (38%) in the isopropyl case.[3a] Alkylation of cumyl hydroperoxide with 2-diazopropane gives a fair yield (41%),[4] but preparation of secondary diazo compounds other than isopropyl is difficult and yields are poor. *tert*-Butyl isopropyl peroxide was recently prepared in 25% overall yield from *tert*-butyl hydroperoxide by reaction of *tert*-butyl-2-chloroethyl peroxide with a methyl Grignard



reagent.[5] This method is hampered by the instability of peroxides toward Grignard reagents.[6] Finally, the recent preparation of secondary alkyl *tert*-butyl peroxides by peroxymercuration of olefins followed by demercuration with sodium

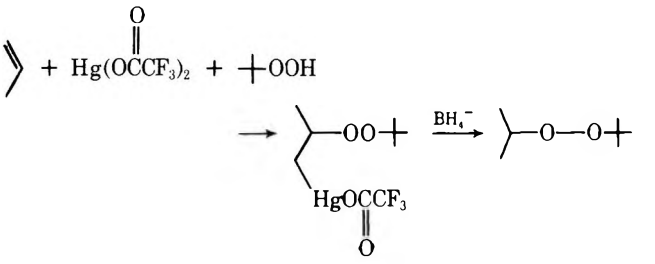
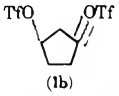
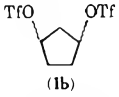
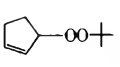
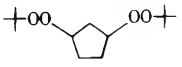
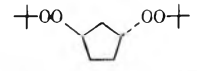


Table I. Synthesis of Mixed Dialkyl Peroxides with Alkyl Triflates

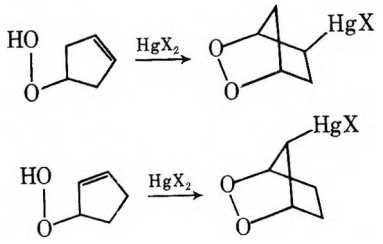
Triflate	Registry no.	Reaction type[a]	Reaction time, h	Product(s)	Yield %	Registry no.
Me_2CHOTf	41029-44-1	$NaHCO_3$/*t*-BuOOH	3	$Me_2CHOO(t\text{-Bu})$	56	15879-99-9
Me_2CHOTf		KOO-*t*-Bu	0.5	$Me_2CHOO(t\text{-Bu})$	33	
Me_2CHCH_2OTf	60306-25-4	$NaHCO_3$[b]/*t*-BuOOH	38	$Me_2CHCH_2OO(t\text{-Bu})$ (42%) + $(t\text{-BuO})_2$ (58%)	37	60306-29-8 110-05-4
Me_2CHCH_2OTf		KOO-*t*-Bu[b]	3	$Me_2CHCH_2OO(t\text{-Bu})$	81	
Me(Et)CHOTf	60306-26-5	$NaHCO_3$/*t*-BuOOH	18	Me(Et)CHOO(*t*-Bu)	33	31469-04-2
Me(Et)CHOTf		KOO-*t*-Bu	0.5	Me(Et)CHOO(*t*-Bu)	48	
 (1b)	60306-27-6	$NaHCO_3$/*t*-BuOOH	1	See Table II	50	
(from cis diol)		KOO-*t*-Bu	1	See Table II	40	
 (1b)	60306-28-7	$NaHCO_3$/*t*-BuOOH	1	See Table II	49	
(from trans diol)		KOO-*t*-Bu	1	See Table II	53	

[a] Reaction temperature 25 °C. [b] Reaction temperature 40 °C.

Table II. Reaction Products from *cis*- and *trans*-1,3-Cyclopentanediols

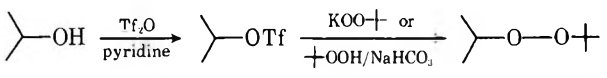
Starting diol	Reaction type	Products, % 		
Cis	$NaHCO_3$/*t*-BuOOH	0	66	34
Cis	KOO-*t*-Bu	43	9	49
Trans	$NaHCO_3$/*t*-BuOOH	0	62	38
Trans	KOO-*t*-Bu	29	23	48

borohydride is quite mild and gives fair yields (ca. 40% for the two-step process).[7] The use of intramolecular peroxymercuration[8] to prepare endoperoxides from 3- or 4-hydroperoxycyclopentenes is under investigation in our laboratories.



Results

We reasoned that a powerful alkylating agent, such as alkyl trifluoromethanesulfonate (triflate), might be capable of alkylating a hydroperoxide in the absence of strong bases which are required to generate alkylperoxy anions for reactions with less powerful alkylating agents, e.g. alkyl mesylates or alkyl halides. In fact, isopropyl triflate readily alkylates *tert*-butyl hydroperoxide in a few hours at room temperature. Cleanest reactions were obtained in the presence of sodium bicarbonate which neutralizes triflic acid by-product. In the case of isopropyl *tert*-butyl peroxide, the distilled product was not completely pure. The impurity, which we could not separate, appears to be di-*tert*-butyl peroxide. Pure isopropyl *tert*-butyl peroxide is obtained by an alternate procedure involving reaction of isopropyl triflate with potassium *tert*-butyl peroxide.



These new methods for preparation of mixed peroxides were extended to several additional examples, including isobutyl and secondary butyl triflates, and the bis triflates (**1b**) prepared from *cis*- and *trans*-cyclopentane-1,3-diol. The results and experimental conditions are summarized in Tables I and II. All of the peroxides except those obtained from the cyclopentanediols were reported previously. The structures of the latter are supported by their ^1H NMR spectra, elemental analyses, and mass spectra (see Experimental Section). In addition, the bis peroxides were reduced with lithium aluminum hydride[11] to the corresponding diols which were acetylated to give mixtures of *cis*- and *trans*-1,3-diacetoxycyclopentane, identified by gas–liquid phase chromatographic comparison with authentic samples.

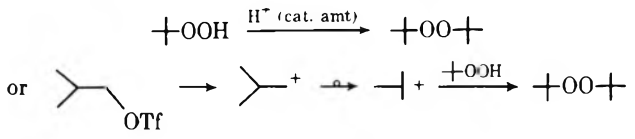
Discussion

These new methods for the synthesis of mixed dialkyl peroxides are quite mild and easy to execute. For monotriflates, the use of potassium *tert*-butyl peroxide is preferred over the *tert*-butyl hydroperoxide–sodium bicarbonate method for both speed of reaction and purity of the product. One complication which is encountered in either method, however, is the instability of some secondary triflates. Isopropyl triflate is stable in solution for several weeks at 0 °C, but 2-butyl triflate, which was obtained in poorer yields (48%), decomposes fairly rapidly at room temperature even in solution (15% after 0.5 h). Elimination of triflic acid to form olefins was a problem with some other triflates whose synthesis was attempted. Thus, reaction of cyclohexanol with triflic anhydride and pyridine gave a mixture of the desired triflate and cyclohexene which was converted entirely to cyclohexene in a few minutes by stirring with sodium bicarbonate. Attempted synthesis of cyclopentyl triflate gave only cyclopentene.

For the synthesis of isobutyl *tert*-butyl peroxide, the reaction of potassium *tert*-butyl peroxie with isobutyl triflate is a major improvement over previously available methodology. Thus, the mixed peroxide is obtained in 83% yield (isolated by distillation) by the new method while the reaction of sodium *tert*-butyl peroxide with isobutyl bromide gives only

a 30% yield.[3] The primary triflate is less reactive than the secondary ones, and a modest amount of heat (40 °C) is necessary to make the reaction proceed at a convenient rate. However, in contrast to secondary alkyl triflates, primary triflates are thermally stable, not prone to elimination, and are readily prepared in excellent yields. This new synthetic method should be easily applicable to long chain primary alkyl triflates, as contrasted by the dialkyl sulfate method which has only been used in the methyl and ethyl cases.[3]

Using the *tert*-butyl hydroperoxide–sodium bicarbonate method, some di-*tert*-butyl peroxide was formed from the reaction of isobutyl triflate with *tert*-butyl hydroperoxide.



This bis tertiary peroxide could arise either from *tert*-butyl hydroperoxide (perhaps catalyzed by traces of triflic acid)[12] or from the rearrangement of isobutyl triflate (or isobutyl carbonium ion) during the reaction.[10a] However, no rearrangement of isobutyl triflate occurs during its synthesis.

Preparation of the bis peroxide of cyclopentane-1,3-diol is a particularly significant result as it shows that the new method may prove applicable to a prostaglandin system. Synthesis of the bis triflate (**1b**) from either *cis*- or *trans*-cyclopentane-1,3-diol proceeds very smoothly in good yield, and no traces of olefin due to elimination of triflic acid can be detected by ^{1}H NMR of the crude bis triflate. The enhanced stability of the bis triflate over cyclopentyl triflate, which we were unable to prepare, indicated an inhibiting effect of the second substituent on elimination. The bis triflates from either the cis or trans diol isomer have nearly identical ^{1}H NMR spectra.

Examination of Tables I and II shows that good yields are obtained using either the *tert*-butyl sodium bicarbonate or the potassium *tert*-butyl peroxide methods, but elimination to form *tert*-butyl 3-cyclopentenyl peroxide was a competing reaction when the latter method was employed. Elimination generally accompanies common methods for the synthesis of dialkyl peroxides by nucleophilic displacement of halide or methanesulfonate with hydroperoxide, superoxide, or alkyl peroxide anions.[2] Thus, for bis alkylation with 1,3-cyclopentyl bis triflates (**1b**), which are models of the prostaglandin nucleus, the nonalkaline reaction with a hydroperoxide in the presence of sodium bicarbonate is superior. The bis triflate is readily prepared in good yield from the diol. The bis peroxides were easily purified by molecular distillation or column chromatography on Florisil.

The bis peroxides prepared by each of the methods described here consisted of similar mixtures of cis and trans isomers starting with either pure diol isomer. The cis bis peroxide was favored by the nonalkaline procedure while trans bis peroxide predominated when the alkaline potassium *tert*-butyl peroxide method was used and considerable elimination occurred. It is tempting to speculate that elimination from the cis bis triflate (or monotriflate monoperoxide) is favored over elimination from the corresponding trans isomer. That is, elimination selectively destroys a precursor of the cis bis peroxide. We have not determined whether the loss of stereointegrity observed in the transformation of cyclopentane diols to the bis peroxides occurs in the preparation of the bis triflates or during the conversion of the latter into the final products.

These studies are being extended to alkylation of hydrogen peroxide and related peroxy nucleophiles with triflates for the preparation of symmetrical dialkyl peroxides in general and prostaglandin endoperoxides in particular.

Conclusion

Mixed dialkyl peroxides are obtained by alkylation of an alkyl hydroperoxide with alkyl trifluoromethanesulfonates *under nonalkaline reaction conditions*. This new method was applied to 1,3-cyclopentane bis(trifluoromethanesulfonate), a model of the prostaglandin F nucleus. Under identical conditions, 1,3-cyclopentanediol bis(methanesulfonates) do not react at all with *tert*-butyl hydroperoxide. Cyclopentyl-1,3-bis(*tert*-butyl) peroxide is obtained in good yield uncontaminated with elimination product. This contrasts with the elimination which generally accompanies common methods for the synthesis of dialkyl peroxides by nucleophilic displacement of halide or methanesulfonate under alkaline conditions with hydroperoxide, superoxide, or alkyl peroxide anions. Thus, reaction of **1b** with potassium *tert*-butyl peroxide gives major quantities of elimination product in addition to the desired bis peroxide. The conversion of alcohol to peroxide via the triflate proceeds with loss of stereochemistry. In some cases, even the relatively basic nucleophile, potassium *tert*-butyl peroxide, gives much better yields of dialkyl peroxides with alkyl triflates than with less reactive alkylating agents. For monotriflates, purer products are usually obtained by reaction with the potassium *tert*-butyl peroxide than by reaction with the hydroperoxide in the presence of bicarbonate.

Experimental Section

Microanalyses were preformed by Chemalytics, Tempe, Ariz. ^{1}H NMR spectra were taken in carbon tetrachloride unless otherwise noted and recorded on a Varian A-60 spectrometer. Mass spectra were taken on a 21-490 Du Pont GC/mass spectrometer with interfaced computer, using 10 ft × 0.125 in. 15% FFAP column at 40 °C unless otherwise noted. Ir spectra were measured as neat films on a Perkin-Elmer Infracord spectrometer.

tert-Butyl hydroperoxide was purified by the method of Bloodworth et al.[7c] Potassium *tert*-butyl peroxide was prepared by the method of Kornblum and De La Mare.[13] Methylene chloride was dried by stirring over phosphorus pentoxide followed by distillation. Tetrahydrofuran was dried by distillation from the blue potassium ketyl of benzophenone. Pyridine was dried by standing over KOH several days followed by distillation and storage over molecular sieves.

Preparation of Triflates. General Procedure.[10a] A mixture of dry alcohol (10 mmol) and pyridine (10 mmol) in dry methylene chloride (3 ml) was added dropwise over 40 min to an ice-cooled, stirred solution of trifluoromethanesulfonic anhydride[10a] (10 mmol) in methylene chloride (7 ml) under nitrogen. The solution was stirred for an additional 15 min, and then washed with water (10 ml) and dried ($MgSO_4$). The solution was filtered and examined by NMR.

1. **Isopropyl triflate**[10a] was prepared according to the general procedure. The crude triflate was purified by bulb-to-bulb distillation at 1 mm (25 °C) and was stored in solution in the refrigerator. The triflate could also be prepared by bubbling propene into a stirred suspension of triflic acid in carbon tetrachloride.[10b]

2. **sec-Butyl triflate** was prepared according to the general procedure using an ice/salt bath and careful slow addition to triflic anhydride. After workup, the solution was examined by NMR and the yield (48%) determined by NMR with chloroform as an internal standard. The product is quite unstable and should be used immediately. NMR (CH_2Cl_2) δ 1.00 (3 H, t, J = 7 Hz), 1.33 (3 H, d, J = 7 Hz), 1.3–2.2 (2 H, m), 4.9–5.4 (1 H, m, partly buried under CH_2Cl_2).

3. **Isobutyl triflate** was prepared according to the general procedure. After the usual workup, the product was distilled, bp 36–37 °C (10 mm) (83%). The triflate is stable for several weeks at 0 °C. NMR δ 1.04 (6 H, d, J = 7 Hz), 1.77–2.43 (1 H, m), 4.26 (2 H, d, J = 6.5 Hz).

4. **1,3-Bis triflate of cyclopentane (1b)** was prepared by the general procedure using 2 mmol of pyridine and 2 mmol of triflic anhydride for every 1 mmol of *cis*-[15] or *trans*[16]-cyclopentane-1,3-diol. After the usual workup, the solvent was removed and the product (79% from cis, 72% from trans) was examined by NMR ($CDCl_3$, cis): δ 2.16–2.35 (4 H, m), 2.5 (2 H, distorted quartet, J = 5 Hz), 5.25–5.85 (2 H, m). The NMR spectra of the products from both the cis and

trans starting materials were virtually the same. The crude triflates were used immediately after preparation.

Reactions of Triflates with Potassium *tert*-Butyl Peroxide. General Procedure. To the triflate (25 mmol) in dry methylene chloride (50 ml) in a Morton flask under nitrogen was added in one portion (dried in vacuo) potassium *tert*-butyl peroxide[14] (50 mmol, 100 mmol for bis triflates) with efficient stirring. Reaction times and temperatures are given in Table I. After NMR analysis showed that no more triflate remained, the crude reaction mixture was washed with 5% KOH (2 × 50 ml) and water (50 ml), and dried (Na_2SO_4).

1. Isopropyl *tert*-butyl peroxide, prepared according to the general procedure by stirring at room temperature for 0.5 h, had bp 45–50 °C (120 mm) [lit.[3a] 52 °C (125 mm)]; NMR δ 1.12 (6 H, partly buried d), 1.16 (9 H, s), 4.06 (1 H, heptet, J = 7 Hz). The material was identical with an authentic sample[3a] by NMR and ir.

2. *sec*-Butyl *tert*-butyl peroxide, prepared according to the general procedure by stirring at room temperature for 0.5 h, had bp 38–42 °C (35 mm) [lit.[7c] 42–44 °C (6 mm)]; NMR δ 0.91 (3 H, t, J = 7 Hz), 1.10 (3 H, d, partly buried), 1.17 (9 H, s), 1.17–1.70 (2 H, m), 3.83 (1 H, hextet, J = 6 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 42 (30), 43 (30), 45 (29), 56 (100), 57 (24), 58 (28), 73 (78), 75 (23), 146 parent peak (52).

3. Isobutyl *tert*-butyl peroxide, prepared according to the general procedure by stirring under reflux for 3 h, had bp 63–64 °C (80 mm) [lit. 53 °C (50 mm[3a])]; NMR δ 0.93 (6 H, d, J = 6.5 Hz), 1.17 (9 H, s), 1.5–2.35 (1 H, m), 3.61 (2 H, d, J = 6.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 42 (27), 43 (62), 55 (21), 56 (100), 57 (24), 73 (56), 146 parent peak (49).

4. 1,3-Bis(*tert*-butyl) peroxide of cyclopentane derived from cis starting diol[15] was prepared in the usual manner at room temperature for 1 h. By NMR analysis, the crude product contained 57% bis peroxide and 43% 3-*tert*-butylperoxycyclopentene (for preparation see below). An olefin-free pure sample could be obtained by careful chromatography on Florisil, eluting with carbon tetrachloride, the olefin (contaminated with bis peroxide) eluting first: NMR δ 1.17 (18 H, s), 1.7–2.0 (6 H, m), 4.32–4.68 (2 H, m).

5. 1,3-Bis(*tert*-butyl) peroxide of cyclopentane derived from trans diol[16] was prepared in the usual manner at room temperature for 1 h. NMR analysis indicated 71% bis peroxide and 29% monoperoxide olefin. After removal of olefin by chromatography, the NMR of the bis peroxide was indistinguishable from that of the cis derived bis peroxide.

Reduction of Cyclopentane 1,3-Bis(*tert*-butyl) Peroxide. The bis peroxide (0.25 mmol) in dry THF (1 ml) was added in one portion to a stirred suspension of lithium aluminum hydride (75 mg, 2 mmol) in dry THF under nitrogen. The mixture was stirred under reflux for 18 h. The reaction was cooled, water (75 μl) added, then 15% sodium hydroxide solution (75 μl), followed by water (225 μl). The white solid was removed by filtration and washed well with THF (3 × 10 ml). The THF was concentrated to obtain the crude diol which was acetylated by addition of pyridine (2 ml) and acetic anhydride (2 ml). After standing for 2 days, the solvents were removed under reduced pressure and the residue was taken up in ether (10 ml) and washed with saturated sodium bicarbonate (10 ml) and saturated cupric sulfate (10 ml). The ether layer was dried ($MgSO_4$) and concentrated to give the crude 1,3-cyclopentane bis acetate (75–100% yield over two steps). The bis acetate was analyzed by VPC (15 ft × 0.125 in. 15% FFAP, 150 °C). Samples of four 1,2 and 1,3 bis acetoxycyclopentanes were prepared by acetylation of the known diols.[15-17] Their relative retention times under these VPC conditions were, trans 1,2,[17] 1.0; cis 1,2,[17] 1.1; trans 1.3,[16] 1.5; cis 1,3,[15] 1.6. Results of the analyses are given in Table II.

3-*tert*-Butylperoxycyclopentene.[18] To 3-chlorocyclopentene[19] (25 mmol) in dry methylene chloride (50 ml) in a Morton flask under nitrogen was added in one portion potassium *tert*-butyl peroxide (50 mmol) with efficient stirring. The mixture was stirred for 3 days, washed with 5% KOH (2 × 50 ml) and water (50 ml), and dried ($MgSO_4$). Removal of solvent gave product (1.64 g, 42%) whose NMR indicates that it is quite pure: δ 1.18 (9 H, s), 1.73–2.12 (2 H, m), 2.12–2.55 (2 H, m), 4.8–5.1 (1 H, m), 5.80 (1 H, d of t, J = 6, 2, 2 Hz), 6.02 (1 H, d with additional fine coupling, J = 6 Hz).

Reaction of Triflates with Sodium Bicarbonate and *tert*-Butyl Hydroperoxide. General Procedure. The triflate (20 mmol, 10 mmol if bis triflate) in dry methylene chloride (30 ml) was placed in a Morton flask under nitrogen. Sodium bicarbonate (5 g) was added followed by purified[7c] *tert*-butyl hydroperoxide (25 mmol). The reaction was stirred vigorously until NMR analysis indicated no more triflate remaining. Reaction times and temperatures are given in Table I. The reaction mixture was washed with cold 5% KOH (50 ml) and water (50 ml) and dried (Na_2SO_4).

1. Isopropyl *tert*-butyl peroxide was prepared by the general procedure at room temperature for 3 h. Even after distillation, the product was impure, being contaminated with about 20% excess *tert*-butyl absorption in the NMR.

2. *sec*-Butyl *tert*-butyl peroxide was prepared by the general procedure at room temperature for 18 h. After distillation the product was still impure, showing about 40% extra *tert*-butyl absorption in the NMR. By VPC analysis (5 ft × 0.25 in., 15% FFAP, 50 °C column, 100 °C injector and detector), the extra *tert*-butyl was not due to di-*tert*-butyl peroxide. A pure sample of *sec*-butyl *tert*-butyl peroxide was collected by preparative VPC and identified by NMR and ir comparison with the sample prepared by the potassium *tert*-butyl peroxide route above.

3. Isobutyl *tert*-butyl peroxide was prepared by the general procedure at reflux for 38 h. After distillation the product was still impure, showing an additional *tert*-butyl peak 1 cycle upfield from the product *tert*-butyl peak. This new peak corresponds to di-*tert*-butyl peroxide. VPC analysis (5 ft × 0.25 in. 15% FFAP, 50 °C) also indicated the presence of di-*tert*-butyl peroxide whose presence was confirmed by GC/mass spectral analysis of the mixture (di-*tert*-butyl peroxide retention time 2.0 min, isobutyl *tert*-butyl peroxide retention time 4.2 min).

4. 1,3-Bis(*tert*-butyl) peroxide of cyclopentane was prepared by the general procedure from either the bis triflate derived from *cis*- or *trans*-cyclopentane-1,3-diol using carbon tetrachloride as the reaction solvent. No cyclopentene-3-*tert*-butyl peroxide was formed from either starting material. Purification can be achieved by passage through Florisil eluting with carbon tetrachloride. Very pure samples were obtained from reactions with either cis or trans starting materials via molecular distillation at 50 °C (0.05 mm). Elemental analysis was performed on the purified bis peroxide from the cis diol. Anal. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64. Found: C, 62.85; H, 10.46.

Mass spectrum of the same material (direct inlet, 70 eV) *m/e* (rel intensity) 39 (48), 41 (53), 42 (43), 43 (62), 45 (22), 55 (33), 57 (100), 58 (41), 59 (46), 73 (71), 83 (23), 101 (21), 117 (20), 146 (28), 190 (22), 246 parent peak (6). Low voltage: 190 (100), 246 parent peak (27).

NMR analysis of the two products from cis and trans diol indicated that they were identical. Under very careful conditions the two different *tert*-butyl absorptions due to the cis and trans mixture of bis peroxide products can be discerned. The cis isomer comes at 0.8 cycles higher field than the trans isomer. By NMR, from either the cis or the trans starting material, the mixture consists of 62% cis and 38% trans bis peroxide.

Attempted reaction of the bis triflate from the cis diol starting material with sodium bicarbonate and *tert*-butyl hydroperoxide in methylene chloride rather than carbon tetrachloride as a solvent led to rapid decomposition after solvents were removed from the crude product.

Acknowledgment. This work was supported by Grant GM-21249 from the Division of General Medical Sciences of the National Institutes of Health.

Registry No.—Trifluoromethanesulfonic anhydride, 358-23-6; *sec*-butyl alcohol, 78-92-2; isobutyl alcohol, 78-83-1; *cis*-cyclopentane-1,3-diol, 16326-97-9; *trans*-cyclopentane-1,3-diol, 16326-98-0; potassium *tert*-butylperoxide, 14970-33-3; *cis*-1,3-bis(*tert*-butyl) peroxide of cyclopentane, 60306-30-1; *trans*-1,3-bis(*tert*-butyl) peroxide of cylopentane, 60306-31-2; 3-*tert*-butylperoxycyclopentene, 38362-74-2; 3-chlorocyclopentene, 96-40-2; *tert*-butyl hydroperoxide, 75-91-2.

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Reaction of Sulfinate Esters with Grignard and Organocopper Lithium Reagents. A Useful Route to Chiral Sulfoxides[1]

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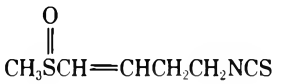
The reaction of sulfinate esters with various Grignard reagents was found to give a complex mixture of sulfoxide and sulfides. The use of organocopper lithium reagents in place of the Grignard effects the conversion of sulfinate esters to sulfoxides in higher yields and cleaner product mixtures. (−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate and (−)-menthyl (−)-(*S*)-benzenesulfinate were treated with organocopper lithium reagents. The reactions were found to proceed with inversion of configuration at sulfur to give sulfoxides of high optical purity.

The sulfoxide moiety, because of its pyramidal structure, can give rise to asymmetry in a molecule. The first known natural product in which optical activity results from chirality of an atom other than carbon is sulforaphen (1),[2] isolated from the black radish.



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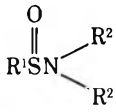
Sulfoxides can be prepared in various states of optical purity by a number of techniques. Asymmetric oxidation of sulfides with several reagents (optically active peracids,[3a-h] iodine in the presence of a chiral catalyst,[3i] or microbes[4]) provides sulfoxides, usually of low optical purity. Alternatively, sulfoxides can be optically enriched by incorporation into inclusion compounds with a chiral host molecule,[5] or by partial oxidation[6] or reduction[7a,b] with chiral reagents. In addition, the use of special techniques such as circularly polarized light[7c] and "chiral" electrodes[7d] have also produced respectable optical yields of chiral sulfoxides. Finally, sulfoxides of high optical purity can be prepared in variable yields by reaction of a variety of sulfinyl compounds (e.g., sulfinamides **2**,[8] heterocycles **3**,[9] or sulfinate esters **4**[10]) with organometallic reagents.



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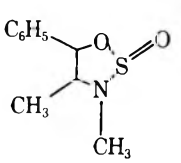

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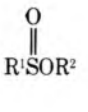

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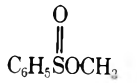
The most widely used synthetic procedure, dating from 1924,[10a] involves the reaction of a sulfinate ester 4 with a Grignard reagent. This reaction was later employed by Andersen[10b,c] to prepare optically active aryl sulfoxides; Mislow subsequently confirmed[10d,e] that the reaction was highly stereospecific, furnishing products of high optical purity.

While this valuable synthetic technique in certain instances can give sulfoxides in high yield, close scrutiny of the literature reveals that yields depend greatly on the structure of the target sulfoxide.[11] It appeared that careful examination of the reaction of a simple sulfinate ester such as methyl phenylsulfinate[12] (**5**) might provide some insight to the causes of this problem. Thus **5** and two cyclic sulfinate esters [1,2-oxathiolane 2-oxide (**6**) and 1,2-oxathiane 2-oxide (**7**)[13]] were treated with a number of Grignard reagents. The reaction of sulfinate esters with organocopper lithium reagents was also examined to evaluate their utility for sulfoxide formation.



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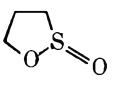

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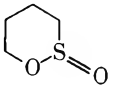

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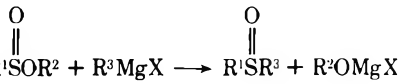
Results and Discussion

It was found that these compounds can react with Grignard reagents to give sulfoxides, but the conditions must be very carefully selected, otherwise considerable quantities of sulfides and other impurities are produced. These impurities can often remain tenaciously with the sulfoxide making separation difficult and thus severely limiting the synthetic utility of the reaction. The results obtained are summarized in Table I.

Reduction of Sulfinates to Sulfoxides by Grignard Reagents. In each case it was possible to characterize some sulfoxide in the reaction mixture, but the yields varied greatly with the structure of both sulfinate ester and Grignard reagent.



From the results of Table I, it is obvious that the sulfoxide, once generated, can react further. In the case where an equivalent amount of Grignard reagent was used, care was

Table I. Reaction of Grignard Reagents with Sulfinate Esters

Sulfinate (1 equiv)	CH_3MgBr (75-16-1)[k] Equiv of Grignard	Products	Yield, %	CH_3CH_2MgBr (925-90-6) Equiv of Grignard	Products	Yield, %	C_6H_5MgBr (100-58-3) Equiv of Grignard	Products	Yield, %
5 (670-98-4)[k]	1.0	$C_6H_5S(=O)CH_3$[a]	27	1.0	$C_6H_5S(=O)CH_2CH_3$[a,h]	32	1.0	$C_6H_5S(=O)C_6H_5$[b,g]	55
		$C_6H_5SCH_3$[a]	24		$C_6H_5SCH_2CH_3$[a,h]	29			
6 (24308-28-9)	3.3	$C_6H_5SCH_3$[b]	50	3.3	$C_6H_5SCH_2CH_3$[b,d]	60	6.0	$C_6H_5S(=O)C_6H_5$[a]	73
								$C_6H_5SC_6H_5$[a]	10
	1.0	$CH_3S(=O)(CH_2)_3OH$[c,i] (8a)	33				1.0	$C_6H_5S(=O)(CH_2)_3OH$[f] (8b)	57
		$CH_3CH_2S(CH_2)_3OH$[c] (11a)	33						
	2.0	$CH_3CH_2S(CH_2)_3OH$[b] (11a)	70				2.0	$C_6H_5S(CH_2)_3OH$[a] (11b)	65
7 (24308-29-0)	1.0	$CH_3S(=O)(CH_2)_4OH$[c] (9a)	40				1.0	$C_6H_5S(=O)(CH_2)_4OH$[e] (9b)	50
		$CH_3CH_2S(CH_2)_4OH$[c,i] (10b)	20				2.0	$C_6H_5S(=O)(CH_2)_4OH$[a] (9b)	24
								$C_6H_5S(CH_2)_4OH$[a] (10c)	6
	2.0	$CH_3CH_2S(CH_2)_4OH$[b,d] (10b)	60					$C_6H_5SCH(C_6H_5)(CH_2)_3OH$[a] (10d)	30
							4.0	$C_6H_5SCH(C_6H_5)(CH_2)_3OH$[b] (10d)	54

[a] Separated by chromatography on silica (eluent benzene–ethyl acetate, 5:1). [b] Separated by distillation. [c] Separated by washing crude product with ether. [d] Purified by preparative VPC (Carbowax 20M at 190–195 °C). [e] Purified by preparative TLC (silica, benzene–methanol 3:1). [f] Purified by preparative TLC (silica, benzene–methanol, 5:1). [g] Purified by crystallization (ether–hexanes). [h] Estimated by NMR. [i] Obtained ~90% pure characterized by NMR, MS, and reaction with MeMgI to give $CH_3CH_2S(CH_2)_3OH$. [k] Registry no.

taken to prevent excess reagent in the reaction mixture. A dilute solution of the organomagnesium compound was added very slowly to a vigorously stirred solution of the sulfinate ester. Even under these conditions, considerable amounts of sulfides were found in some of the product mixtures.

When **5** reacted with 1 equiv of phenylmagnesium bromide the sole product isolated is diphenyl sulfoxide; it has been shown[14] that this compound is insensitive to reduction by Grignard reagents. Cyclic sulfinates **6** and **7** can be made to yield pure sulfoxides in their reaction with phenylmagnesium bromide if the conditions of the reaction are carefully controlled.

Sulfinate esters **5–7** react with alkyl Grignard reagents to give mixtures of sulfoxide and sulfides which are sometimes very difficult to separate; the mixture formed by reaction of **5** with ethylmagnesium bromide proved to be especially recalcitrant.

Reduction of Sulfoxides to Sulfides. The nature of the sulfide formed depends on the structure of the intermediate sulfoxide and the quantity of Grignard reagent present. If the sulfoxide contains a phenyl group and a twofold (or greater) excess of organomagnesium reagent is used, the sulfide is generally that corresponding in structure to the sulfoxide; however, when **7** reacts with phenylmagnesium bromide, the sulfide **10d** (corresponding to double addition of the Grignard reagent) is the predominant product.

7 **10c** **10d**

Although the reaction of sulfoxides with Grignard reagents is exceedingly complex,[15,16] Manya and co-workers suggested routes to the two types of sulfides.[16] The formation of sulfide corresponding in structure to the sulfoxide is rationalized in terms of a sulfenic acid precursor, formed by decomposition of **12.** The formation of sulfides of the type **10d** was also explained by a process involving the intermediate sulfonium methylide **12,** but through a rearrangement process (Scheme I).

Scheme I

When R^3 is phenyl we detected benzene in the reaction mixture, corroborating the above proposal.

Organocopper Compounds. Because of the complexity encountered in the reaction of sulfinate esters with Grignard reagents, we decided to explore the reaction with organocopper reagents. Reagents of the type **14** have been known for some time to be more specific in many of their reactions than Grignard reagents.[17]

R_2CuLi

14

It was thought that perhaps the selectivity might extend to their reaction with sulfinate esters. It was found that treatment of **5** with lithium dimethylcuprate yielded methyl phenyl sulfoxide in 59% yield. Treatment of sulfinate esters **6**, **7**, and methyl *n*-butylsulfinate (**15**) with organocopper lithium reagents yielded sulfoxides in moderate yields (Table II).

In most cases, the yield of isolated sulfoxide was greater than that of sulfoxide from the parallel Grignard reaction. In addition, the quantity of sulfide corresponding in structure to the target sulfoxide was considerably less. Furthermore, sulfide corresponding to double addition (vide supra, **13**) was not found in any of these reactions.

A notable exception was provided by the reactions of sulfinate esters **5** and **15** with lithium di-*n*-butylcuprate and lithium diphenylcuprate, respectively. In both cases *n*-butyl phenyl sulfide was formed; no sulfoxide was detected.[18]

In contrast to the Grignard reagents, in most cases, an excess of the organocopper reagent can be tolerated in the reaction mixture. Thus treatment of **5** with a four molar excess of lithium dimethylcuprate gave methyl phenyl sulfoxide in 43% yield. The best yield of sulfoxide obtained with the corresponding Grignard reagent was 27%; treatment of **5** with 3.3 mol of Grignard yielded only sulfide.

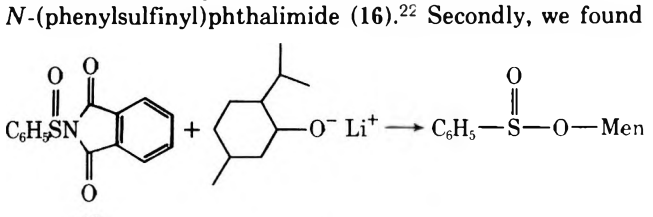
In these reactions considerable quantities of starting material remained unaccounted for. Despite our ability to regain 94% of a sample of diphenyl sulfoxide which had been treated for an extended period of time with lithium diphenylcuprate (Table III), it proved impossible to isolate the sulfoxide in greater than 50% yield by the reaction of **5** with lithium diphenylcuprate. The only other organic material isolated in this reaction was biphenyl, a compound often found as a contaminant in the phenyllithium used in the reaction. *n*-Butyl phenyl sulfoxide was reduced by excess lithium di-*n*-butylcuprate at −40 °C to the corresponding sulfide (Table III). This may account in part for the absence of sulfoxide in the reaction of **5** with lithium di-*n*-butylcuprate (Table II).[18]

The low yield of methyl phenyl sulfoxide in the reaction of *p*-tolyl phenylsulfinate (**4**, $R^1 = C_6H_5$; $R^2 = p\text{-}CH_3C_6H_4$) with lithium dimethylcuprate may be due to the instability of aryloxy sulfinate esters.[19]

Stereochemistry. From the above results it has been shown that organocopper reagents give higher yields of sulfoxides on reaction with sulfinate esters. If the reactions are stereospecific, they would be the preferred reagents for the synthesis of chiral sulfoxides.

(−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate and (−)-menthyl (−)-(*S*)-benzenesulfinate were treated with lithium organocuprates. The reactions were found to proceed with inversion of configuration at sulfur to give sulfoxides of high optical purity (Table IV).

There are two noteworthy features to our modified procedures for the preparation of optically active sulfoxides. The first is that we were able to effect the preparation of menthyl benzenesulfinate by the reaction of lithium menthoxide with *N*-(phenylsulfinyl)phthalimide (**16**).[22] Secondly, we found



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that high-pressure liquid chromatography (HPLC) is the method of choice in the purification of these sulfoxides, giving compounds of high purity with little loss of material.

In conclusion, the reaction of organocopper lithium reagents with menthyl sulfinates provides a viable route to optically active sulfoxides.

Table II. Reaction of Diorganocopper Lithium Reagents with Sulfinate Esters

	$C_6H_5S(=O)OCH_3$ (5)		$n\text{-}C_4H_9S(=O)OCH_3$ (15)[h]		6		7		$C_6H_5S(=O)OC_6H_4CH_3\text{-}p$[i]	
R_2CuLi, R	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)	Temp, °C	Products (% yield)
CH_3 (15681-48-8)[g]	0	$C_6H_5S(=O)CH_3$ (59)	0	$n\text{-}C_4H_9S(=O)CH_3$[a] (50)	0	$CH_3S(=O)(CH_2)_4OH$[b] (59)			0	$C_6H_5S(=O)CH_3$[c] (22) $C_6H_5SCH_3$[c] (53)
C_2H_5 (38297-20-0)	−78	$C_6H_5S(=O)CH_2CH_3$[d] (36)								
$n\text{-}C_4H_9$ (24406-16-4)	−40	$C_6H_5S\text{-}n\text{-}C_4H_9$[a] (36)	0	No isolable products						
			−30	$(n\text{-}C_4H_9)_2S(=O)$[c] (15)						
			−78	$(n\text{-}C_4H_9)_2S(=O)$[d] (52)						
C_6H_5 (23402-69-9)	0	$C_6H_5S(=O)C_6H_5$[e] (50)								
	−78	$C_6H_5S(=O)C_6H_5$[e] (48)	−78	$C_6H_5S\text{-}n\text{-}C_4H_9$[a] (64)	0	$C_6H_5S(=O)(CH_2)_4OH$[f] (32)	0	$C_6H_5S(=O)(CH_2)_3OH$[f] (52)		

[a] Purified by distillation. [b] Purified by preparative TLC (silica, chloroform). [c] Purified by column chromatography (silica, ethyl acetate), then Kugelrohr distillation at 100 °C (1 mmHg). [d] Purified by column chromatography (silica, ethyl acetate), distillation, then rechromatographed (dry column alumina) with benzene–pyridine (19:1) or 1,4-dioxane. [e] Purified by column chromatography (silica, hexanes then chloroform). [f] Purified by column chromatography [silica, ethyl acetate–cyclohexane (4:1), then methanol]. [g] Registry no., 673-80-3. [i] Registry no., 60270-05-5.

Table III. Reaction of Organocopper Lithium Reagents with Sulfoxides

Registry no.	Sulfoxide (1 mol)	$(R^3)_2CuLi$ R^3	Mol	Temp, °C	Time, h	Products, % yield $R^1-\overset{O}{\overset{\|}{S}}-R^3$	Others (% yield)
945-51-7	$C_6H_5\overset{O}{\overset{\|}{S}}C_6H_5$	C_6H_5	2	0	3	94	
13153-10-1	$n\text{-}C_4H_9\overset{O}{\overset{\|}{S}}C_6H_5$	$n\text{-}C_4H_9$	2	−40	1	11	$n\text{-}C_4H_9SC_6H_5$ (80)
1193-82-4	$CH_3\overset{O}{\overset{\|}{S}}C_6H_5$	CH_3	2	0	3	49[a]	$CH_3SC_6H_5$ (11) $C_6H_5\overset{O}{\overset{\|}{S}}CH_2CH_2\overset{O}{\overset{\|}{S}}C_6H_5$[a] (10) $C_6H_5SCH_2CH_2SC_6H_5$ (3)
2976-98-9	$n\text{-}C_4H_9\overset{O}{\overset{\|}{S}}CH_3$	CH_3	2	0	3	88	

[a] Isolated as sulfone.

Table IV. Synthesis of Chiral Sulfoxides

$$R^1\overset{O}{\overset{\|}{S}}\text{—OMen} + R_2{}^3CuLi \rightarrow R^1\overset{O}{\overset{\|}{S}}R^3$$

Registry no.	R^1	R^3	Yield, %	$[\alpha]_D$	$[\alpha]_D{}^{lit.}$	Optical purity, %
34513-32-1	C_6H_5	CH_3	16	+133.9°	+146°[a]	96
1517-82-4	$p\text{-}CH_3C_6H_4$	CH_3	55	+143.2°	+145.5°[b]	99
	$p\text{-}CH_3C_6H_4$	C_6H_5	59	+21.8°	+22°[a]	100

[a] Highest value in the same solvent. [b] For literature values see Experimental Section.

Experimental Section[21]

Preparation of Sulfinate Esters. Methyl phenylsulfinate (5) and methyl *n*-butylsulfinate (15) were prepared by the method of Douglass;[12] 1,2-oxathiane 2-oxide (6) and 1,2-oxathiolane 2-oxide (7) were prepared by the method of Harpp and Gleason.[13]

***p*-Tolyl Phenylsulfinate (4, $R^1 = C_6H_5$; $R^2 = p\text{-}CH_3C_6H_4$).** *p*-Cresol (2.16 g, 2.0 mmol) was added to a stirred suspension of sodium hydride [0.824 g of a 58% suspension in paraffin oil (2.0 mmol) in pentane (100 ml)]. The salt was washed well (pentane), then suspended in carbon tetrachloride. Phenyl sulfinylphthalimide (16,[22] 5.42 g, 2.0 mmol) was added and the mixture was stirred for 1 h. The mixture was filtered and the solvent removed to give *p*-tolyl phenylsulfinate as a colorless oil (4.30 g, 93%) pure by TLC (silica, benzene R_f 0.6); NMR ($CDCl_3$) gave signals at δ 8.8–7.5 (multiplet, 5 H), 7.3 (singlet, 4 H), and 2.22 (singlet, 3 H). The compound decomposed exothermically to give a red polymeric tar when distillation was attempted; decomposition also occurred when the compound was stored overnight at −20 °C.

Preparation of Grignard Reagents. Stock solutions of methylmagnesium iodide, ethylmagnesium bromide (in ether), and phenylmagnesium bromide (in ether–tetrahydrofuran, 50:50) were prepared in the usual manner. They were standardized by addition of the solution (1 ml) to a solution of iodine (4 ml) in benzene (100 ml). After stirring with water (50 ml), excess iodine was titrated with 0.1 N sodium thiosulfate. After standardization of the iodine solution the concentration of organomagnesium compound was calculated.

Reaction of Grignard Reagents with Sulfinate Esters. The sulfinate ester (5 g) in anhydrous ether (50 ml) was placed in a 500-ml three-necked flask fitted with a dropping funnel, a mercury sealed stirrer, and a condenser with a drying tube attached. The stirred solution was cooled to 5–10 °C, then the Grignard reagent was added dropwise. When addition was complete the stirred mixture was refluxed (50–60 °C) for 5 h and then cooled in an ice bath and hydrolyzed with water (100 ml, C_6H_5MgBr) or saturated aqueous sodium thiosulfate solution (C_2H_5MgBr and CH_3MgBr). The magnesium salts were removed by filtration or centrifugation, and the aqueous layer was extracted several times with chloroform–tetrahydrofuran (1:1). The organic extracts were dried ($MgSO_4$) and the solvent was flash evaporated. The resulting oil was analyzed as indicated in Table I. Products were characterized by comparison with authentic samples.

Preparation of Organocopper Reagents.[23] Purified cuprous iodide[23,24] (1.9 g, 10 mmol) was placed in a three-necked flask fitted with two dropping funnels with equilibrating side arm, and a magnetic stirrer. The apparatus was flame dried under a stream of prepurified nitrogen, anhydrous ether (10 ml) was added, and the stirred suspension was cooled to the required temperature. Two equivalents of alkyl- or aryllithium were then added dropwise, at 0 °C for methyl- or phenyllithium and at −30 °C for ethyl- or *n*-butyllithium.

Reaction of Lithium Organocopper Reagents with Sulfinate Esters. The sulfinate (10 mmol) in anhydrous ether (40 ml) was added dropwise to the organocopper reagent under a stream of prepurified nitrogen. The mixture was stirred (~15 min) and then hydrolyzed with saturated aqueous ammonium chloride (50 ml). After stirring for 15 min at room temperature, the mixture was filtered and both the copper salts and the aqueous layer were washed well with chloroform–tetrahydrofuran (1:1). The organic extracts were dried ($MgSO_4$) and evaporated to give an oil that was worked up as indicated in Table II. All products were identified by comparison with authentic samples.

Synthesis of Sulfides. *n*-Butyl methyl sulfide, diphenyl sulfide, and methyl phenyl sulfide were all available from commercial sources. Ethyl phenyl sulfide, ethyl propan-3-ol sulfide, butan-4-ol ethyl sulfide, phenyl propan-3-ol sulfide, and butan-4-ol phenyl sulfide were prepared by the method of McMurdy and Prager.[25]

Di-*n*-butyl sulfide was prepared by reduction of the sulfoxide with sodium bisulfite.[26] *n*-Butyl phenyl sulfide and butan-4-ol methyl sulfide were prepared by slight modifications of the method of Windus and Shildneck.[27] Phenyl 1-phenylbutan-4-ol sulfide (10d) was prepared by the method of Lehto and Shirley.[28] All sulfides were pure by TLC and gave NMR spectra consistent with their structures. They showed the following properties.

Di-*n*-butyl Sulfide: bp 70–72 °C (12 mm) [lit. 187 °C (1 atm),[29] 91.0–91.5 °C (10 mm)[30]]; $n^{25}D$ 1.4509 (lit. $n^{20}D$ 1.45297,[29] $n^{30}D$ 1.4532[30]).

Ethyl Phenyl Sulfide: bp 92–96 °C (0.5 mm) [lit. 123 °C (12 mm),[31] 90 °C (10 mm),[32] 98 °C (22 mm),[33] 102–104 °C (15 mm)[34]].

***n*-Butyl Phenyl Sulfide:** bp 120–122 °C (18 mm) [lit. 117 °C (15 mm),[33] 78–83 °C (2.3 mm),[35] 123–129 °C (25 mm)[36]], $n^{25}D$ 1.5423 [lit. $n^{21}D$ 1.5472,[33] $n^{28}D$ 1.5432,[35] $n^{25}D$ 1.5312[36]].

Ethyl Propan-3-ol Sulfide (11a): bp 132 °C (15 mm) [lit. 85–86 °C (5 mm)[25]]; ir ν_{max} (film) 3340, 2910, 2810 and 1060 cm^{-1}; MS *m/e* 120 (P^+) and 87 ($CH_3CH_2SCH_2^+$; base peak). Anal. Calcd for

$C_5H_{12}OS$: C, 50.00; H, 10.00, S, 26.66. Found: C, 50.21; H, 10.21; S, 26.47.

Phenyl Propan-3-ol Sulfide (11b): bp 105 °C (0.1 mm) [lit. 134–135 °C (2 mm)[37], 155–159 °C (8 mm);[38] ir ν_{max} (film) 3350, 2940, 2880, 1060, and 1030 cm^{-1}; MS *m/e* 168 (P^+), 150 ($P^+ - H_2O$), 123 ($C_6H_5SCH_2^+$), 110 ($C_6H_5H^+$), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$). Anal. Calcd for $C_9H_{12}OS$: C, 64.28; H, 7.14; S, 19.04. Found: C, 64.53; H, 7.19; S, 18.78.

Butan-4-ol Methyl Sulfide (10a): bp 103–105 °C (10 mm) [lit. 81–85 °C (3 mm)[25]; ir ν_{max} (film) 3340, 2910, 2850, 1055, and 1030 cm^{-1}; MS *m/e* 120 (P^+), 102 ($P^+ - H_2O$), and 61 ($CH_3SCH_2^+$).

Butan-4-ol Ethyl Sulfide (10b): bp 132 °C (15 mm), 71–73 °C (0.75 mm) [lit. 81–85 °C (3 mm)[25]; ir ν_{max} (film) 3340, 2910, 2810, and 1060 cm^{-1}; MS *m/e* 134 (P^+), 87 ($CH_3CH_2SCH{=}CH^+$), and 75 ($CH_3CH_2SCH_2^+$). Anal. Calcd for $C_6H_{14}OS$: C, 53.73; H, 10.44; S, 23.88. Found: C, 53.89; H, 10.36, S, 23.61.

Butan-4-ol Phenyl Sulfide (10c): bp 112 °C (0.1 mm) [lit. 150 °C (6 mm),[39] needles, mp 24 °C [40]; ir ν_{max} (film) 3380, 2950, 2870, 1060, and 1030 cm^{-1}; MS *m/e* 182 (P^+), 164 ($P^+ - H_2O$), 123 ($C_6H_5SCH_2^+$), 110 ($C_6H_5SH^+$, base peak), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$). Anal. Calcd for $C_{10}H_{14}OS$: C, 70.07; H, 6.58; S, 23.35. Found: C, 70.24; H, 6.67; S, 23.36.

Phenyl 1-Phenylbutan-4-ol Sulfide (10d): bp 190 °C (1 mm), 180 °C (0.5 mm); ir ν_{max} (film) 3350, 3050, 3030, 2940, 2870, 1060, and 1030 cm^{-1}; MS *m/e* 258 (P^+), 240 ($P^+ - H_2O$), 199 ($C_6H_5SCHC_6H_5^+$), 149 ($C_6H_5CHCH_2CH_2CH_2OH^+$), 131 ($CH_2{=}CHCH_2CHC_6H_5^+$, base peak), 117 ($CH_2{=}CHC_6H_5^+$), 110 ($C_6H_5SH^+$), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$). Anal. Calcd for $C_{16}H_{18}OS$: C, 74.41; H, 6.97; S, 12.40. Found: C, 74.14; H, 6.94; S, 12.70.

Synthesis of Sulfoxides. Di-*n*-butyl sulfoxide was commercially available. All other sulfoxides were identified by comparison (TLC, VPC, NMR, ir) with authentic samples prepared by oxidation of the corresponding sulfide with sodium metaperiodate ($NaIO_4$)[41] or *m*-chloroperbenzoic acid. They showed the following properties.

***n*-Butyl Methyl Sulfoxide:** bp 101 °C (8 mm), $n^{25}D$ 1.4679.

Methyl Phenyl Sulfoxide: bp 95–97 °C (0.1 mm) [lit. 78–79 °C (0.1 mm),[41] 115 °C (2 mm)[42], $n^{25}D$ 1.5762 (lit. $n^{25}D$ 1.5880[42]).

Ethyl Phenyl Sulfoxide: bp 80–82 °C (0.15 mm) [lit. 146 °C (13 mm)[43], $n^{22}D$ 1.4679.

n-Butyl Phenyl Sulfoxide: bp 99–99.5 °C (0.4 mm), $n^{26.5}D$ 1.5433, $d^{26.5}$ 1.0652, $[R_L]D^{exp}$ 53.99 (calcd, 53.88).

Methyl Propan-3-ol Sulfoxide (8a): decomposes before boiling; NMR (CCl_4) δ ~2.00 (m, 2 H, CCH_2C), 2.20 (s, 3 H, $CH_3S{=}O$), 2.7 (m, 2 H, $CH_2S{=}O$), 3.90 (m, 2 H, CH_2O–), and 4.20 (s, 1 H, OH).

Phenyl Propan-3-ol Sulfoxide (8b): decomposition before boiling; MS *m/e* 184 (P^+), 166 ($P^+ - H_2O$), 126 ($C_6H_5OH^+$, base peak), 107 [$O{=}S(CH_2)_3OH^+$], 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$); ir ν_{max} (film) 3340, 2900, 2815, and 1010 cm^{-1}. Anal. Calcd for $C_9H_{12}O_2S$: C, 58.69; H, 6.52; S, 17.39. Found: C, 58.01, H, 6.64; S, 16.87.

Butan-4-ol Methyl Sulfoxide (9a): decomposes before boiling; MS *m/e* 136 (P^+), 119 ($P^+ - OH$), and 64 ($P^+ - CH_3SOH$); NMR ($CDCl_3$) δ 1.68 (m, 4 H, $-CH_2CH_2-$), 2.60 (s, 3 H, $CH_3S{=}O$), 2.80 (t, 2 H, $-CH_2S{=}O$), 3.50 (t, 2 H, $-CH_2O-$), and 4.25 (s, 1 H, OH).

Butan-4-ol Phenyl Sulfoxide (9b): decomposes before boiling; MS *m/e* 198 (P^+), 180 ($P^+ - H_2O$), 166 ($C_6H_5SCH{=}CH_2^+$), 107 ($HOCH_2CH_2CH_2CH_2SH_2^+$, base peak), 91 ($C_7H_7^+$), and 77 ($C_6H_5^+$); ir ν_{max} (film) 3340, 2900, 2815, 1040, and 1010 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_2S$: C, 60.60; H, 7.07; S, 16.16. Found: C, 60.84; H, 7.24; S, 15.86.

Preparation of Methyl Phenylsulfenate (17, $R^1 = C_6H_6$; $R^2 = CH_3$). Freshly prepared phenylsulfenyl chloride, bp 43–48 °C (1.5 mm) [lit.[44] 58–60 °C (3 mm)] (19.8 g, 0.14 mol), was added to a solution of sodium methoxide [prepared from 3.5 g, (0.15 g-atom) of sodium] in methanol (200 ml) at 0 °C. The mixture was allowed to warm up to room temperature, filtered, and evaporated to give methyl phenylsulfenate (5.3 g), pure by VPC: bp 95 °C (6 mm) [lit. 88–89 °C (0.4 mm)[44]]; $n^{26}D$ 1.5508; d^{26} 1.1081; $[R_L]D^{exp}$ 40.75 (calcd, 40.89).

Reaction of Methyl Phenylsulfenate (17, $R^1 = C_6H_5$; $R^2 = CH_3$) with Lithium Dimethylcuprate. The sulfenate ester (1.4 g, 10 mmol) was treated with lithium dimethylcuprate (20 mmol) at 0 °C for 1 h. Distillation afforded a sample of methyl phenyl sulfide (1.08 g, 87%), pure by VPC, TLC (silica, hexanes, or CCl_4), identical with an authentic sample (NMR, ir).

Synthesis of Chiral Sulfoxides. Menthyl Sulfinate Esters. (−)-Menthyl (−)-(*S*)-benzenesulfinate was prepared from lithium menthoxide [obtained from menthol (15.6 g, 100 mmol) and *n*-butyllithium] and *N*-(phenylsulfinyl)phthalimide (**16**,[22] 27.1 g, 100 mmol) in a similar manner to that described for *p*-tolyl phenylsulfinate. The resultant oil (20 g), containing one major component (TLC, silica, chloroform R_f 0.77), was purified by filtration through silica (60 g), followed by crystallization from methanol (−78 °C) to give a colorless solid (4.0 g). This was recrystallized twice from pentane to give (−)-menthyl (−)-(*S*)-benzenesulfinate as colorless needles, mp 51–52 °C (lit.[47] 49–51 °C), $[\alpha]D$ −205.5° (*c* 2.4, acetone) (lit.[47] −205.5°).

(−)-Menthyl (−)-(*S*)-*p*-toluenesulfinate was prepared by the method of Estep and Tavares[48] (71%), mp 102–104.5 °C (lit.[48] 108–109 °C), $[\alpha]D$ −210° (c 2.0, acetone) (lit.[48] −210°).

Chiral Sulfoxides. The sulfinate ester was treated with the lithium organocuprate as described previously. The resulting organic materials were chromatographed on silica to give several fractions that were monitored by TLC and VPC. Methyl phenyl (+)-(*R*)-sulfoxide was purified by Kugelrohr distillation, preparative TLC (silica, ethyl acetate), and a final Kugelrohr distillation to give material 95.2% pure (VPC), $[\alpha]D$ +133.9° (lit.[45] 128–149°).

The *p*-tolyl sulfoxides were purified by HPLC. After the initial separation on a silica column to remove the starting material and menthol, the sulfoxide fraction was separated from high molecular weight material on a μ-styragel column (tetrahydrofuran as eluent). Reversed phase chromatography on a C_{18}-Porasil column (3:1 tetrahydrofuran–water as eluent) gave methyl *p*-tolyl (+)-(*R*)-sulfoxide[10] and phenyl *p*-tolyl (+)-(*R*)-sulfoxide,[10] pure by TLC and NMR.

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Registry No.—**8a**, 15163-71-0; **8b**, 49639-22-7; **9a**, 60270-06-6; **9b**, 49639-23-8; **10a**, 20582-85-8; **10b**, 18721-62-5; **10c**, 5851-37-6; **10d**, 60270-07-7; **11a**, 18721-61-4; **11b**, 24536-40-1; **16**, 40167-15-5; **17** ($R^1 = C_6H_5$; $R^2 = CH_3$), 26905-22-6; *p*-cresol, 106-44-5; CH_3Li, 917-54-4; C_2H_5Li, 811-49-4; n-C_4H_9Li, 109-72-8; C_6H_5Li, 591-51-5; cuprous iodide, 7681-65-4; di-*n*-butyl sulfide, 544-40-1; ethyl phenyl sulfide, 622-38-8; *n*-butyl phenyl sulfide, 1126-80-3; ethyl phenyl sulfoxide, 4170-80-3; phenylsulfinyl chloride, 931-59-9; lithium menthoxide, 25531-51-5; methyl phenyl (+)-(*R*)-sulfoxide, 4850-71-9; methyl *p*-tolyl (+)-(*R*)-sulfoxide, 1519-39-7; phenyl *p*-tolyl (+)-(*R*)-sulfoxide, 16491-20-6.

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$$R^1SOR^2 \xrightarrow{(R^3)_2CuLi} R^1SOR^3 \xrightarrow{(R^3)_2CuLi} R^1SR^3$$

17

then react with the organometallic reagent. We are able to show that methyl phenylsulfenate (**17**, $R^1 = C_6H_5$; $R^2 = CH_3$) reacts rapidly and smoothly with $(CH_3)_2CuLi$ to give methyl phenyl sulfide in good yield. This, however, does not allow us to explain the anomous reactions that produce *n*-butyl phenyl sulfide.
(19) Phenyl *p*-tolylsulfinate ester could be prepared in good yield, as a colorless liquid which decomposed on standing overnight (at −20 °C) to give a brown tar. This observation is corroborated by Baarschers and Krupay, who attempted to obtain phenyl methylsulfinate (**4**, $R^1 = CH_3$; $R^2 = C_6H_5$).[20]
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Enzymic-Like Aromatic Oxidations. Metal-Catalyzed Peracetic Acid Oxidation of Phenol and Catechol to *cis,cis*-Muconic Acid[1]

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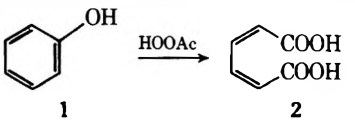
Phenol is oxidized to *cis,cis*-muconic acid (CCMA) by peracetic acid in the presence of catalytic quantities of Cu(II) and Fe(III). No CCMA is formed in the absence of these metals or in the presence of other specified metals. The yield of CCMA depends on the kind and quantity of metal ion used, being higher for oxidations with Fe(III) than Cu(II). Trace quantities of Fe(III) are effective at catalyzing the formation of CCMA. Catechol has been identified as an intermediate in the reaction. Kinetic studies indicate that the rate of disappearance of phenol is independent of metal and first order in both phenol and peracetic acid. The results are accommodated by a scheme which involves hydroxylation of phenol to give a mixture of catechol and *p*-hydroquinone followed by the formation of a metal–catechol complex which is rapidly and cleanly oxidized to CCMA.

In 1931 Boeseken and Engelberts[2] reported the oxidative cleavage of phenol (1) to *cis,cis*-muconic acid (CCMA, 2)[3]



1 2

using peracetic acid (HOOAc). The carbon–carbon bond adjacent to the OH is cleaved leaving the stereochemistry about the two remaining double bonds unchanged. This reaction represents a rare example of a specific, nonenzymatic oxidative cleavage of an aromatic system. Other workers have since reported the peracetic acid oxidation of catechol[4] (3) to CCMA

Table I. Fe(III)-Catalyzed HOOAc Oxidation of Phenol[a]

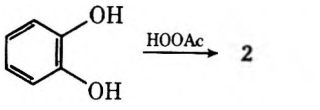
$[Phenol]_0/[Fe(III)]^b$	Yield of CCMA, %
100	40
1 000	40
20 000	37
100 000	18
300 000	12
600 000	9
1 000 000	<7[c]

[a] These results are for oxidations carried out in 20 wt % HOOAc. The same results are obtained in 10 wt % HOOAc. [b] $[Phenol]_0 = 0.92$ M. [c] Limit of detectability.

Table II. Cu(II)-Catalyzed Peracetic Acid Oxidation of Phenol[a]

$[Phenol]_0/[Cu(II)]^b$	Yield of CCMA, %
100	24
1 000	24
2 000	18
3 000	11
5 000	<7[c]

[a,b,c] See corresponding footnotes in Table I.



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and the oxidation of other derivatives of phenol,[5] such as *p*-cresol, *p*-bromophenol, and *p*-chlorophenol, to the corresponding β-substituted muconic acids. In addition, catechol has been reportedly oxidized to *cis,cis*-muconic acid with molecular oxygen activated by copper(I) chloride.[6]

In a well-known enzymatic reaction, catechol is oxidized to CCMA by oxygen in the presence of pyrocatechase.[7] Our interest in this enzymatic oxygenation involving the iron-containing enzyme pyrocatechase led us to study the peracetic acid oxidation of phenol in the presence of Fe(III) and other metal ions. We were also particularly interested in the effects of copper since it is found in the enzyme phenolase which catalyzes the hydroxylation of phenol to catechol and also the oxidation of catechol to *o*-benzoquinone.[8]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on a Perkin-Elmer R12B and chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane: s = singlet, d = doublet, m = multiplet, etc. Mass spectra were recorded on a AEI MS-9 mass spectrometer, direct inlet, 70 eV. A Varian Model 635 visible–uv recording spectrophotometer was used to obtain uv spectra. VPC work was carried out with a Varian Aerograph Model 920 chromatograph (60 ml He/min). Atomic absorption work was carried out with a Perkin-Elmer 103 instrument.

Materials. The phenol used was Mallinckrodt analytical reagent or MCB, reagent. The acetic acid was Matheson Scientific, reagent. The peracetic acid was obtained from FMC Corp. as a 40 wt % solution in acetic acid solvent. Catechol was supplied by Eastman. The ferric acetate (purified powder basic) was obtained from City Chemical Corp. The cupric acetate monohydrate (reagent grade) was supplied by MCB and was found to contain 0.0007 wt % Fe as determined by atomic absorption analysis. All other metals employed in reactions were reagent grade and used as received.

General Procedure for Metal-Catalyzed Oxidations of Phenol in 10 and 20% Peracetic Acid. With the exception of varying the kind and quantity of metal used, the same procedure was followed for all phenol oxidations in 10 or 20% peracetic acid. The metal salt was usually directly weighed out for use in a reaction. However, in oxidations where $[phenol]_0/[metal]$ was > 1000 [in Cu(II) and Fe(III) oxidations, see Tables I and II], aliquots of standard solutions of the metal salt in acetic acid were used in order to accurately dispense the required quantity of metal.

The following procedure for the Fe(III)-catalyzed peracetic acid oxidation of phenol is typical of those oxidations carried out in 20% peracetic acid. Phenol (5.00 g, 0.0532 mol), glacial acetic acid (20.0 g), and basic ferric acetate (0.0104 g, 0.0000544 mol) were placed in a glass-stoppered 125-ml Erlenmeyer flask and stirred magnetically with a Teflon-coated stirring bar. After the ferric acetate was dissolved, a mixture of 10.5 g of acetic acid and 30.5 g of 40% peracetic acid (12.2 g, 0.161 mol HOOAc) was added from an addition funnel over a period of 5 min to the magnetically stirred phenol–Fe(III) solution. White *cis,cis*-muconic acid (CCMA) precipitated from solution as the reaction proceeded. After stirring at 25 °C for 5 days, the reaction mixture was cooled to about 10 °C and the product was collected by suction filtration, washed with 1 ml of cold water, and air dried to give 2.47 g of CCMA, mp 180 °C dec (lit.[9] 184 °C). The uv spectrum [λ_{max} (95% EtOH) 257 nm (ϵ_{max} 21 000)] of the product was identical with that previously reported[7] for CCMA. An NMR spectrum (CCl_4) of the dimethyl ester, dimethyl *cis,cis*-muconate, was identical with that previously reported[10] and showed the following absorptions: δ 3.68 (s, 6, carbomethoxy), 5.9 (m, 2, olefinic α to carbomethoxy), 7.9 (m, 2, olefinic β to carbomethoxy). The absence of absorptions at δ 7.28 and 6.15 indicated that no *trans,trans*-muconic acid was present in the product.[10] Purification of the product with aqueous sodium bicarbonate did not change the yield. The yield was corrected for the quantity of CCMA which was soluble under the reaction conditions. The solubility of CCMA was determined to be 9 mg/ml under conditions approximating those of the reaction.[11] Since the reaction volume was 59 ml, the observed yield was corrected by adding to it 0.52 g (7%) to account for the quantity of CCMA remaining in solution. The total corrected yield of CCMA is then calculated to be 2.99 g (40%). A corrected yield of 40% was also obtained in a Fe(III)-catalyzed oxidation in 10% HOOAc.

Oxidations carried out in the absence of metal or with the following metals gave no visible product: Ni(II), Co(II), V(0), Ag(I), Zn(II), Fe(II), Na(I), Hg(II), Cr(III), Mn(II). The reaction mixtures became very dark, essentially black, after 5 days at room temperature but no CCMA precipitated from solution in either 10 or 20% HOOAc oxidations. These results limit the yield of CCMA to <7%, which corresponds to the solubility of CCMA in 20% HOOAc solutions.

Stability of Fe(III)–HOOAc Solutions. The reaction was carried out as described above for oxidations with 20% HOOAc, except that no phenol was added. Basic ferric acetate (0.0101 g, 0.0000529 mol) was used as the source of Fe(III). Samples of reaction mixture (0.5–0.7 g) were withdrawn periodically, accurately weighed, and iodometrically analyzed using a 0.1 M standardized sodium thiosulfate solution and starch indicator. The wt % HOOAc was calculated as a function of time and found to be the following: 22.0 ± 0.5% (0 day), 21.5 (4 days), 20.7 (6 days), 20.0 (8 days), 18.0 (13 days), 16.7 (18 days).

Metal-Catalyzed Peracetic Acid Oxidations of Catechol. The following Fe(III)-catalyzed oxidation illustrates the general procedure for catechol oxidations. To a magnetically stirred solution of 10.5 g of HOAc, 30.5 g of 40% HOOAc (12.2 g, 0.161 mol HOOAc), and 0.0106 g (0.0000554 mol) of ferric acetate in a glass-stoppered 125-ml Erlenmeyer flask was slowly added, dropwise over a period of 7–9 h from a micrometer addition funnel, a solution of 5.90 g (0.0537 mol) of catechol in 20.0 g of acetic acid. The entire reaction was carried out under a nitrogen atmosphere over a 5-day period. The CCMA precipitated from solution as the reaction proceeded. The product was isolated in the same manner described above for phenol oxidations yielding 3.83 g of CCMA. Purification with aqueous $NaHCO_3$ did not change the yield. The observed yield was corrected by adding 0.52 g for the solubility of CCMA in the reaction medium as previously discussed. The total corrected yield of CCMA was then calculated to be 4.35 g (58%). After comparing a number of runs, it was found that the yield depended on the rate of catechol addition and varied from 45 to 65%. Too fast or too slow an addition cut the yield, with the optimum addition time being 7–9 h. Since it was difficult to reproduce the addition rate, the yield of CCMA varied from run to run.

Similar results were obtained with Cu(II) as the catalyst; however, the yields of CCMA were lower and varied from 20 to 40%.

A small yield (<0.2 g) of CCMA was obtained in an oxidation of catechol carried out in the absence of metal.

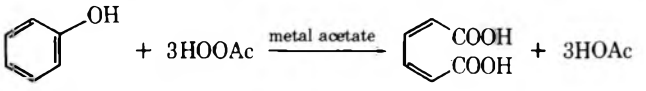
Intermediates in Phenol Oxidations. The procedure described above for phenol oxidations in 20% HOOAc was followed. The following analysis was carried out for oxidations with Cu(II), Fe(III), and no metal. A 5-ml aliquot of reaction mixture was removed after ap-

proximately 20 h of reaction and was treated with aqueous sodium sulfite to reduce any peroxides present.[12] Sufficient saturated, aqueous sodium bicarbonate was added to neutralize the solution, after which it was continuously extracted with ether for 24 h. The ether layer was dried with magnesium sulfate and the solvent evaporated, leaving an oily residue which was dissolved in a small amount of ether and analyzed by VPC. A 3% SE-30 on 100–120 Varaport 30, 5 ft × 0.25 in. stainless steel column was used. The temperature was varied. The retention times of catechol and *p*-hydroquinone were 2.2 and 3.6 min, respectively, at 125 °C. Both catechol and *p*-hydroquinone were identified by their retention times and coinjection with authentic samples. In one analysis of an uncatalyzed oxidation, the catechol peak was collected by VPC and a mass spectrum recorded which was identical with that of an authentic sample.

Kinetic Method. The disappearance of phenol was followed by VPC for oxidations with Fe(III), Cu(II), and no metal at 25 °C in 20% peracetic acid according to the general procedure previously described. The molar ratio of phenol to metal catalyst was 1000 for Fe(III) and 100 for Cu(II) oxidations. The VPC method consisted of quenching 5-ml aliquots of reaction mixture at various times by treatment with aqueous sodium sulfite to reduce all peroxides present. After sufficient aqueous sodium bicarbonate was added to neutralize the solution, it was continuously extracted with ether for at least 24 h. The ether layer was dried with magnesium sulfate and the solution evaporated. An accurately weighed sample of naphthalene was added to the residue as an internal standard, and the mixture was dissolved in a few milliliters of ether. A sample was analyzed by VPC (column 3% SE-30 on 100–120 Varaport 30, 5 ft × 0.25 in. stainless steel, T = 85 °C, retention time of phenol 2.0 min, retention time of naphthalene 5.8 min), and the areas of phenol and naphthalene were determined. VPC analysis of a standard solution containing equimolar quantities of phenol and naphthalene indicated that the ratio of the area of hydrocarbon to phenol was 1.21:1. The concentration of phenol as a function of time was calculated from the VPC data, and a plot of $[\text{phenol}]^{-1}$ vs. time was made for each run. Second-order rate constants were obtained from the slopes of the best straight lines through the data points.

Results

The balanced reaction (below) for the oxidation of phenol to CCMA requires 3 mol of peracetic acid per mole of phenol.



Reactions were carried out in the presence of various metal acetate salts at room temperature in 10 or 20 wt % peracetic acid in acetic acid solvent employing stoichiometric quantities of reactants. The concentrations were 0.46 M phenol, 1.39 M HOOAc in 10% HOOAc runs, and 0.92 M phenol, 2.78 M HOOAc in 20% HOOAc runs. The metal and the quantity used were varied. Reactions were carried out for 5 days at 25 °C; less than 2% phenol remained after this time in oxidations carried out in 20% peracetic acid.

Contrary to the earlier reports of Boeseken and Engelberts[2] and others,[5] we have found that CCMA is not formed in the absence of metal. The oxidation of phenol with peracetic acid leads to a complex mixture of products resulting from the oxidative degradation of quinones and polyhydroxylated aromatics formed during the course of the reaction. Two metal ions, Fe(III) and Cu(II), have been found to effectively promote the formation of CCMA. After examining our data, it is reasonable to conclude that the results of earlier workers were due to trace metal impurities, probably Fe, in their chemicals or equipment.

The results of oxidizing phenol with peracetic acid in the presence of Fe(III) are summarized in Table I. It is clear from these results that very small quantities of Fe(III) are effective in promoting the formation of CCMA, and that the yield of CCMA depends on the quantity of Fe(III) present. A maximum yield of 40% CCMA is obtained when the molar ratio of phenol to Fe(III) is 1000. The yield does not increase when the amount of Fe(III) is increased to a ratio of 100:1. As the molar ratio of phenol to Fe(III) is increased, and, hence, the quantity of Fe(III) decreased, the yield of CCMA decreases and essentially goes to zero at ratios greater than 1 000 000:1. Fe(0) was also found to catalyze the formation of CCMA. A yield of 36% CCMA was obtained in a reaction in which iron filings were used as the catalyst; the molar ratio of phenol to Fe(0) was 100. An attempted oxidation with Fe(II) led to the violent decomposition of the peracetic acid probably via a free-radical process.

Ferric acetate was used as the source of Fe(III) in all reactions listed in Table I. The same results were obtained using ferric chloride, which indicates that the reaction is independent of the source of Fe(III).

The rate of decomposition of peracetic acid was measured in the absence of phenol to determine if the Fe(III)–HOOAc solutions were stable. The conditions were identical with those employed in runs where the ratio of phenol to Fe(III) was 1000 except the phenol was not included. The extent of decomposition was found to be less than 2 wt % over a period of 5 days indicating the Fe(III)–HOOAc mixtures to be relatively stable in the absence of phenol.

Reactions carried out under nitrogen gave the same results indicating that the presence of oxygen does not affect the course of the reaction.

The results summarized in Table II indicate that Cu(II) is less effective than Fe(III) in promoting the formation of CCMA. A maximum yield of 24% is obtained when the molar ratio of $[\text{phenol}]_0/[\text{Cu(II)}]$ is 100. As with Fe(III), the yield of CCMA is dependent on the concentration of Cu(II), decreasing to essentially zero when the phenol to Cu(II) ratio is 5000. The phenol/Cu(II) ratio was not decreased below 100, since higher Cu(II) concentrations lead to appreciable decomposition of peracetic acid.

In order to determine if the results with Cu(II) were indeed due to Cu(II) and not Fe(III) impurities, the cupric acetate employed in the Cu(II) oxidations was analyzed by atomic absorption and found to contain 0.0007 wt % Fe. This quantity of iron would give a phenol/Fe ratio of 3.8×10^7 in a Cu(II)-catalyzed run in which the phenol/Cu(II) ratio was 1000. Hence, there is insufficient Fe impurity in the cupric acetate to account for the results in Table II, confirming that Cu(II) is the catalyst.

Catechol and *p*-hydroquinone were found to be present in metal-catalyzed reactions as well as in reactions containing no metal. In all cases, these compounds were present in very small quantities (<1% of total material balance) throughout the oxidations. Both were identified and isolated from reaction mixtures by VPC. The relative quantities of these substances detected under various conditions were as follows: no metal, *p*-hydroquinone ≃ catechol; Cu(II), *p*-hydroquinone > catechol; Fe(III), *p*-hydroquinone and no catechol. The absence of detectable quantities of catechol in Fe(III) oxidations is particularly noteworthy.

Kinetic studies indicate that the rate of disappearance of phenol is independent of metal (Figure 1); i.e., *phenol disappears at the same rate whether metal is present or not.* A second-order plot of the data[13] gives a good straight line indicating that the reaction is second order overall, first order each in phenol and peracetic acid.[14] The measured rate constant for the disappearance of phenol at 25 °C is $3.4 \pm 0.4 \times 10^{-2}\ M^{-1}\ h^{-1}$.

We have oxidized catechol to CCMA with peracetic acid in the presence of Fe(III) in 50–60% yield.

$$3 + 2\text{HOOAc} \xrightarrow{\text{Fe(III)}} 2 + 2\text{HOAc}$$

Very small amounts (<3%) of CCMA were formed when the oxidation was carried out in the absence of Fe(III). To carry out a successful oxidation, it is essential that the catechol be introduced to a mixture of metal and peracetic acid in such

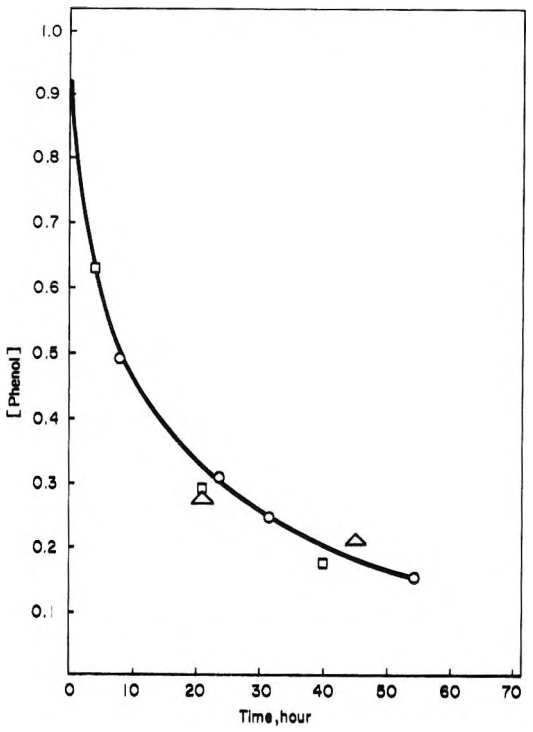
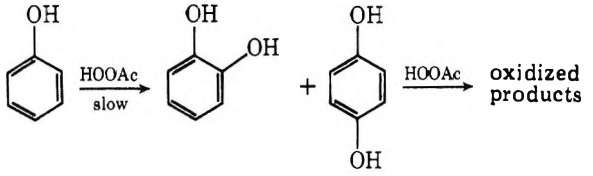


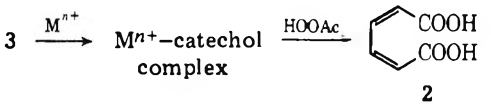
Figure 1. Plot of [phenol] vs. time for oxidations of phenol with peracetic acid in the presence of Fe(III), ○; Cu(II), □; and no metal, △. These data represent 84% reaction.

a manner that it is always kept at a very low concentration to simulate the conditions under which the catechol is produced and converted to CCMA in the phenol oxidations. Mixing all the reactants at once leads to a black solution and no CCMA.

Discussion

Our results lead us to postulate the following scheme for the metal-catalyzed peracetic acid oxidation of phenol.





The first step involves hydroxylation of phenol to give a mixture of catechol (3) and *p*-hydroquinone (4). Both of these compounds were identified in reaction mixtures. The first step is rate determining and independent of metal as indicated by the kinetic results and supported by the observation that 3 and 4 are found in uncatalyzed as well as catalyzed reactions. In the presence of Fe(III) or Cu(II), it is proposed that catechol forms a complex with the metal which is rapidly and cleanly oxidized to CCMA. The observation that small quantities of metal give relatively large amounts of CCMA indicates the catalytic nature of the reaction and further supports the idea that the oxidation of the complex is relatively fast.

In the absence of Fe(III) or Cu(II), and as a competing reaction in the presence of these metals, catechol and *p*-hydroquinone are oxidized and degraded to give products other than CCMA. For example, 3 and 4 may be oxidized to quinones or further hydroxylated to give polyhydroxylated aromatics and then degraded as observed by other workers[15] under similar conditions. The formation of the red molecular complex phenoquinone[16] has been observed in our reaction. It results from the oxidation of *p*-hydroquinone to *p*-benzoquinone which then combines reversibly with 2 mol of phenol to form the complex. Phenoquinone is highly dissociated under our conditions, and we estimate that no more than 1% of the phenol is tied up in this complex at any time during the reaction. The stepwise formation of *p*-benzoquinone and phenoquinone could be observed in the oxidation of phenol by a change in the color of the reaction mixture from clear to yellow (*p*-benzoquinone) and then to red (phenoquinone) as the reaction proceeded.

The hydroxylation of phenol and other activated aromatic compounds employing reagents such as H_2O_2–$AlCl_3$,[17] H_2O_2–HF,[15] and CF_3CO_3H[18,19] have been reported. Vesely and Schmerling obtained a mixture of 56% *p*-hydroquinone and 44% catechol on hydroxylating phenol with H_2O_2–HF at room temperature. In our reaction only catechol is oxidized to CCMA, and, hence, the maximum yield of CCMA that we could expect, using the results of Vesely and Schmerling as a model for our first step, is about 44% of theoretical. Thus our yields of 24 and 40%, based on phenol, actually correspond to 55 and 91% based on the maximum amount of catechol that could form in the first step using the data of Vesely and Schmerling for the hydroxylation of phenol with H_2O_2–HF.

If the oxidation of a catechol–metal complex leads to CCMA, then it should be possible to oxidize catechol to CCMA in the presence of Fe(III) and Cu(II). As reported earlier in this paper, we have oxidized catechol to CCMA with peracetic acid in the presence of Fe(III) and Cu(II).

The postulation of a metal–catechol complex as an intermediate in the phenol oxidation is reasonable in light of the observation that phenol is not oxidized to CCMA in the absence of Fe(III) or Cu(II) in spite of the fact that catechol is formed in the absence of these metals.[22b] Thus it appears that the role of Fe(III) and Cu(II) is to provide a reaction path whereby catechol can be oxidized to CCMA with little or no side reaction. In the absence of these metals, catechol is probably oxidized to products other than CCMA since the "directing" effect of the metal is absent. This interpretation is consistent with our observation and those of Vesely and Schmerling who found that the oxidation of catechol with hydrogen peroxide leads to complex reaction mixtures containing tri- and tetrahydroxylated benzene and products derived from these polyhydroxylated aromatics.[15]

Metal–catechol complexes of the type ML^{n-2}, ML_2^{n-4}, and ML_3^{n-6} (M^{n+} = Fe^{3+} or Cu^{2+}, H_2L = catechol) are reasonable to postulate.[20-22] Cu(II) can form complexes with one or two catechol ligands whereas Fe(III) can coordinate to as many as three catechols. It is interesting to note that a relatively stable salt of CuL_2^{2-} has been prepared.[23,24]

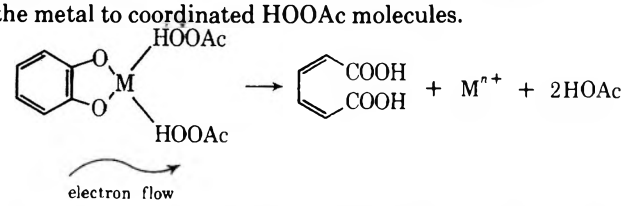
A comparison of stability constants for Fe(III) and Cu(II) complexes with catechol indicates that Fe(III) forms the more stable complex. The log of the stability constant for CuL is 13.8[21a,c,22,25] while that for FeL^+ is 20.9.[26] None of the other metals used in our studies have log stability constants for ML^{n-2} greater than about 8.[21]

Our results strongly suggest that a correlation exists between the ability of a metal to catalyze the formation of *cis,cis*-muconic acid and the stability of the metal–catechol complex. Fe(III)–catechol complexes are among the most stable metal–catechol complexes known.[21] We feel that this is the reason Fe(III) is more effective than other metals in catalyzing the formation of *cis,cis*-muconic acid. The fact that Cu(II) forms a less stable complex with catechol than Fe(III), but a more stable complex than the other metals used in this study, is consistent with it giving a yield of *cis,cis*-muconic

acid intermediate between that of Fe(III) and the other metals.

The idea that Fe(III) is more effective than Cu(II) in removing free catechol from the reaction mixture, and thus increasing the yield of *cis,cis*-muconic acid, is supported by our observation that no detectable quantity of catechol is present during the course of the reaction (as determined by VPC) in oxidations containing Fe(III) whereas detectable quantities are present in Cu(II) oxidations. If the ratio of metal–ligand complex to free metal is calculated under the reaction conditions using the formation constants cited in the previous paragraph for Cu(II) and Fe(III), one finds the ratio $[CuL]/[Cu^{2+}] \simeq 10^{-7}$ and $[FeL^{+}]/[Fe^{3+}] \simeq 10^{0}$ indicating that Fe(III) is approximately 10^{7} times more effective in coordinating to catechol than Cu(II) under the reaction conditions.[27]

There are several mechanisms possible for the proposed oxidation of the metal–catechol complex. One possibility could involve a concerted electron transfer from the ligand through the metal to coordinated HOOAc molecules.



Another scheme could involve a stepwise oxidation of the metal–catechol complex through o-benzoquinone in a manner similar to that postulated for the oxidation of catechol to *o*-benzoquinone by the Cu(II)-containing enzyme phenolase.[8]

The relationship between the Fe(III) and Cu(II)-catalyzed peracetic acid oxidations of phenol as reported in this paper and the corresponding enzymatic oxidations of catechol and phenol by the iron-containing enzyme pyrocatechase and the copper-containing enzyme phenolase is very apparent. We believe that our reaction may serve as a useful model for these enzymatic oxygenations, and therefore we are continuing our work in an effort to further elucidate the mechanism of the metal-catalyzed phenol oxidation in the hope that it may shed more light on the corresponding enzymatic processes.

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Registry No.—Peracetic acid, 79-21-0; phenol, 108-95-2; Cu(II), 15158-11-9; Fe(III), 20074-52-6; *cis,cis*-muconic acid, 1119-72-8; dimethyl *cis,cis*-muconate, 1119-43-3; catechol, 120-80-9.

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(12) Sodium sulfite reduces any *p*-benzoquinone and *o*-benzoquinone present in reaction mixtures to *p*-hydroquinone and catechol, respectively. *p*-Benzoquinone, *p*-hydroquinone, and catechol were identified in an experiment in which the reaction mixture was analyzed by VPC without employing sodium sulfite or any other reducing agent in the workup.
(13) S. W. Benson, "The Foundations of Chemical Kinetics", McGraw-Hill, New York, N.Y., 1960, p 20.
(14) A second-order plot of $[phenol]^{-1}$ vs. time indicates that the reaction is second order overall. The fact that the rate was first order in each reactant was established by initial rate studies which indicated that the rate depended on both phenol and peracetic acid.
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(27) In making these calculations, $[H^{+}]$ and [catechol] were set equal to 10^{-2} and 10^{-3} M, respectively, and the first formation constants for CuL and FeL^{+} of 1.26×10^{14} and 1×10^{21}, respectively, were used.[25,26]

Chlorinations of Olefins and Dienes with Antimony Pentachloride

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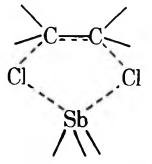
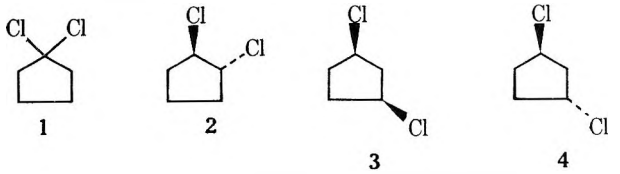
The addition of antimony pentachloride to several olefins and dienes is reported. In some cases, the reactions of the olefins and dienes and $SbCl_5$ have been examined in previous studies; we report on them here either because our data are in disagreement, or because we interpret these data differently. For example, it was reported previously that cyclopentene and $SbCl_5$ reacted to give 1,1-dichlorocyclopentane, *trans*-1,2-dichlorocyclopentane, *cis*-1,3-dichlorocyclopentane, and *trans*-1,3-dichlorocyclopentane by addition of HCl to intermediates 1-chlorocyclopentene and 3-chlorocyclopentene. Our data suggests that this cannot be the case since 1-chlorocyclopentene and 3-chlorocyclopentene do not react with HCl under the reaction conditions. We propose instead that all of the dichlorides result from addition of chloride ion to intermediate chlorocyclopentyl carbonium ions; the 1,1-dichloride and 1,3-dichlorides result from carbonium ions which are formed by hydride shifts. Two previous studies propose that $SbCl_5$ reacts with butadiene to give 3,4-dichloro-1-butene and *trans*-1,4-dichloro-2-butene by concerted additions. On the basis of our study on the reaction of cyclopentadiene and $SbCl_5$, we suggest that both butadiene and cyclopentadiene react with $SbCl_5$ by a carbonium ion mechanism. In spite of a report that *trans,trans*-2,4-hexadiene and $SbCl_5$ react to give only polymeric material, we found that 1,2- and 1,4-dichlorides are obtained under appropriate conditions. The 1,4 addition cannot be concerted since symmetry considerations indicate that a concerted addition should give only anti 1,4 addition; nearly equal amounts of syn and anti 1,4 additions were obtained experimentally. Evidence from previous studies on the reactions of $SbCl_5$ with olefins and dienes, and from our studies on cyclopentadiene, the isomeric 2,4-hexadiene, *cis*- and *trans*-piperylene, isoprene, and *cis*- and *trans*-β-methylstyrene, leads us to the conclusion that $SbCl_5$ can add to olefins and dienes either by a carbonium ion mechanism or a concerted mechanism, depending on the stability of the intermediate carbonium ion. As has been reported previously with butadiene, isoprene, *cis*- and *trans*-piperylene, *trans,trans*- and *cis,trans*-2,4-hexadiene, but not *cis,cis*-2,4-hexadiene, give *cis*-1,4-dichloride. Mechanisms for the reaction of $SbCl_5$ with these dienes to give the thermodynamically less stable *cis*-1,4-dichloride are discussed.

Recently Uemura and co-workers reported on the chlorination of several olefins, butadiene, and 1,5-octadiene with antimony pentachloride ($SbCl_5$).[1-3] With the simple olefins a preponderance of syn 1,2 addition was observed, with the exception of cyclopentene. They explained the syn 1,2 addition on the basis of a concerted molecular addition of $SbCl_5$ to the olefins as shown below.

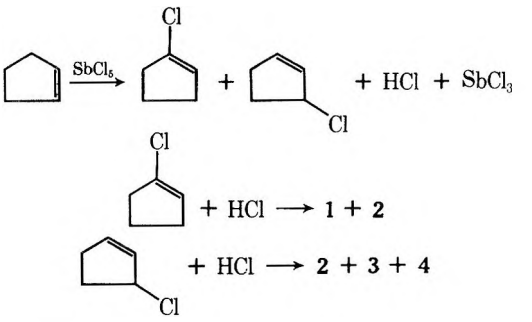


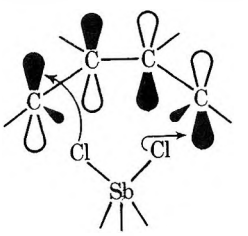
In the case of cyclopentene they observed no syn 1,2 addition but reported the formation of the following products (some 1-chlorocyclopentane was also detected).



To account for these products they suggested that cyclopentene reacted with $SbCl_5$ to give initially 1-chlorocyclopentene and 3-chlorocyclopentene, and that these intermediates reacted further with HCl to give **1**, **2**, **3**, and **4**. However, they did not establish this experimentally.

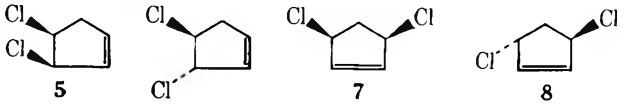
Uemura and co-workers also observed that 1,3-butadiene reacts with $SbCl_5$ to give an unexpectedly large amount of *cis*-1,4-dichloro-2-butene, in addition to the expected 3,4-dichloro-1-butene and *trans*-1,4-dichloro-2-butene. They proposed that the cis 1,4 addition resulted from a concerted 1,4 addition of $SbCl_5$ to the s-cis conformer of butadiene. At this same time, Vignes and Hamer[4] also reported on the reaction of 1,3-butadiene and $SbCl_5$. Their experimental observations were essentially identical with those of Uemura and co-workers. Vignes and Hamer also accounted for the large amount of cis 1,4 addition on the basis of a concerted 1,4 addition to the s-cis conformer, but they correctly suggested that because of orbital symmetry control the addition must occur in an antarafacial direction, as shown below.





It seemed to us that an antarafacial addition of $SbCl_5$ to the s-cis conformer of butadiene was unlikely because of steric hindrance between the large antimony system and the cis 1,4-vinyl hydrogens. We felt that this proposed mechanism could be probed by studying the reaction of cyclopentadiene and $SbCl_5$. In the case of cyclopentadiene an antarafacial, concerted 1,4 addition is impossible because of interference between the antimony system and the methylene group in

cyclopentadiene. Therefore if anti 1,4 addition does occur (to give *trans*-3,5-dichlorocyclopentene) it would mean either (or both) that cyclopentadiene and butadiene react with $SbCl_5$ by different mechanisms, or that another interpretation is required to explain the data from the reaction of butadiene and $SbCl_5$. It should also be pointed out that syn 1,4 addition of $SbCl_5$ to cyclopentadiene by a concerted mechanism is symmetry forbidden. We recently reported an investigation[5] of the chlorination of cyclopentadiene with molecular chlorine, and, therefore, the dichloride products (shown below) were already known.



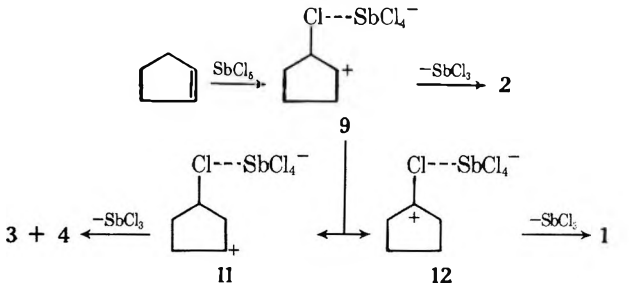
5 6 7 8

Results and Discussion

The results from the reaction of cyclopentadiene and $SbCl_5$ in different solvents are summarized in Table I, along with results from our previous study[5] with molecular chlorine, for comparative purposes. The data in Table I show that much larger amounts of *trans*-3,5-dichloropentene (**8**) were formed with $SbCl_5$ than were formed with chlorine. Therefore, at least in the case of cyclopentadiene, another mechanism other than a concerted 1,4 addition is required to account for the formation of **8**, and indeed of *cis*-3,5-dichlorocyclopentene (**7**).

At this point we carefully reexamined the reactions of $SbCl_5$ with cyclopentene, cyclohexene, and butadiene, and obtained essentially the same results as were reported previously. However, when we tested Uemura and co-workers' explanation for the formation of the dichlorides from cyclopentene, we found that it is incorrect since 1-chlorocyclopentene and 3-chlorocyclopentene *do not* react with HCl to give **1**, **2**, **3**, and **4**.

Scheme I



Scheme I outlines a series of reactions which we feel can be used to account for the dichloride products in the reaction of cyclopentene and antimony pentachloride.[6,7] According to Scheme I the ion-pair precursors (**11** and **12**) of dichlorides **3**, **4**, and **1**, respectively, result from appropriate hydride shifts[8,9] in intermediate **9**. We have established that molecular chlorine does not produce detectable amounts of a dichlorides **1**, **3**, or **4**, presumably because this reaction proceeds through a chloronium ion-type transition state (**13**) to give ion pair **14**, with little carbonium ion development in the transition state and no opportunity for hydride shift. Apparently intermediate **9** forms from transition state **15** and does not collapse to chloronium ion **14** because of stabilizing bonding between chlorine and the $SbCl_4^-$ ion.

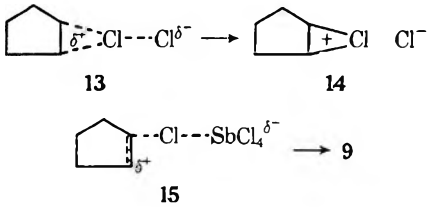
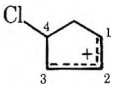


Table I. Reactions of Cyclopentadiene and $SbCl_5$

Chlorinating agent	Solvent[a]	Product distribution 5	6	7	8	Yield, %
$SbCl_5$	CCl_4	6	22	38	34	96
$SbCl_5$	CH_2Cl_2	7	12	52	29	27
$SbCl_5$	C_5H_{12}	19	21	27	33	71
Cl_2[b]	CCl_4	27	23	39	11	60
Cl_2[b]	CH_2Cl_2	38	35	18	9	52
Cl_2[b]	C_5H_{12}	13	29	29	29	68

[a] The mole fraction of diene was 0.02 in all cases. [b] See ref 5 for a description of this study.

We are now in a position to discuss the mechanism for the reaction of cyclopentadiene with $SbCl_5$. We have already shown that the products in this reaction cannot be accounted for on the basis of a concerted 1,4 addition. Therefore, since cyclopentene reacts with $SbCl_5$ by a carbonium ion mechanism, it would seem reasonable that cyclopentadiene would also react by this mechanism, particularly since the carbonium ion from the diene is both secondary and allylic, and, hence, more stable. Dichlorides **5**, **6**, **7**, and **8** would then result from an appropriate attack on cation **16**. The increase in anti 1,4



16

addition (**8**) with $SbCl_5$ compared to chlorine probably results from the fact that the large anion ($SbCl_4^-$) experiences little steric hindrance during anti attack at C_1. Conversely the small amount of syn 1,2 addition with $SbCl_5$ can be explained on the basis of increased steric interaction as the anion ($SbCl_4^-$) approaches C_3 from a syn direction.[10]

Vignes and Hamer[4] correctly suggested that the reaction of $SbCl_5$ with *trans,trans*-2,4-hexadiene (**16**) would be an excellent method for determining whether the 1,2 and 1,4 additions were symmetry controlled. However, when they attempted this reaction they obtained only polymeric material. We repeated this reaction under our conditions and obtained the products reported in Table II. Reactions between antimony pentachloride and the following dienes and olefins were also studied: *cis,cis*-2,4-hexadiene (**17**), *cis,trans*-2,4-hexadiene (**18**), *trans*- and *cis*-piperylene (**19** and **20**), and *trans*- and *cis*-β-methylstyrene (**21** and **22**). These results are reported in Table II.

The results which would be predicted if the reaction of *trans,trans*-2,4-hexadiene and $SbCl_5$ is symmetry controlled are outlined in Scheme II. As shown, a symmetry controlled 1,2 addition to **16** (concerted molecular addition) should occur in the syn direction to give the threo dichloride, and the 1,4 addition should occur from opposite sides (anti) of the diene (as illustrated earlier with butadiene and cyclopentadiene) to give the meso 1,4 dichloride. Anti 1,4 and syn 1,4 addition to **18** will give *dl*-1,4- and meso 1,4-dichlorides, respectively. Syn 1,2 additions to **17** will give the erythro 1,2-dichloride; the interpretation of syn 1,2 addition to **18** is more complex (see footnote *b*, Table II).[11]

The data in Table II indicate that 1,4 additions of $SbCl_5$ to **16** (and dienes **17** and **18**) is not under orbital control since the ratio of meso to *dl* attack is approximately equal. Perhaps one can imagine that some orbital control is involved since syn 1,4 addition should be favored inasmuch as the anion is generated on the same side of the diene as the attacking electrophile, and is situated correctly for syn 1,4 attack.[12]

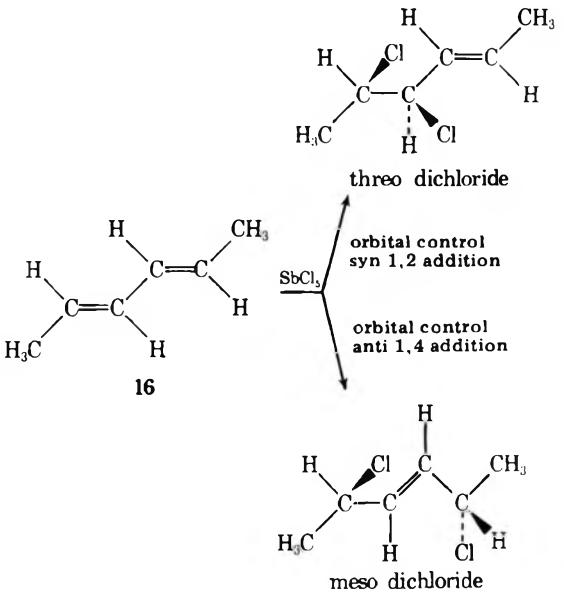
1,2 addition, in contrast to 1,4 addition, is highly stereospecific (syn) for the cis 2,4-hexadienes (**17**, **20**) but not for the

Table II. Chlorination of Dienes and Olefins with $SbCl_5$

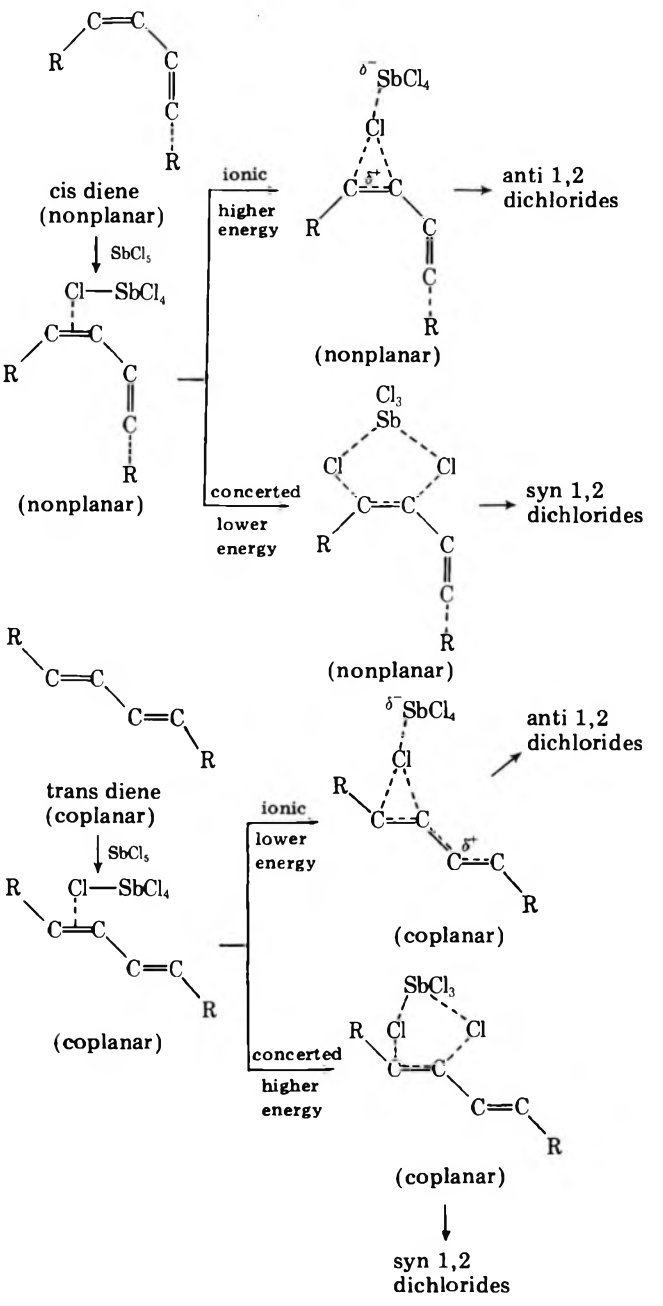
Diene or olefin	Threo/erythro	Syn 1,2 addition, %	*meso*-1,4-*dl*-1,4	Syn 1,4 addition, %	1,2/1,4	Yield, %
16	0.75	43	1.11	47	0.52	49[c]
17	0[a]	100	1.12	47	1.54	28
18	*b*	*b*	1.15	54	0.78	27
19[e]	0.11	10			0.77	94[d]
20[e]	0.41	71			1.05	34[d]
21	3.04	75				63
22	0	100				67

[a] Analysis procedures did not eliminate the possibility of a trace (2%) of threo product. [b] Since diene 18 has both a cis and trans bond, the stereochemistry of 1,2 addition must be stated for each bond: syn 1,2 addition (%) to the cis bond, 47; syn 1,2 addition (%) to the trans bond, 69. [c] Includes a 14% yield of a compound expected of being the cis 1,4-dichloride. [d] These percentages include the following yields (%) of the cis 1,4-dichlorides, respectively: 28 and 10. [e] Only 3,4-dichloro-1-pentene is formed.

Scheme II



Scheme III



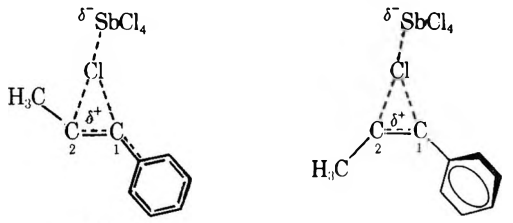
trans dienes (**16**, **19**). At least one explanation for these data is that $SbCl_5$ adds to the cis bonds by a concerted molecular mechanism, and to the trans bonds by an ionic mechanism. (In the ionic addition, the anion would undergo some reorientation leading to anti 1,2 product). Why should concerted addition be preferred for the cis dienes?

Conceivably, slight differences in the stabilities of the intermediate carbonium ions can determine whether $SbCl_5$ adds by a concerted or an ionic mechanism. For example, syn (concerted) addition is lowest[1-3] for those olefins and dienes involving the most stable carbonium intermediates (cyclopentene, *cis*-cyclooctene, *cis,cis*-1,5-cyclooctadiene, and norbornene), and highest for those olefins which would involve the least stable carbonium ion intermediates (2-butene, 2-octene, and cyclohexene). The lower stability of the latter intermediates may tip the scales in favor of a nonionic, concerted addition.[13]

The differences in intermediate carbonium ion stabilities may explain why addition of $SbCl_5$ is more stereospecific (concerted, syn) for cis dienes than for trans dienes. With cis dienes the two double bonds are probably nonplanar in the ground state because of 1,3 interactions between a methyl group and a hydrogen. This same type of interference also would be expected to exist in the transition state, hindering formation of the more stable, allylic carbonium ion, whose formation would require coplanarity of the double bonds. Thus the lower energy, concerted route becomes significant. With trans dienes this type of 1,3 interaction does not exist, an allylic carbonium ion is possible, and the ionic route is followed. These concepts are illustrated in Scheme III.[14]

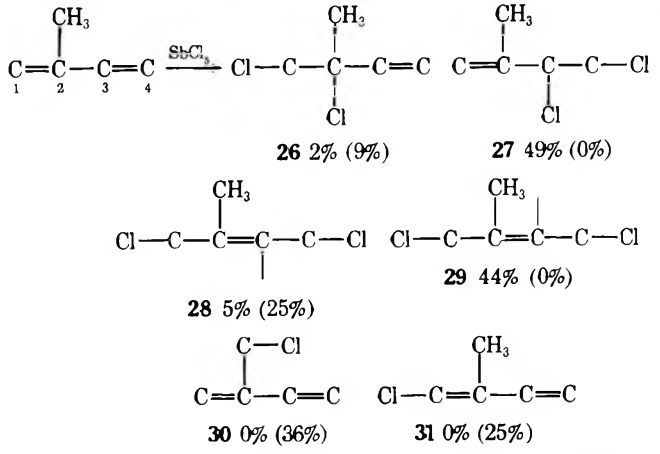
The data in Table II show that chlorination of *cis*-β-methylstyrene (**22**) is completely stereospecific but that chlorination of *trans*-β-methylstyrene (**21**) is far less stereospecific. The line of reasoning which was used to explain the

differences in stereospecificity of the cis and trans dienes also can be applied to these olefins. Attack of $SbCl_5$ on the trans olefin (**21**) could lead to a benzylic carbonium ion-type transition state (**23**), whereas formation of a benzylic ion with the cis olefin (**22**) would be hindered because of steric interaction between the methyl hydrogen and the ortho hydrogens of the phenyl ring, forcing the ring out of the plane of the C_1–C_2 bond, decreasing resonance stabilization (**24**). Concerted addition is of lower energy in the latter case.



23 **24**

With the preceding discussion of ionic vs. concerted pathways as a background, we can now consider in some detail the chlorination of isoprene (**25**) with $SbCl_5$. The results of this study are summarized in the following reaction, along with the results from the chlorination[15] with molecular chlorine (in parentheses).



26 2% (9%) **27** 49% (0%)

29 44% (0%)

28 5% (25%)

30 0% (36%) **31** 0% (25%)

There are two principal differences in the chlorinations of isoprene with $SbCl_5$ and Cl_2: (a) Cl_2 attacks primarily (ionic) the 1,2 bond (**26** + **30** + **31** = 70%) and little at the 3,4 bond,[16] whereas $SbCl_5$ attacks significantly (nonionic) the 3,4 bond (**27**, 49%) and a trace at the 1,2 bond (**26**, 2%); and (b) $SbCl_5$ gives much cis 1,4 addition (**29**, 44%) and Cl_2 gives none.

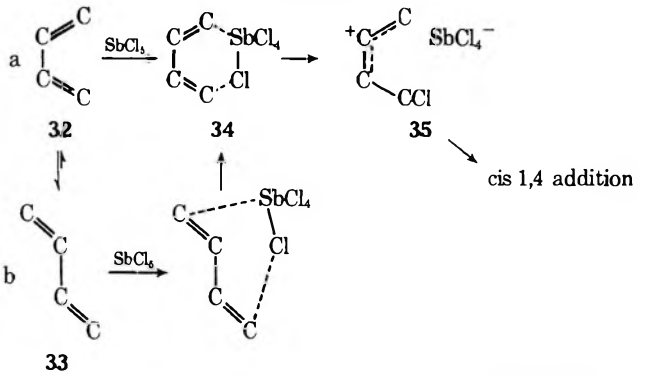
Chlorine attacks the 1,2 bond because it is most basic and because the most stable carbonium ion intermediate is formed (tertiary, allylic vs. secondary, allylic at the 3,4 bond). Perhaps $SbCl_5$ prefers to attack the 3,4 bond because of steric hindrance from the methyl group at the 1,2 bond. Reaction at the 3,4 bond appears to occur by a concerted mechanism since ionic products, $C{=}C(CH_3)C{=}CCl$ and **28**, are absent or formed in small amounts. Absence of an ionic reaction between $SbCl_5$ and **25** may result from the fact that formation of a stable, allylic cation in the transition state is hindered by nonplanarity of the double bonds (caused by 1,3 methyl, vinyl hydrogen interaction).

Certainly the most unexpected product in the reaction of butadiene and $SbCl_5$ is *cis*-1,4-dichloro-2-butene. Also a large amount of cis 1,4 addition (**29**) occurs with isoprene. Significant amounts of cis 1,4 addition products form with $SbCl_5$ and dienes **16** and **19**. *cis*-Piperylene (**20**) gives approximately one-third as much cis 1,4-dichloride as the trans isomer (**19**), and no cis 1,4-dichloride is formed from *cis,cis*-2,4-hexadiene (**17**).

The simplest explanation for the formation of cis 1,4-dichlorides is that $SbCl_5$ reacts with the s-cis (**32**) form of butadiene (used as an example) by the carbonium ion mechanism to give cis 1,4-dichloride (Vignes and Hamer[4] and Uemura and co-workers[2] suggested a concerted addition of antimony pentachloride to the s-cis form of butadiene). However, this explanation faces some real difficulties. For one thing, it was recently shown that butadiene exists in the s-trans conformation.[17] Another point is that all of the other chlorinating agents (Cl_2,[18] NCl_3,[19] and $C_6H_5ICl_2$[10]) give no more than a trace of cis 1,4 addition with butadiene.

Therefore, we conclude that the initial reaction is one in which $SbCl_5$ in some way is involved in enriching the concentration of the s-cis conformer (**32**). Two mechanisms for accomplishing this are suggested in Scheme IV. In one case

Scheme IV



(a) $SbCl_5$ complexes (**34**) extremely rapidly with the small amount of s-cis conformer (**32**), thus shifting the equilibrium in favor of **34**. In b, $SbCl_5$ reacts with the s-trans conformer (**33**) forming a complex which rearranges to the s-cis complex (**34**). Decomposition of **34** gives the cis allylic ion pair (**35**) which adds chloride ion giving cis 1,4 addition.

Less cis 1,4 addition for **20** than **19** and none for **17** can apparently be explained on the basis of difficulty of formation of the s-cis conformer for these dienes because of steric hindrance between the vinyl hydrogen and methyl groups in **19** and the two methyl groups in **17**.

Experimental Section

Materials. All solvents were obtained commercially in high purity and were used without further purification. Cyclopentadiene was prepared from its dimer; all other olefins and dienes were obtained commercially in high purity. Antimony pentachloride was obtained from Ventron Corp.

Reaction Conditions. Antimony pentachloride, dissolved in solvent to give a 0.3 M solution, was added dropwise to a solution of the dienes and olefins in the corresponding solvent (mole fractions of dienes and olefins, 0.02) at 0 to −10 °C in such amount to react with ca. 25% of the dienes and olefins. Antimony pentachloride was also added neat to a solution of the hydrocarbons, but without effect on the ratio of products; the yield was somewhat reduced. As indicated in Table I, cyclopentadiene was studied in a variety of solvents; however, the other dienes and olefins were chlorinated with antimony pentachloride only in carbon tetrachloride since the yields were higher in this solvent. All yields were based on the amount of $SbCl_5$ added.

Identification of the Products and Analyses Procedures. Establishment of the structures of many of the dichloride products and the conditions for VPC analysis of them have been described previously: cyclopentadiene,[5,10] the 2,4-hexadienes and piperylenes,[12] and the β-methylstyrenes.[20] A modified procedure was used for the VPC analyses of the β-methylstyrenes: column (6 ft × 0.25 in., ss) at 65 °C, packed with SE-30 (2.5%) on 80–100 mesh Chromosorb W (AW DMCS) at a flow rate of 90 ml/min (He), and with retention times (min) of 28.3 and 33.1, respectively, for the erythro and threo isomers.

We suspect that *cis*-2,5-dichloro-3-hexene is formed in the reaction of *trans,trans*-2,4-hexadiene (**16**) with $SbCl_5$ since VPC analysis of the reaction product shows a substantial peak after the trans 1,4-

dichlorides. However, whenever this reaction solution was concentrated so that the suspected peak could be isolated by preparative VPC, the compound decomposed. Decomposition even occurred when the reaction solution was flash distilled and then concentrated. Conceivably, a trace amount of an unknown antimony compound catalyzes decomposition when the cis 1,4-dichloride is in a concentrated solution; perhaps the cis 1,4-dichloride is simply unstable, except when very dilute.

Information concerning the chlorination products from isoprene follows. **26, 28, 30,** and **31** have been described previously.[15] *cis*-1,4-Dichloro-2-methyl-2-butene (**29**) was obtained by preparative VPC. It was identified by its NMR spectrum, and by the similarity of its NMR spectrum to the spectrum of **28:** δ 1.92 (s, 3, CH_3), 4.03 (d, z, CH_2CH), 4.10 (s, z, CH_2CCH_3), 5.63 (t, 1, CH). 3,4-Dichloro-2-methyl-1-butene (**27**) was identified in three ways. (a) It was obtained by preparative VPC and confirmed by its NMR: δ 1.88 (s, 3, CH_3), 3.68 [d, 1, C(**H**)H, J = 5.0 Hz], 3.73 [d, 1, C(H)**H**, J_2 = 3.5 Hz], 4.50 (dd, 1, CH, J_1 = 5.0, J_2 = 3.5 Hz), 5.08 (m, 1, cis $CHCCH_3$), 5.17 (s, 1, trans $CHCCH_3$). (b) The NMR and ir spectra of VPC collected **27** were identical with those of **27** synthesized unambiguously by dehydration (P_2O_5) of 3,4-dichloro-2-methylbutan-2-ol. (c) Rearrangement of **27** by heating with zinc chloride gave small amounts of dichlorides **26, 28,** and **29,** although extensive decomposition occurred.

Studies on the Addition of Hydrogen Chloride to 1-Chlorocyclopentene and 3-Chlorocyclopentene. Three experiments were conducted to establish that hydrogen chloride (HCl) does not add to 1-chlorocyclopentene[21] or 3-chlorocyclopentene.[22] (a) Gaseous HCl was added to a mixture of 1-chlorocyclopentene and 3-chlorocyclopentene in the appropriate solvent. No addition occurred to give **1, 2, 3,** and **4.** (b) Conceivably $SbCl_3$ or another antimony intermediate could catalyze the addition of HCl to the chlorocyclopentenes. To equimolar amounts of *trans*-1-phenylpropene and the chlorocyclopentenes under appropriate reaction conditions was added $SbCl_5$. **1, 2, 3,** or **4** were not formed during addition, or subsequently when gaseous HCl was added. *trans*-1-Phenylpropene should react more rapidly with $SbCl_5$, perhaps generating antimony intermediates and HCl which could then catalyze addition of the HCl (from the reaction or from that added) to the chlorocyclopentenes. This did not occur. (c) $SbCl_5$ was added to cyclopentene under appropriate reaction conditions (30% completion). The amounts of **1, 2, 3,** and **4** were determined. 1-Chlorocyclopentene and 3-chlorocyclopropene were added and HCl was bubbled into the solution. Analysis showed no increase in the amounts of **1, 2, 3,** and **4.**

Stability of the Dichlorides to the Reaction Conditions. A detailed study was made of the stability of the cyclopentadiene dichlorides to the reaction conditions. Since these dichlorides are probably the least stable of any of the dichlorides, they can serve as a model for stability. All of the cyclopentadiene dichlorides were found to be unaffected by antimony trichloride ($SbCl_3$). We determined that antimony pentachloride ($SbCl_5$) did not react with the dichlorides during the course of the reaction in the following manner. To an initial reaction mixture of diene and solvent was added a mixture of dichlorides. The appropriate amount of antimony pentachloride was now added to react with the diene. Analysis of this reaction product and subsequent calculations showed that the dichlorides that had been added originally were present at the end of the reaction.

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Registry No.—**16,** 5194-51-4; **17,** 6108-61-8; **18,** 5194-50-3; **19,** 2004-70-8; **20,** 1574-41-0; **21,** 873-66-5; **22,** 766-90-5; **27,** 53920-89-1; **28,** 51892-55-8; **29,** 51620-16-7; $SbCl_5$, 7647-18-9; HCl, 7647-01-0; cyclopentadiene, 542-92-7; isoprene, 78-79-5; 1-chlorocyclopentene, 930-29-0; 3-chlorocyclopentene, 96-40-2.

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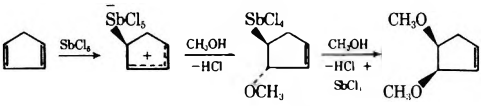
(6) The structure of the actual chlorinating agent is uncertain. Vignes and Hamer,[4] on the basis of conductivity studies, conclude that $SbCl_5$ is not ionized in carbon tetrachloride; Uemura et al.[2] are uncertain as to the structure of the chlorinating agent, but suggest that $SbCl_4^+$ may be the active chlorinating species. We show monomeric $SbCl_5$ as being the source of the chlorine atoms, but we have no evidence that $SbCl_4^+$ is not involved.
(7) Since antimony pentachloride is known to be a strong Lewis acid, we considered that the initial attack on the olefin might involve the antimony atom directly. However, when $SbCl_5$ was added to cyclopentadiene in carbon tetrachloride containing varying amounts of methanol, no dimethoxycyclopentene was detected. Dimethoxycyclopentene would be expected if the attack was made by antimony, as shown in the following equations.



(8) 1,2-Hydride shifts have been previously reported in cyclopentyl systems: J. L. Fry and G. J. Karabatos, "Carbonium Ions", Vol. II, Wiley-Interscience, New York, N.Y., 1970, p 522.
(9) Uemura et al.[3] accounted for the formation of 1,4-dichlorocyclooctane (mixture of cis and trans) from *cis*-cyclooctene and $SbCl_5$ on the basis of a 1,5-hydride shift.
(10) We have recently compared and discussed the stereochemistry of the dichlorides that result from chlorinating cyclopentadiene with Cl_2, $C_6H_5ICl_2$, NCl_3, and $SbCl_5$: V. L. Heasley, K. D. Rold, D. B. McKee, and G. E. Heasley, *J. Org. Chem.*, **41,** 1287 (1976).
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(12) syn 1,4 addition predominates in the bromination[11] and chlorination of dienes **16, 17,** and **18;** for the chlorination of these dienes see G. E. Heasley, D. C. Hayse, G. R. McClung, D. K. Strickland, V. L. Heasley, P. D. Davis, D. M. Ingle, K. D. Rold, and T. S. Ungermann, *J. Org. Chem.*, **41,** 334 (1976).
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(14) We assume that there is an ionic component to all $SbCl_5$ additions to dienes since the 1,4 addition products must arise by an S_N2'-type attack by the $SbCl_4^-$ anion on the π bond of the intermediate cation.
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(16) It is impossible to determine which bond initially was attacked in the formation of the 1,4-dichlorides.
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Fluorination with Xenon Difluoride. Reaction with Phenyl-Substituted Olefins[1]

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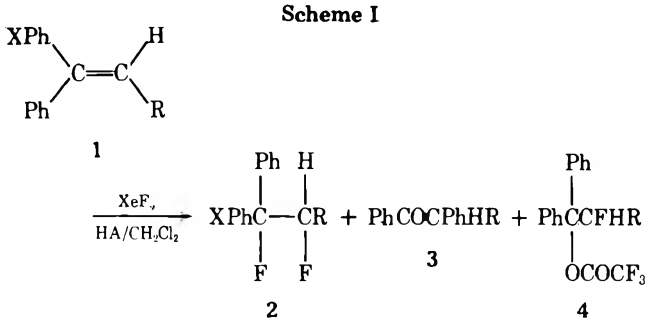
Xenon difluoride reacts with 1,1-diphenylethylenes in the presence of hydrogen fluoride or trifluoroacetic acid as catalyst to form the corresponding 1,2-difluoro-1,1-diphenylethanes in nearly quantitative yields. Reaction with 1,1-diphenyl-2-fluoroethene in the presence of trifluoroacetic acid results in 1,2,2-trifluoro-1,1-diphenylethane and 2,2-difluoro-1,1-diphenyl-1-trifluoroacetoxyethane. Reaction with styrenes gives vicinal difluorides in lower yield.

Filler and co-workers[2-6] have demonstrated the utility of xenon difluoride as a selective fluorinating agent of aromatic compounds in the liquid phase. Furthermore, Mackenzie and Fajer[7] have fluorinated aromatic compounds in the vapor phase, but only limited data are available on fluorine addition to olefins with this reagent.[8] In the course of our efforts to elucidate the reaction of xenon difluoride with olefins, we found it instructive to fluorinate some 1,1-diphenylethylenes and substituted styrenes. The fluorination of 1,1-diphenylethylene has been achieved with a variety of reagents such as lead tetraacetate–hydrogen fluoride,[9] aryliodoso difluorides,[10] and molecular fluorine at low temperatures.[11] The process with lead tetraacetate–hydrogen fluoride and aryliodoso difluorides led to rearranged products, e.g., phenyl migration to yield 1,1-difluoro-1,2-diphenylethane[9,10] and fluorination with molecular fluorine[11] gave both addition and substitution products.

The preparation of fluoroalkanes represents a different problem from that of the preparation of other haloalkanes and necessitates a specific method of fluorination.[12] Earlier workers[2-8] have used vacuum lines and autoclaves for fluorination of organic molecules with xenon difluoride. We now report the reaction of xenon difluoride using very simplified laboratory techniques, e.g., Kel-F vessels, weighing of xenon difluoride in Teflon epruvettes, room temperature, atmosphere pressure, etc. By fluorination of substituted 1,1-diphenylethylenes **1a–h** (Scheme I) 1,1-diphenyl-1,2-difluorides

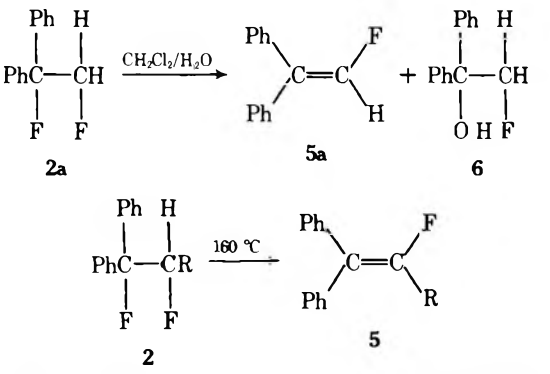
Scheme I



a, X = R = H
b, X = H; R = CH_3
c, X = H; R = F
d, X = *p*-OCH_3; R = H
e, X = *p*-CH_3; R = H
f, X = *m*-CH_3; R = H
g, X = *p*-Cl; R = H
h, X = *m*-Cl; R = H

2a–h were isolated using hydrogen fluoride as catalyst. In addition to vicinal difluorides (**2a–h**) small amounts of deoxybenzoin **3a** (5%) and **3b** (15%) were formed (Table I). The fluorination reaction when catalyzed by trifluoroacetic acid results in a high yield of **2a** and **2b** without formation of deoxybenzoin **3a** or **3b**, but reaction with 1,1-diphenyl-2-fluoroethylene in the presence of trifluoroacetic acid results in the formation of trifluoro product **2c** (60%) and the trifluoroacetate derivate **4c** (35%). The addition of trifluoroacetic anion was in accordance with Markownikoff type regioselectivity forming corresponding 1,1-diphenyl-1-trifluoroacetoxy-2,2-difluoroethane (**4c**). The structures of the products were determined by NMR and mass spectrometry and their NMR data are presented in Table II. Treatment of 1,2-difluoro-1,1-diphenylethane (**2a**) in methylene chloride solution with water for 30 min resulted in two products: 1,1-diphenyl-2-fluoroethene (**5a**, 70%) and 30% of 1,1-diphenyl-1-hydroxy-2-fluoroethane (**6**) (relative ratios determined by NMR) (Scheme II). The products were separated by prepar-

Scheme II

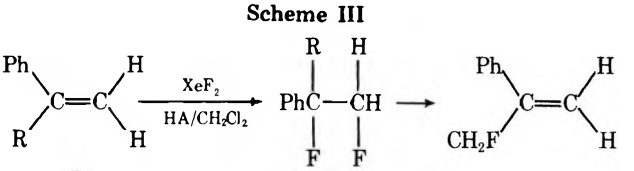


ative TLC. On the other hand, heating of the vicinal difluorides **2** to 160 °C resulted in formation of the eliminated products **5**.

The reactions of xenon difluoride with aryl substituted alkenes **1d–h** resulted in formation of vicinal difluorides for all, but the reaction with the *p*-methoxy derivate **1d** is quicker than that with the *m*-chloro derivate. From the NMR data of all the substituted derivates **2d–h** (Table II) we can see no significant effect of different substituents bonded to the phenyl ring on the chemical shift of fluorine or hydrogen atoms. Furthermore, we also have not observed any greater effect of substituents on coupling constants.

The reaction with styrene (**7a**) catalyzed by hydrogen fluoride resulted in formation of 1,2-difluoro-1-phenylethane (**8a**, Scheme III), which could be purified by preparative GLC. The

Scheme III



a, R = H
b, R = CH_3

product is very unstable and must be stored at −15 °C. The reaction with 2-phenylpropene (**7b**) gave very unstable 1,2-difluoro-2-phenylpropane (**8b**) which could be purified by

Table I. Fluorination of Substituted Diphenylethylenes with XeF_2 in CH_2Cl_2 at 20 °C. Yields of Products (%)

Olefin	HA	2	3	4
1a	HF	90	5	
	CF_3COOH	95		
1b	HF	80	15	
	CF_3COOH	95		
1c	HF	95		
	CF_3COOH	60		35

preparative GLC. However, the product decomposed (elimination of HF) in methylene chloride in 45 min, thus forming 2-phenyl-3-fluoropropene-1 (9).

Fluorine addition to phenyl-substituted olefins with xenon difluoride appears to be strongly catalyzed by hydrogen fluoride or trifluoroacetic acid, as indicated by observations that in the absence of these catalysts reactions are very slow. We found no evidence either for the formation of fluorine-substituted products which might arise via a substitution fluorination of the phenyl ring, or of an ethylenic hydrogen atom, or for the presence of hydrogen fluoride addition products, as observed in gas-phase fluorinations[8] with xenon difluoride. Extensive work is in progress on acid-catalyzed liquid-phase fluorinations of various alkenes in order to establish the mechanism of these reactions.

Experimental Section

Ir spectra were recorded by using a Perkin-Elmer 257 spectrometer, and ^1H and ^{19}F NMR spectra by a JEOL JNM-PS-100 from CCl_4 solution with Me_4Si or CCl_3F as internal reference. Mass spectra and high-resolution measurements were taken on a CEC-21-110 spectrometer. Gas–liquid partition chromatography was carried out on a Varian Aerograph Model 1800 and TLC on Merck PSC-Fertigplatten silica gel F-254 (activated for 3 h at 120 °C before use).

Materials. Pure samples of olefins were prepared by known methods: 1,1-diphenylethylene,[13] 1,1-diphenylpropene,[14] phenyl-substituted 1,1-diphenylethylenes.[13] Other olefins were commercially available and purified before use. Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride was purified[15] and stored over molecular sieves. Xenon difluoride was prepared by a photosynthetic method[16] and its purity was better than 99.5%.

1,2-Difluoro-1,1-diphenylethane (2a). To a solution of 1 mmol of **1a** in methylene chloride (6 ml), 1 mmol of xenon difluoride was added at 25 °C and under stirring 1 ml of 1 M trifluoroacetic acid was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was slowly evolved. After 30 min the gas evolution had ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (15 ml), washed with 10 ml of 5% $NaHCO_3$ and water, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. The crude product was purified with preparative TLC (SiO_2, *n*-hexane–methylene chloride, 9.5:0.5). The product **2a** (205 mg, 95%) with mp 38–40 °C (lit.[11] mp 40–42 °C) was isolated. NMR data are stated in Table II.

1,1-Diphenyl-2-fluoroethene (5a). To a solution of 1 mmol of **1a** in methylene chloride (6 ml), 1 mmol of xenon difluoride was added at 25 °C and under stirring anhydrous hydrogen fluoride (0.5–1 mmol) was introduced into the reaction mixture. After a few seconds the colorless solution turned dark blue and xenon gas was evolved. After 30 min the reaction mixture was diluted with methylene chloride, washed with 10 ml of aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4 and solvent was evaporated in vacuo. The crude, oily product was purified by preparative VPC (SE-30, Chromosorb A, AW, 15%, 210 °C). 1,1-Diphenyl-2-fluoroethene (**5a**, 170 mg, 86%) and 10 mg (5%) of deoxybenzoin were isolated. The spectroscopic data are in agreement with those in the literature.[11]

1,1-Diphenyl-1-hydroxy-2-fluoroethane (6). 1,2-Difluoro-1,1-diphenylethane (**2a**, 1 mmol) was dissolved in methylene chloride (5 ml) and treated for 30 min with 10 ml of water. After separation the methylene chloride layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo. The crude reaction mixture was analyzed by NMR spectroscopy and a 70:30 ratio of 1,1-diphenyl-2-fluoroethene (**5a**) and 1,1-diphenyl-1-hydroxy-2-fluoroethane (**6**), respectively, was found. GLC separation yielded 86% of 1,1-diphenyl-2-fluoroethene (**5a**). On the other hand, the separation of the crude reaction mixture by preparative TLC (SiO_2, *n*-hexane–methylene chloride 9.5:0.5) resulted in 26% of a colorless oily product (**6**) [mass spectrum calcd for $C_{14}H_{13}OF$ *m/e* 216.0955, found *m/e* 216.0940, *m/e* 216 (M^+, 3), 198 (100), 183 (50), 165 (24), 105 (22), 77 (14); NMR δ H 4.65 ppm (d), δ Ph 7.2 ppm (m), J_{FH} = 45 Hz] and 63% of 1,1-diphenyl-2-fluoroethene (**5a**).

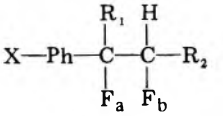
1,2-Difluoro-1,1-diphenylpropane (2b). The fluorination, workup procedure, and TLC purification were essentially the same as described for **2a**. **2b** was isolated in 95% yield as an unstable liquid product, which easily eliminated hydrogen fluoride: NMR data are stated in Table II; mass spectrum calcd for $C_{15}H_{14}F_2$ *m/e* 232.1072, found *m/e* 232.1059, *m/e* 232 (M^+, 8), 212 (6), 185 (100), 165 (22), 77 (13).

1,1-Diphenyl-2-fluoropropene (5b). The fluorination, workup procedure, and the VPC purification were essentially the same as described for **5a**. **5b** (82%) [oily product; mass spectrum calcd for $C_{15}H_{13}F$ *m/e* 212.1006, found *m/e* 212.0985, *m/e* 212 (M^+, 100%), 198 (15), 197 (16), 165 (15), 133 (11); NMR δ CH_3 1.95 ppm (d), δ Ph 7.2 ppm (m), $J_{CH_3,F}$ = 17.2 Hz] and 50% of methyldeoxybenzoin (**3b**) [mass spectrum calcd for $C_{15}H_{14}O$ *m/e* 210.1004, found *m/e* 210.1027, NMR δ CH_3 1.52 ppm (d), δ H 4.6 ppm (q), δ Ph 7.7 ppm (m), J_{H,CH_3} = 6.7 Hz] were isolated.

1,2,2-Trifluoro-1,1-diphenylethane (2c). The fluorination, workup procedure, and VPC purification were essentially the same as described for **5a** (Carbowax 20M, Varaport-30 70/80, 10%, 165 °C). **2c**: a colorless, stable liquid, yield 95%. Mass spectrum: calcd for $C_{14}H_{11}F_3$ *m/e* 236.0813, found *m/e* 236.0813. NMR data are stated in Table II.

2,2-Difluoro-1-trifluoroacetoxy-1,1-diphenylethane (4c). The fluorination and workup procedure were essentially the same as described for **2a**. VPC separation yielded 60% of 1,2,2-trifluoro-1,1-diphenylethane (**2c**) and 35% of liquid product 2,2-difluoro-1-tri-

Table II. NMR Data for Vicinal Difluorides (2a–h, 7a, 7b)



Compd	δ_{F_a}, ppm	δ_{F_b}, ppm	δ_H, ppm	δ_{R_1}, ppm	δ_{R_2}, ppm	$J_{F_aF_b}$, Hz	J_{F_bH}, Hz	J_{F_aH}, Hz	$J_{F_aR_1}$, Hz	J_{R_2H}, Hz
2a	−169.5	−245	4.85	7.2	4.85	18	47	22		
2b	−173.3	−194.3	5.3	7.2	1.33	17	45	18		6
2c	−172.5	−141.7	6.2	7.2	−141.7	11.7	54	5.5		54
2d	−167.5	−254	4.8	7.3	4.8	18	47	22		
2e	−169.5	−254	4.8	7.2	4.8	18	47	22.5		
2f	−170	−245	4.8	7.2	4.8	18	47	24		
2g	−169.5	−245	4.8	7.2	4.8	18	47	23		
2h	−169.5	−245	4.8	7.2	4.8	18	47	24		
7a	−208.5	−247.5	4.6	5.66	4.6	16	48	30	50	$J_{F_aR_2}$ = 22 Hz
							J_{R_1H} = 7 Hz	$J_{R_1R_2}$ = 4 Hz		$J_{F_bR_1}$ = 16 Hz
7b	−172.5	−246	4.5	1.68	4.5	13.5	48	33	21	$J_{F_aR_2}$ = 18 Hz
							$J_{R_1F_b}$ = 3 Hz			

fluoroacetoxy-1,1-diphenylethane (**4c**): mass spectrum calcd for $C_{16}H_{11}O_2F_5$ *m/e* 330.0701, found *m/e* 330.0670, *m/e* 330 (M^+, 46), 279 (100), 165 (33), 105 (42), 77 (21); NMR δ H 7.1 ppm (t), J_{FH} = 55.5 Hz.

Phenyl-Substituted Derivates of 1,2-Difluoroethanes (2d–h). The reaction time for **1d** was 10 min, while the reaction time for **1h** was 1 h. The fluorination, workup procedure, and TLC purification were the same as described for **2a**. The products were unstable, oily compounds. NMR data are listed in Table II. Mass spectra: **2d**, calcd for $C_{15}H_{14}F_2O$ *m/e* 248.1013, found *m/e* 248.1000, *m/e* 248 (M^+, 1), 228 (100), 215 (12), 198 (14), 183 (16), 165 (20), 77 (10); **2e**, calcd for $C_{15}H_{14}F_2$ *m/e* 232.1064, found *m/e* 232.1063, *m/e* 232 (M^+, 16), 199 (100), 184 (13), 183 (13), 119 (10), 84 (22); **2f**, calcd for $C_{15}H_{14}F_2$ *m/e* 232.1064, found *m/e* 232.1063, *m/e* 232 (M^+, 14), 199 (100), 184 (14), 183 (12), 119 (12); **2g**, calcd for $C_{14}H_{11}F_2Cl$ *m/e* 252.0517, found *m/e* 252.0518, *m/e* 254 (M^+ + 2, 6), 252 (M^+, 17), 221 (33), 219 (100), 183 (26), 92 (17); **2h**, calcd for $C_{14}H_{11}F_2Cl$ *m/e* 252.0517, found *m/e* 252.0518, *m/e* 254 (M^+ + 2, 7), 252 (M^+, 20), 221 (33), 219 (100), 183 (30), 92 (18).

1,2-Difluoro-1-phenylethane (8a). The fluorination, workup procedure, and VPC purification were essentially the same as for **5a** (SE-30, Chromosorb A, AW, 10%, 150 °C). Liquid unstable product (50%) was isolated. NMR data are stated in Table II. Mass spectrum: calcd for $C_8H_8F_2$ *m/e* 142.0603, found *m/e* 142.0592, *m/e* 142 (M^+, 33), 109 (100), 83 (7), 77 (8).

1,2-Difluoro-2-phenylpropane (8b), 2-Phenyl-3-fluoropropene-1 (9). The fluorination, workup procedure, and VPC purification were essentially the same as for **5a** (SE-30, Chromosorb A, AW, 10%, 150 °C). **8b** was isolated in 22% yield as a liquid, unstable product. NMR data are listed in Table II. Mass spectrum: calcd for $C_9H_{10}F_2$ *m/e* 156.0759, found *m/e* 156.0748, *m/e* 156 (M^+, 10), 136 (100), 103 (65), 87 (35), 77 (31). **9** was isolated in 38% yield as a liquid product: mass spectrum calcd for C_9H_9F *m/e* 136.0688, found *m/e* 136.0687, *m/e* 136 (M^+, 100), 103 (80), 78 (27), 77 (27); NMR δ F −237 ppm (td), J_{FH} = 51, 2 Hz.

Acknowledgment. We thank Professor J. Slivnik for the xenon difluoride, Professor J. Marsel for providing facilities, and the Boris Kidric Foundation for financial assistance.

Registry No.—**1a**, 530-48-3; **1b**, 778-66-5; **1c**, 390-75-0; **1d**, 4333-75-9; **1e**, 948-55-0; **1f**, 4333-70-4; **1g**, 18218-20-7; **1h**, 29265-81-4; **2a**, 379-83-9; **2b**, 309-45-5; **2c**, 14090-30-3; **2d**, 59888-08-3; **2e**, 59888-09-4; **2f**, 59888-10-7; **2g**, 59888-11-8; **2h**, 59888-12-9; **3b**, 2042-85-5; **4c**, 52108-02-8; **5a**, 390-75-0; **5b**, 59888-13-0; **6**, 337-72-4; **7a**, 100-42-5; **7b**, 98-83-9; **8a**, 33315-79-6; **8b**, 59888-14-1; **9**, 14584-33-9; xenon difluoride, 13709-36-9.

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Mechanism of Bromination of 6-Azauracil in Aqueous Acid Solutions

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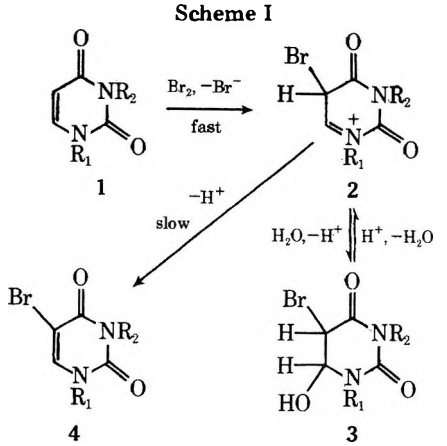
In dilute aqueous sulfuric acid solution the rates of bromination of 6-azauracil and 3-methyl-6-azauracil vary inversely with the hydronium ion concentration, whereas under the same conditions 1,3-dimethyl-6-azauracil is barely reactive. It is suggested that 6-azauracil and its 3-methyl derivative react with bromine via their anions resulting from deprotonation at N_1. It appears that a 6-aza nitrogen depresses the rate of bromine attack at the 5 position of a uracil by at least 10^{10}.

We have recently obtained evidence that the primary route for the monobromination of uracils (**1**, R_1, R_2 = H or Me) in aqueous acidic solutions involves two discrete steps[1] (Scheme I). Firstly, there is a rapid reaction of **1** and bromine

Scheme I



to give the cation **2** which is then captured by water to yield an observable intermediate[1] **3**. Secondly, there is a slow acid-catalyzed[1] dehydration **3** ⇄ **2** → **4**. Such a mechanism would appear to be less likely for the analogous brominations of 6-azauracils (**6** in Scheme II), since the cationic intermediate **5** should be much less stable than **2**.

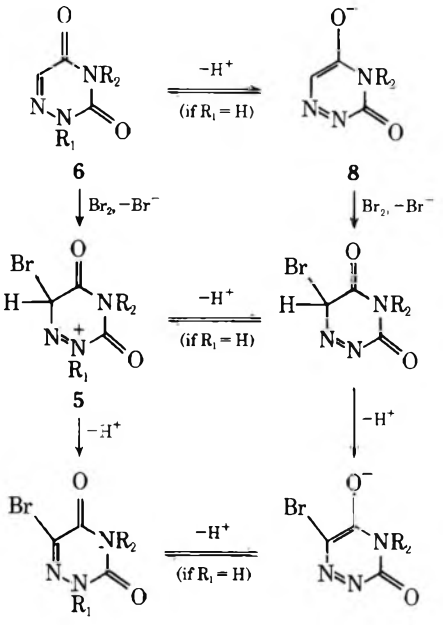
In aqueous solution, the 6-azauracils (**6**, R_1, R_2 = H or Me) react smoothly with bromine to give the appropriate 5-bromo derivatives[2,3] (**7**). In contrast to the behavior of uracils, this reaction is quite slow, and may be conveniently followed by monitoring the decrease in uv absorbance at 400 nm due to bromine. In dilute aqueous acid, and in the presence of an excess of a substrate (**6**), the rate of disappearance of bromine obeys first-order kinetics. Table I lists the derived second-order rate constants[4] for the reaction of bromine with substrates **6** (R_1 = R_2 = H) and **6** (R_1 = H; R_2 = Me) at various acid concentrations. These clearly show an inverse dependence upon the hydronium ion concentration, and thus suggest a mechanism in which bromine attacks the anion **8** (Scheme II). Support for this interpretation is the observation

Table I. Variation of the Rate of Disappearance of Bromine with $[H_3O^+]$ Due to Reaction with 6-Azauracils (6)[a,b]

$[H_2SO_4]$, N	$1/[H_3O^+]$, M^{-1}	$k_2^{obsd} \times 10^3$, M^{-1} s^{-1} 6 ($R_1 = R_2 = H$)[c]	$k_2^{obsd} \times 10^3$, M^{-1} s^{-1} 6 ($R_1 = H$; $R_2 = Me$)[d]
0.05	31.3	8.15	11.5
0.07	23.3	6.06	8.70
0.10	16.9	5.17	6.55
0.15	11.9	3.86	4.69
0.30	6.25	2.44	2.76
0.50	3.85	2.12	

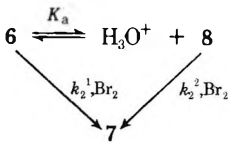
[a] $[6] = 1 \times 10^{-2}$ to 4×10^{-2} M; $[Br_2]_0 = 2 \times 10^{-3}$ to 4×10^{-3} M. [b] Each k_2^{obsd} is an average of two or three determinations. At 30 °C. [c] These data fit $k_2^{obsd} \times 10^3 = 1.2 + 0.22/[H_3O^+]$ (corr coeff = 0.997). [d] These data fit $k_2^{obsd} \times 10^3 = 0.56 + 0.35/[H_3O^+]$ (corr coeff = 0.999).

Scheme II



that, under the same conditions, the dimethyl derivative **6** ($R_1 = R_2 = Me$) reacts with bromine much more slowly ($k_2^{obsd} \simeq 10^{-4}$ M^{-1} s^{-1}) than the other two substrates.

The known[5] pK_a for deprotonation of 3-methyl-6-azauracil (**6**, $R_1 = H$; $R_2 = Me$) is 9.52 (at 25 °C), whereas that for 6-azauracil[5] is 7.00 (at 25 °C). However, this last value is for the loss of the 3-H, and presumably the pK_a for loss of the 1-H is also about 9.5. In any event, it is clear that under the conditions of our kinetic runs (pH 0.58–1.50) the actual concentration of **6** and the stoichiometric concentration of **6** are virtually identical. Given these circumstances, the proposed mechanism



requires that

$$k_2^{obsd} = k_2^1 + k_2^2 K_a/[H_3O^+] \quad (1)$$

as the data in Table I support.

Table II lists the individual second-order rate constants associated with **6** and **8** derived by fitting eq 1 to the data in Table I. For the reaction of bromine with the anions **8** we have $k_2^2 \simeq 10^6$ M^{-1} s^{-1}. This value seems quite reasonable in that phenoxide ions react with bromine at similar rates (10^6–10^9 M^{-1} s^{-1}).[6] The slight difference in reactivity between the two anions **8** ($R_2 = H$) and **8** ($R_2 = Me$) is in the direction expected for methyl substitution.

Table II. Kinetic Parameters for the Reaction of 6 with Bromine[a]

Parameter in eq 1	6 ($R_1 = R_2 = H$)	6 ($R_1 = H$; $R_2 = Me$)	6 ($R_1 = R_2 = Me$)
$k_2^1 \times 10^3$, M^{-1} s^{-1}	1.2	0.56	~0.1
$k_2^2 K_a \times 10^3$, s^{-1}	0.22	0.35	
pK_a (25 °C)[b]	9.5?	9.52	
$k_2^2 \times 10^{-6}$, M^{-1} s^{-1}	~0.7	~1.0	

[a] Obtained by fitting eq 1 to the data in Table I. See footnotes *c* and *d* in Table I. At 30 °C. [b] Reference 5.

More curious is the apparent range of reactivities for attack of bromine upon the un-ionized forms **6**. It seems that the dimethyl derivative **6** ($R_1 = R_2 = Me$) is about one-tenth as reactive as the parent **6** ($R_1 = R_2 = H$). On the basis of the simple pathway

$$6 + Br_2 \xrightarrow{slow} 5 + Br^- \xrightarrow{fast} 7 + HBr$$

one might expect a reverse order to obtain. Without further data it is difficult to rationalize the observed order, but it might be understandable if the deprotonation **5** → **7** were partially or completely rate determining.

As a final point, we return to the comparison with uracils (**1**). In view of the rapidity of attack upon **1**,[7] we estimate that the presence of the 6-aza nitrogen (in **6**) depresses the rate of this reaction by at least 10^{10}. It should also be pointed out that uracils having an ionizable 1-H (i.e., **1**, $R_1 = H$) may react via their anions since the pK_a's for this proton loss[5] are also about 9.5.

Experimental Section

The following compounds used in this study were prepared by literature procedures: 6-azauracil (**6**, $R_1 = R_2 = H$),[2] 3-methyl-6-azauracil (**6**, $R_1 = H$; $R_2 = Me$),[5] 1,3-dimethyl-6-azauracil (**6**, $R_1 = R_2 = Me$),[5] 5-bromo-6-azauracil (**7**, $R_1 = R_2 = H$),[2] 5-bromo-3-methyl-6-azauracil (**7**, $R_1 = H$; $R_2 = Me$),[3] and 5-bromo-1,3-dimethyl-6-azauracil (**7**, $R_1 = R_2 = Me$).[3]

The kinetics of bromine disappearance were measured spectrophotometrically using a Cary 14 instrument with cells thermostatted at 30.00 ± 0.02 °C. In the presence of an approximate tenfold excess of substrates (**6**) good first-order rate constants (k_1^{obsd}) were obtained. These were converted to second-order rate constants using[8] $k_2^{obsd} = k_1^{obsd}/([6] - [Br_2]_0)$, since the excess of substrate over bromine was not particularly large. The values given in Table I are the average of two or three such determinations. As previously,[9] hydronium concentrations were calculated from the acid concentrations assuming the second dissociation constant of sulfuric acid[10] to be 1.20×10^{-2}.

Acknowledgments. We thank the National Research Council of Canada for continued financial support.

Registry No.—**6** ($R_1 = R_2 = H$), 461-89-2; **6** ($R_1 = H$; $R_2 = Me$), 1627-30-1; **6** ($R_1 = R_2 = Me$), 15677-10-8.

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Fluorine-19 Nuclear Magnetic Resonance Studies of Nitrogen-Substituted Fluorobenzenes

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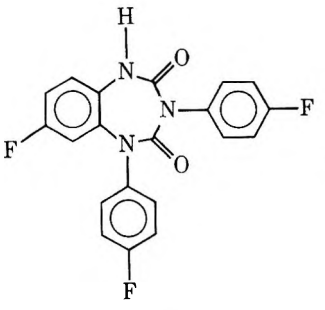
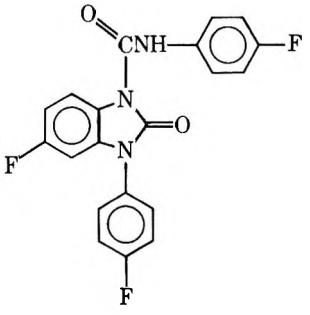
^{19}F chemical shifts of a series of nitrogen-substituted fluorobenzenes have been investigated to demonstrate their use as a probe in determining structure. σ constants are evaluated for selected nitrogen substituents from chemical shifts of the meta- and para-substituted fluorobenzenes. The results are discussed in terms of inductive, resonance, and conformational effects of the substituents on nitrogen.

Although many ^{19}F chemical shifts of fluorobenzenes with nitrogen substituents have been reported,[1-5] the appropriate model compounds required for the structure elucidation of a by-product from the reaction of nitrobenzene with carbon monoxide[6] were not available. A series of carbonyl-substituted nitrogen derivatives were compiled (Tables I and II) and analzed to show that the structure was **58a** or **58b**, but the final assignment of **58b** had to be accomplished



58a



58b

by preparing authentic samples of the nonfluorinated analogues and comparing spectral properties. In addition, we prepared and measured the ^{19}F chemical shifts for a series of meta- and para-substituted fluorobenzenes to determine σ constants for a number of nitrogen functions not previously reported.

Results and Discussion

In Table I the meta- and para-^{19}F chemical shifts for a series of nitrogen-substituted fluorobenzenes are reported relative to fluorobenzene. For this series, Taft's inductive and resonance parameters, σ_I and σ_R,[1] are calculated and compared to literature values. Although this is not a complete compilation of substituent effects for nitrogen functions from ^{19}F shift measurements, it is comprehensive and includes much new data. Table II gives the ^{19}F NMR chemical shifts of a further series of para-nitrogen-substituted fluorobenzenes. The data in Table I are arranged in order of increasing inductive power of the substituent (downfield shift of *m*-fluorine) in contrast to Table II which emphasizes the resonance effects.

Oxygen Bonded to Nitrogen (ArNO). The *p*-fluoro resonance for nitrobenzene (**34**) appears at very low field because the large resonance withdrawal effect of nitro reinforces its strong inductive withdrawal effect. However, the *p*-fluoro shift for nitrosobenzene (**17**) is slightly further downfield although the nitroso group is inductively less effective (expected from the electronegative substitution by one vs. two oxygens). Steric factors may inhibit the resonance interaction of nitro relative to nitroso. The azoxyphenyl group [–N(O)=NAr, see **25**] has an inductive effect intermediate between nitroso (NO) and nitro (NO_2) as expected from replacement of one oxygen by the less electronegative NAr group. The resonance interaction of this group is less than nitro or nitroso ($\sigma_R \sim +0.06$ vs. +0.21 for nitro and +0.32 for nitroso; note that the *p*-fluoro shifts in azoxybenzenes have not been definitely assigned but are not significantly different) as would be expected if the bulky ArN group inhibits coplanarity required for effective resonance interaction.

Nitrogen Substituents of Nitrogen (ArNN). The *p*-fluoro shifts for both the phenylhydrazine **3b** and hydrazobenzene **40** are only slightly downfield from aniline. Both fluorines in azoxybenzene **25** are very similar, and close to *cis*-azobenzene rather than the trans isomer. The ammonium cation (see **35**) has almost no effect on the *p*-fluoro resonance, whereas the resonance effect of the diazonium ion (see **39**) shifts its resonance to the lowest field of all fluoroaromatic compounds.

The meta shifts move downfield in order NH_2, NHOH, N=NAr (trans), N=N(→O)Ar, N=NAr (cis), –N=O. The cis form of azobenzene **22** has an inductive effect larger than the =N(→O)Ar group (assuming the assignment indicated for the *m*-fluoro shifts for the azoxybenzene). Direct interaction of the π system of the phenyl groups may occur in the cis isomer causing this unusual downfield shift. The resonance effects suggest that the phenyl groups must be twisted and the N=N system cannot effectively conjugate to withdraw charge density from the ring [σ_R(cis) −0.04 vs. σ_R(trans) +0.08, see Figure 1]. In the cis form, resonance donation of charge density (Figure 1) may become the major factor. Such electron donation by resonance has been proposed for arylazoplatinum compounds.[7a] Our conclusions on the cis and trans structures are supported by other experimental evidence.[7b]

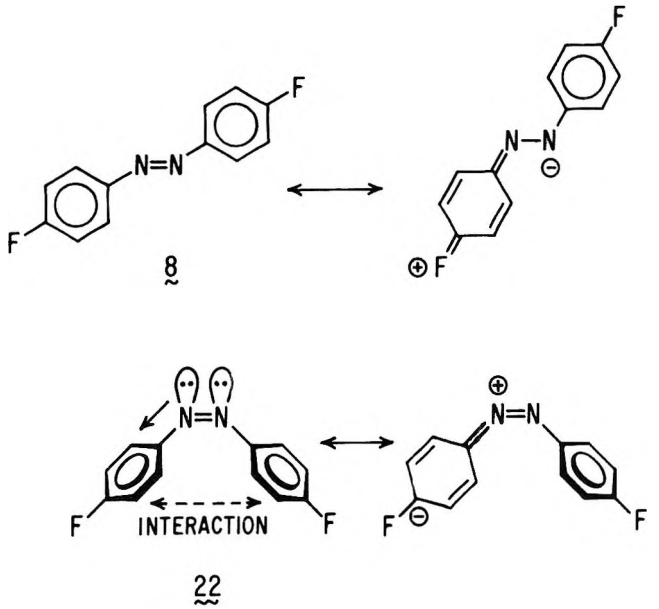
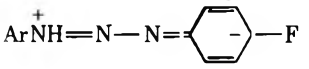


Figure 1. Resonance interactions of *cis*- and *trans*-azobenzenes.

Only one para [19]F resonance is seen for diphenyltriazene **52** owing to rapid proton exchange. The triazene anion **41** shows a singlet at slightly higher field. In 1-methyl-1-phenyl-3-(4-fluorophenyl)triazene (**55**) the single resonance may be similar to the corresponding resonance in the parent compound **52.** Simple arithmetic predicts the second reso-

$C_6H_5NN{=}NAr$	$ArNHN{=}NAr$
CH_3	
−117.0	$(-120.6 - 117.0)/2 = -118.8$
55	**52**

nance in the parent compound to be about −120.6. The marked upfield shift (−117) of the triazene **55** relative to that of azobenzene (δ −110) **8** may arise from a resonance interaction involving the nitrogen as shown. The downfield shift



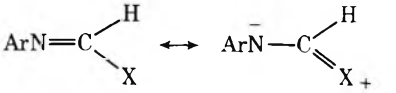
of the other resonance relative to phenylhydrazine **3** (−120.6 vs. −125) is similarly explained. The utility of the fluorinated triazenes in structural studies of transition metal complexes has been discussed.[7c]

Two resonances are seen for *N*-nitrosobis(4-fluorophenyl)amine (**27**), demonstrating that rotation about the N–N bond and inversion at nitrogen is slow. The fluorine chemical shift difference of 4 ppm is extremely large for rotational isomers at so remote a position, but the available data do not allow unambiguous assignment of the resonances to their respective rings.

The effect of nitrogen substitution on a nitrogen substituent should be contrasted with a recent report of phosphorus substitution on nitrogen.[14] The $N{=}P(C_6H_5)_3$ group (see compound **0,** Table I) appears to be the most electron-donating group on record. A very strong inductive electron donation (σ_I −0.20) is enhanced by a strong resonance donation (σ_R −0.45). Although the ressonance donation is slightly less effective than a NH_2 group, the strong inductive effect makes the $N{=}P(C_6H_5)_3$ group the strongest electron-donating group that has been measured.

The electron-donating ability of the $N{=}P(C_6H_5)_3$ group suggests a large contribution from the ylide resonance structure. The aminyl anion ^-NR should be one of the most powerful electron-donating groups, and since the electronegativity of phosphorus is close to that of hydrogen, the phosphinimines are probably a reasonable model for the anilide anion Ar^-NH.

Nitrogen Bonded to Carbon. A. ArN=C. The *p*-fluoro shifts for isocyanate **18** and carbodiimide **16** are quite close, suggesting little resonance difference between these groups. The isocyanate group is inductively a little stronger because of the greater electronegativity of the C=O compared to C=NAr. The *p*-fluoro shift differences between various types of imines are very significant, suggesting large and variable resonance contributions from ionic forms.

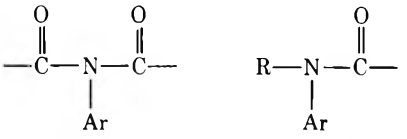


X	Compd	−δ
C_6H_5	**54**	117.5
OC_2H_5	**47**	120.4
$N(CH_3)_2$	**42**	123.9

The isonitrile group (see compound **30**) is inductively more electron withdrawing than nitroso, suggesting that an electron-deficient carbon is more electronegative than oxygen. However, the isonitrile does not accept the charge by resonance nearly as effectively as a nitroso group since the σ_R of $-N{\equiv}C$ is only +0.02 vs. +0.30 for nitroso.

B. ArNC=O. Because of our interest in products derived from phenyl isocyanate, this class of compounds is the largest of those we studied. The *p*-fluoro shifts of ureas and urethanes occur at highest field in the −121-ppm range. Substitution at the three position of ureas (compounds **6** and **7**) causes little shift of the one aryl resonance unless there is also a conformation change (see compound **46a**). Amides have a slightly lower field *p*-fluoro resonance in the range of −119 ppm. The shift differences between various types of amides is less than 1 ppm and, in general, shifts from isomeric amides can be resolved though not assigned.

The *p*-fluoro shifts of N,N-disubstituted compounds, of which imides are a special case, appear at low field in the range



of −113 ppm. The shift ranges for imides and N,N-disubstituted amides overlap so much that these classes cannot be distinguished by [19]F NMR (see below). Thus we could not predict the positions of the [19]F NMR resonances of **58a** and **58b** with sufficient accuracy to unambiguously assign the correct structure to the then unknown product.[6] Phenyl substitution on nitrogen causes a 5-ppm downfield shift, independent of the remaining substitution. Compare amines **1, 9,** and **19** and ureas **7** and **46b.**

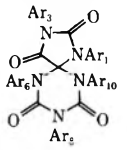
The meta shifts also vary considerably, and again both substitution and configuration have significant effects. Two striking examples are the effect of a 5-aryl substituent in the biurets **10** and **24** in producing a marked upfield shift.

The data for the isocyanate groups and their dimers and trimers should be compared with those of the related bisamide and biuret in Table I. The isocyanate trimers **15** have chemical shifts and σ parameters similar to those of the bisamides **23** and the biurets **51.** The two carbonyl functions on the nitrogen make the nitrogen electron withdrawing inductively and damp

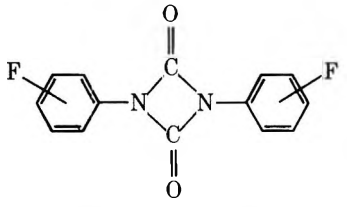
Table I. ^{19}F NMR Chemical Shifts of Nitrogen Substituted Fluorobenzenes and Substituent Parameters

	Compd (Ar = C_6H_4F)	Chemical shift, ppm[a] $\int_H^m$	$\int_H^p$	$\int_m^p$	Substituent parameters σ_I	σ_R	Solvent	Ref
0	ArN=P(C_6H_5)$_3$	+2.02	+15.45	+13.43	−0.20	−0.46	$CDCl_3$	14
1	$ArNH_2$	+0.50	+14.20	+13.70	+0.01	−0.48	CCl_4	1
2	$ArN(CH_3)_2$	−0.08	+15.65	+15.73	+0.10	−0.54	CCl_4	1
3a	ArNHOH	−0.27	+11.11	+11.38	+0.12	−0.39	CH_3CN	
3b	$ArNHNH_2$	−0.38	+12.25	+12.63	+0.14	−0.43	Meta in CCl_4, para in CH_3OH	1
4	ArNHCNHC$_6$H$_5$ (O)	−0.50	+8.55	+9.05	+0.15	−0.31	Acetone	
5	ArN=NC$_6$H$_5$ (trans)	−0.78	−3.25	−2.47	+0.19	+0.08	CCl_4	1, *b*
6	ArNHCNH$_2$ (O)	−0.78	+8.21	+8.99	+0.19	−0.30	CH_3CN	
7	ArNHCNHAr (O)	−0.96	+7.58	+8.54	+0.22	−0.29	CH_3CN	
8	ArN=NAr (trans)	−1.06	−3.39	−2.33	+0.23	+0.08	CCl_3F	*b*
9	Ar_2NH	−1.33	+9.35	+10.68	+0.27	−0.36	CCl_3F	
10	ArNHCNHCNHAr (O, O)	−1.36	+5.86	+7.22	+0.28	−0.24	CH_3CN	
11	ArNHCCH$_3$ (O)	−1.36 (−1.42, −1.70)	+5.37 +5.15	+6.76	+0.28	−0.23	$C_2H_4Cl_2$ hydrocarbon, CCl_4	5 1
12	ArN=NAr (O)	−1.38 [c](−1.38	−3.84 −4.17	−2.46 −2.79	+0.28 +0.28	+0.08 +0.09)	CCl_3F	
13	ArNHCH (O)	−1.42	+4.59	+6.01	+0.29	−0.20	CH_3OH	4a
	Z form	−1.40	+5.15	+6.55	+0.28	−0.22	CD_3CN	4b
	E form	−1.70	+5.1	+6.80	+0.32	−0.24	CD_3CN	4b
14	ArNHCNH$_2$ (S)	−1.44	+2.50	+3.94	+0.29	−0.13	CH_3CN	3
15	(ArNCO)$_3$ (cyclic trimer)	−1.53	−1.07	+0.46	+0.30	−0.20	CH_3CN	
16	ArN=C=NAr	−1.59	+4.02	+5.61	+0.31	+0.19	CCl_3F	
17	ArNO	−1.78	−11.10	−9.32	+0.34	+0.32	CCl_4	1
		−1.86	−10.78	−8.92	+0.35	+0.30	CCl_3F	
18	ArNCO	−1.92	+3.11	+5.03	+0.35	−0.17	CCl_3F	2
19	Ar_3N	−1.97	+6.73	+8.70	+0.36	−0.29	CCl_3F	
20	ArNHCN	−2.00	+7.36	+9.36	+0.37	−0.31	CH_3CN	3
21	ArN_3	−2.02	+4.73	+6.75	+0.37	−0.23	CH_3CN	
22	ArN=NAr (cis) (O)	−2.05	−0.85	+1.20	+0.37	−0.04	CCl_3F	
23	ArN(CCH$_3$)$_2$ (O)	−2.06	−0.95	+1.11	+0.37	−0.04	$ClCH_2CH_2Cl$	5
24	ArNHCNHCNH$_2$ (O, O)	−2.15	+6.39	+8.54	+0.38	−0.29	CH_3CN	
25	ArN=NAr (O)	−2.23 [c](−2.23	−4.17 −3.84	−1.94 −1.61	+0.40 +0.40	+0.07 +0.05)	CCl_3F	
51	ArN(CONHAr^2)$_2$	−2.23	−0.93	+1.3	+0.39	−0.04	CH_3CN	
26	ArNCS	−2.39	−0.20	+2.19	+0.42	−0.07	CCl_3F	2
27	Ar_2NNO	−2.41 [d](−2.41	+1.96 −2.17	+4.37 +0.24	+0.42 +0.42	−0.15 −0.01)	CH_3CN	
28	ArNHSO$_2$CH$_3$	−2.42	+3.69	+6.11	+0.42	−0.21	$ClCH_2CH_2Cl$	5
29	ArN(SO$_2$CH$_3$)$_2$	−2.56	−3.56	−1.00	+0.45	+0.04	$ClCH_2CH_2Cl$	5
30	ArNC	−2.76	−3.21	−0.45	+0.47	+0.02	CCl_3F	4
31	Ar_2NNO	[d]−2.85 (−2.85	−2.17 +1.96	+0.68 −4.81	+0.49 +0.49	−0.02 −0.16)	CH_3CN	
32	ArN(CF$_3$)$_2$	−2.86	−3.19	−0.33	+0.49	+0.01	CCl_3F	2
33	(ArNCO)$_2$ (cyclic dimer)	−3.01	+4.02	+7.03	+0.51	−0.24	CH_3CN	
34	$ArNO_2$	−3.45	−9.55	−6.10	+0.57	+0.21	CCl_4	1
35	$ArNH_3^+$	−3.63			+0.58		CH_3OH	1
		−5.01	−3.75	+1.26	+0.79	−0.04		*e*
36	ArN(SO$_2$CF$_3$)$_2$	−4.41	−7.29	−2.88	+0.70	+0.10	$ClCH_2CH_2Cl$	5
37	ArN(CN)$_2$	−5.75	+0.64	+6.39	+0.89	−0.22	CCl_3F	*f*
38	$ArN^+(CH_3)_3$	−5.95			+0.93		CH_3OH	1

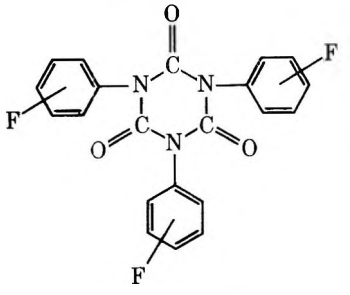
Table I (*Continued*)

	Compd (Ar = C_6H_4F)		Chemical shift, ppm[a] f_H^m	f_H^p	f_m^p	Substituent parameters σ_I	σ_R	Solvent	Ref
39	$ArN_2^+PF_6^-$		−10.28	−30.55	−20.27	+1.53	+0.69	CH_3CN	*g*
60		Ar							
		1	−4.73	−1.43	+3.3	+0.75	−0.06 ± 0.05	CH_3CN	
		3	−3.13	−2.43	+0.7	+0.52	−0.06 ± 0.05	CH_3CN	
		6,10	−3.43	−3.33	+0.1	+0.56	−0.003	CH_3CN	
		8	−1.33	−0.53	+0.8	+0.27	−0.03	CH_3CN	

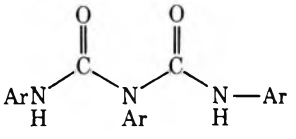
[a] Chemical shift relative to fluorobenzene (in CCl_3F, −113.10 ppm; in CH_3CN, −113.83; acetone, 113.4) using the designation (ref 1) of + to higher field. [b] A recent summary of substituent effects for the phenylazo group is given in ref 15. [c] Positive assignment of fluoroaryl was not possible. Consequently, both combinations of meta and para values are possible. Entries **12** and **25** should be compared. [d] Positive assignment of fluoroaryl was not possible. Consequently, both combinations of meta and para values are possible. Entries **27** and **31** should be compared. [e] Unpublished work by Professor Olah reported in G. A. Olah and P. R. Schleyer, "Carbonium Ions", Vol. IV, Wiley-Interscience, New York, N.Y., 1973, p 1740. [f] Unpublished data by W.A.S. and referenced in J. W. Rakskys, R. W. Taft, and W. A. Sheppard, *J. Am. Chem. Soc.*, **90**, 5236 (1968). [g] Approximate values were reported for $FC_6H_4N_2^+$ by R. W. Taft, *J. Am. Chem. Soc.*, **85**, 3152 (1963), Figure 4, as f_H^m −9.8 and f_H^p −29.8 (CH_3CN).



isocyanate dimer **33**



isocyanate trimer **15**



biuret **51**

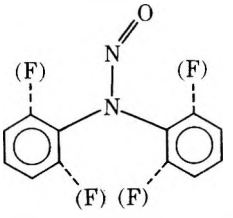
the normal resonance donation. The isocyanate dimer **33** and the isocyanate **18** both have an inductive electron-withdrawing effect (the dimer significantly more strongly), but the nitrogen remains strongly electron donating. Apparently the strain in the four-membered ring dimer makes it behave like the isocyanate rather than a nitrogen substituted by two carbonyl groups. Conformational effects as noted for *N,N'*-diarylureas[8] may also be important in these systems.

The single resonance in each of the isocyanate oligomers shows that no unsymmetrical structures are present, and provides confirmation of the structures proposed for **33** and **15**.

C. $ArNR_2$. Methyl substitution on nitrogen causes a small upfield shift, so that *N,N*-dimethyl-*p*-fluoroaniline (**2**) has a higher shift than the aniline. Electronegative groups such as cyano, trifluoromethyl, and trifluoromethylsulfonyl (see compounds **37, 32,** and **36**) cause progressive shifts to lower field, presumably by making the nitrogen lone pair less available for resonance interaction with the aromatic ring. The *m*- and *p*-fluoro shift differences between aniline (**1**), diphenylamine (**9**), and triphenylamine (**19**) may also be explained similarly since a phenyl group is electron withdrawing, but with the additional constraint that coplanarity of even two rings is not possible because of hydrogen–hydrogen repulsions.

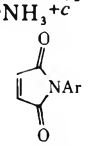
Two cyano substituents on nitrogen (compound **37**) appear very effective in making the nitrogen as electron withdrawing as if it had a full positive charge (note, however, the difference between NH_3^+ and $N(CH_3)_3^+$; see ref 1 for a discussion of this difference). However, the $N(CN)_2$ group has a σ_R of −0.22 in contrast to $N(CF_3)_2$, $N(SO_2CH_3)_2$, and $N(SO_2CF_3)_2$, which all have a positive σ_R. No obvious explanation is available other than steric interaction with the large or bulky electron-withdrawing groups prevent coplanarity needed for resonance donation of the electron pair on nitrogen and direct p–π interaction of the SO_2 or CF_3 groups gives abnormal resonance effects.

***N*-Nitrosodiphenylamines.** After observing the large chemical shift in bis(4-fluorophenyl)nitrosamine (**31**), and cognizant of the work of Randall on the ^{13}C NMR spectrum of *N*-methyl-*N*-phenylnitrosamine,[9a] we prepared the bis(3-fluorophenyl) and bis(2-fluorophenyl) analogues and observed their ^{19}F NMR spectra. If slow rotation about the *N*-phenyl bonds occurred for either of these compounds, we would expect four resonances. Only two were seen for the meta derivative. The four-line pattern of the ortho derivative arises from two resonances and an inter-ring fluorine–fluorine coupling of 3.6 Hz, δ −116.8 and −122.8. No change was seen on cooling the sample to −60 °C. Either one fluorine rotational isomer is greatly preferred or there is rapid rotation about the *N*-phenyl bond; the latter is more likely.



Use of a 4-Fluorophenyl Label in Mechanism Studies. To within the accuracy we desired for our investigation, peak heights of the proton decoupled ^{19}F NMR spectrum could be equated to mole ratios. We recognize that nuclear Overhauser effects can be quite significant, but are unlikely to vary dramatically when a para substituent is changed.[9b] The progress of a chromatographic separation is easily monitored by the changing ratio of peaks in the ^{19}F NMR spectrum. The com-

Table II. Fluorine Chemical Shifts in Nitrogen Substituted 4-Fluorobenzenes

	Compd[a]	– Chemical shift, ppm[b]		Compd	– Chemical shift, ppm
(2)	$ArN(CH_3)_2$[c]	129.7	(16)	ArN=C=NAr	117.1
(1)	$ArNH_2$	128.8	55	$C_6H_5N(CH_3)N{=}NAr$[e]	117.0
40	ArNHNHAr	126.9	(33)	$(ArNCO)_2$	116.8
(9)	Ar_2NH	124.1	56	$ArNHC(S)NH_2$[f]	116.6
41	ArN—N=NAr[d,e]	124.0	(18)	ArNCO	116.6
42	$ArN{=}CHN(CH_3)_2$	123.9	46b	$Ar_2NCONHAr$	116.0
(6)	$ArNHCONH_2$	121.8	(27)	ArN(NO)Ar	115.8
43	Ar_2NNH_2	121.6	(48)	$Ar_2NCON(Ar)CONHAr$	115.6
(20)	ArNHCN[f]	121.5	(48)	$Ar_2NCON(Ar)CONHAr$	115.3
(7)	ArNHCONHAr	121.2	(37)	$ArN(CN)_2$[h]	114.7
44	$ArNHCOOCH_3$	121.1	(35)	$ArNH_3{}^+$[c]	114.5
45	PhNHN(Ph)CONHAr	120.8			
(19)	Ar_3N	120.6	57		114.2
46a	$Ar_2NCONHAr$	120.5			
47	$ArN{=}CHOC_2H_5$	120.4			
(24)	$ArNHCONHCONH_2$	120.2			
48	$Ar_2NCONArCONHAr$	119.8		fluorobenzene	113.8
(10)	ArNHCONHCONHAr	119.7	(22)	ArN=NAr (cis)	113.0
(11)	$ArNHCOCH_3$	119.3	(51)	$(ArNHCO)_2NAr$	112.9
			(15)	$(ArNCO)_3$	112.8
(13)	ArNHCOH	119.3	(27)	ArN(NO)Ar	111.6
49	$ArNHCOCH{=}CH_2$	119.2	(32)	$ArN(CF_3)_2$[i]	110.9
50	$ArNHCOC_6H_5$	119.1	(30)	ArNC[j]	110.2
51	$(ArNHCO)_2NAr$	119.0	(8)	ArN=NAr (trans)	110.0
52	ArNHN=NAr[d,e]	118.8	(12)	ArN=N(O)Ar	109.2
(21)	ArN_3	118.6			108.9
53	$ArNHCOCH{=}CHCO_2H$	118.0[f]	(34)	$ArNO_2$[c]	103.4
54	$ArN{=}CHC_6H_5$	117.5	(17)	ArNO[c]	101.0
			(39)	$ArN_2{}^+PF_6{}^-$	83.3

[a] Ar is 4-fluorophenyl, Ph is phenyl. Number in parentheses is from Table I or earlier in Table II. [b] Unless indicated otherwise, chemical shift was determined at less than 5% concentration in CH_3CN relative to internal standard of CCl_3F; C_6H_5F is at −113.8 ppm under these conditions. [c] Reference 1. [d] Reference 7b, average of the two shifts. [e] In tetrahydrofuran solvent. [f] Reference 3. [g] In Me_2SO solvent. [h] See footnote *f*, Table I. [i] Reference 2. [j] Reference 4a.

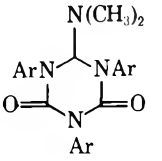
bination of broad chemical shift range with narrow absorption and the sensitivity to volatile and nonvolatile materials makes the fluorine labeling technique uniquely valuable as an analytical tool.

We have several times encountered the problem of whether or not two isomers were produced in a reaction. Gas chromatography and the ^1H NMR spectrum could not answer the question. Preparing a derivative using 4-fluorophenyl instead of phenyl provided a quick answer to the question. In all cases more than one peak was seen in the proton decoupled ^{19}F NMR spectrum, indicating a mixture of isomers. A rough quantitative analysis was possible even when the peaks could not be assigned to their respective structures. This method complements the use of ^{13}C NMR and peak counting to establish the presence of isomers, and may be the technique of choice depending on the instrumentation available.

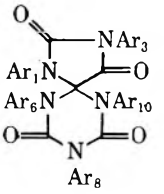
Recent examples where fluorophenyl was used as a probe to determine information on the mechanism of reactions are in studies on reactivity of intermediates from decomposition of diazodicyanoimidazole[10] and 5-diazomethyl-1,4-diphenyl-1,2,3-triazole with fluorobenzene[11] and arylbicyclooctyl cations.[12] We also used the fluorophenyl probe to study the isocyanate DMF adducts **59** and **60**.[13]

The imide and amide *p*-fluorophenyl resonances in triazine **59a** differ by less than 0.1 ppm, but when the triazinedione **59c** is prepared from a mixture of 4-fluorophenyl and phenyl isocyanates, six of the expected seven resonances for the six structures are resolved. In principle they could be assigned by preparing **59c** from various ratios of the isocyanates.

The fluorine resonances of the *m*-fluorophenyl isomer **60b** show large separations. Two resonances of spiro compounds **60a** and **60b** were assigned by reference to the mixed compounds **60c** and **60d**. However, the resonance parameters calculated from the para shifts are all small, suggesting that



59a, Ar = 4-FC_6H_4
b, Ar = C_6H_5
c, Ar = 4-FC_6H_4 or C_6H_5



60a, Ar = 4-FC_6H_4
b, Ar = 3-FC_6H_4
c, $Ar_1 = Ar_3 = C_6H_5$; $Ar_6 = Ar_8 = Ar_{10}$ = 4-FC_6H_4
d, $Ar_1 = Ar_3 = C_6H_5$; $Ar_6 = Ar_8 = Ar_{10}$ = 3-FC_6H_4
e, Ar = C_6H_5 or 4-FC_6H_4

the *N*-phenyl groups are not coplanar with the adjacent carbonyls. The same argument holds for the isocyanate trimer **15** and the central nitrogen in biuret **51**. The larger σ_R for isocyanate dimer **33** may arise because the bond angle deformation in the small ring allows the phenyl group to be coplanar with the uretidione ring. The inductive effect of one of the aryl groups on the five-membered ring is abnormal. Inspection of models suggests that in all conformations the phenyl on N-1 interacts strongly with the aryl groups in the six-membered ring. The inductive parameter for Ar_3 and isocyanate dimer

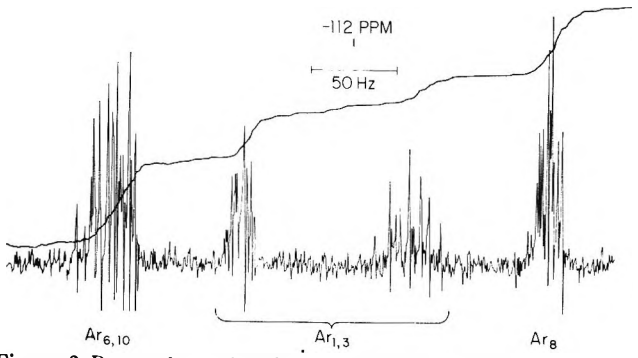


Figure 2. Proton decoupled ^{19}F NMR spectrum of **60e**.

33 are similar. The effect for Ar_8 is similar to that of the isocyanate trimer **15**, as expected for the six-membered position, but $Ar_{6,10}$ also shows an abnormally large inductive effect. Again steric interaction on $Ar_{6,10}$ could cause this apparent abnormal effect, although perhaps proximity to the spiro ring junction could create the abnormal effects for $Ar_{6,10}$ as well as Ar_1.

The immense resolving power of this fluorine labeling technique is seen in Figure 2 when the spiro compound **60e** is prepared from a mixture of phenyl and 4-fluorophenyl isocyanates. As suggested by Ulrich,[13] a statistical mixture of all possible isomers is produced. Although most unique fluorine resonances are resolved, assigning each peak to its proper isomer is essentially impossible. Changing a para hydrogen to a para fluorine has a discernible effect on a fluorine resonance as far as 15 bonds and 13 Å away.

Experimental Section

Synthesis. New compounds listed in Tables I and II were prepared by literature procedures.

NMR. ^{19}F NMR spectra were run as dilute solutions in the indicated solvents with proton noise decoupling on a Varian HA-100 instrument locked to internal $CFCl_3$.

Substituent Parameters. The inductive and resonance substituent parameters σ_I and σ_R were calculated by the procedure described by Taft et al.,[1] and as used in other substituent studies.[2-4]

$$\int_H^{m-X} = (-7.10)\sigma_I + 0.60$$

$$\int_{m-X}^{p-X} = -29.5\sigma_R$$

***N,N*-Dimethyl-*N'*-(4-fluorophenyl)formamidine (42).** A solution of 10 ml of 4-fluorophenyl isocyanate and 50 ml of DMF was heated at 115 °C overnight. Distillation at reduced pressure gave 7.5 g of colorless liquid. Anal. Calcd for $C_9H_{11}FN_2$: C, 65.0; H, 6.7. Found: C, 65.1; H, 6.9. Ir 3.4, 6.1, 6.7, 7.3, 8.2, 8.3, 9.1, 12.0, 12.9 μ; ^{1}H NMR ($CDCl_3$/Me_4Si) δ 2.92 (s, 2 CH_3), 6.90 (d, J = 7 Hz, 4 H), 7.42 (s, =CH); ^{19}F NMR (CH_3CN/CCl_3F) δ −123.9.

1,3,5-Tris(4-fluorophenyl)-6-dimethylaminohexahydro-1,3,5-triazine-2,4-dione (59a). A solution of 2 g of imine **42** and 4 g of 4-fluorophenyl isocyanate was kept at room temperature for 2 days. The solid glass was triturated with ether to give 4.2 g of white solid, mp 161–162.5 °C. Anal. Calcd for $C_{23}H_{19}F_3N_4O_2$: C, 62.7; H, 4.4; N, 12.7. Found: C, 62.8; H, 4.5; N, 12.6. Ir 3.26, 3.39, 3.52, 3.58, 5.82, 5.96, 6.24, 6.63, 8.25, 12.15 μ; ^{1}H NMR (Me_2SO-d_6/Me_4Si) δ 3.98 (s, 2 CH_3), 6.10 (s, CH), 7.13–7.80 (m, 12 H); ^{19}F NMR (CH_3CN/CCl_3F) δ −114.53 (2), −144.44 (1).

1,3,6,8,10-Pentakis(4- and 3-fluorophenyl)-1,3,6,8,10-pentaazaspiro[4.5]decane-2,4,7,9-tetraone (60a and 60b). A solution of 2.4 g of imine **42** and 10 g of 4-fluorophenyl isocyanate was refluxed for 3 h under N_2. The viscous mass was poured into 60 ml of ether and during trituration 7.5 g crystallized. The analytical sample was recrystallized from CH_3CN, mp 249–250.5 °C. Anal. Calcd for $C_{35}H_{20}F_5N_5Oinfn4$: C, 62.8; H, 3.0; N, 10.4. Found: C, 62.6; H, 3.4. Ir 3.23, 5.53, 5.74, 5.87, 6.23, 6.61, 11.99 μ; ^{19}F NMR (CH_3CN/CCl_3F) δ −110.5 (2), −111.4 (1), −112.4 (1), −113.3 (1). The 3-fluorophenyl analogue **60b** was similarly prepared. Anal. Found: C, 63.1; H, 3.2; N, 10.4. ^{19}F NMR (CH_3CN/CCl_3F) δ −109.1 (1), −110.4 (2), −110.7 (1), −112.5 (1).

1,3-Bis(fluorophenyl)-6,8,10-triphenyl-1,3,6,8,10-pentaazaspiro[4.5]decane-2,4,7,9-tetraone (60c and 60d). A mixture of 3.9 g of **59b** and 7.5 g of 4-fluorophenyl isocyanate was heated at 150 °C overnight. Excess isocyanate was removed under vacuum and the residue triturated with acetone giving 5.5 g of white solid, mp 209 °C. Anal. Calcd for $C_{35}H_{23}F_2N_5O_4$: C, 68.3; H, 3.8; N, 11.4. Found: C, 68.5; H, 4.0; N, 11.3. ^{19}F NMR (CH_3CN/$CFCl_3$) δ −111.6, −112.7.

The 3-fluorophenyl analogue was similarly prepared, mp 214–218 °C. Anal. Found: C, 68.4; H, 3.9; N, 11.5. ^{19}F NMR (CD_3CN/$CFCl_3$) −111.3, −109.4.

Spiro Compounds 60e. A mixture of 3.6 g of phenyl isocyanate, 4.1 g of 4-fluorophenyl isocyanate, and 0.7 g of DMF was heated overnight at 150 °C under nitrogen. The glass was triturated with methanol precipitating 4.2 g of white crystals, mp 181–186 °C. The ^{1}H NMR spectrum showed only aromatic absorptions and the infrared spectrum was consistent with the spiro structure. The ^{19}F NMR spectrum is given in Figure 2. The distribution of fluoroaryl groups is not entirely random. The integral indicates an excess of this isocyanate at position 8.

Triazinediones 59c. A mixture of 3.0 g of *N,N*-dimethyl-*N'*-phenylformamidine and 5.5 g of 4-fluorophenyl isocyanate was allowed to stand at room temperature for 5 days. The viscous glass was triturated with ether precipitating 6 g of triazinedione **59c**: ^{19}F NMR ($CDCl_3$/$CFCl_3$) −113.61 (32%), −113.78 (21%), −113.79 (17%), −113.94 (19%), −113.96 (5%), and −114.07 (6%).

Registry No.—**0** para isomer, 18523-51-8; **1** para isomer, 371-40-4; **2** para isomer, 403-46-3; **3a** para isomer, 406-00-8; **3b** para isomer, 371-14-2; **4** meta isomer, 350-79-8; **4** para isomer, 330-98-3; **5** para isomer, 332-00-3; **6** meta isomer, 770-19-4; **6** para isomer, 659-30-3; **7** meta isomer, 369-83-5; **7** para isomer, 370-22-9; **8** meta isomer, 60253-47-6; **8** para isomer, 51788-93-3; **9** meta isomer, 333-53-9; **9** para isomer, 330-91-6; **10** para isomer, 60253-48-7; **11** para isomer, 351-83-7; **12**, meta isomer, 330-42-7; **12** para isomer, 326-04-5; **13** para isomer, 459-25-6; **14** para isomer, 459-05-2; **15** meta isomer, 60253-49-8; **15** para isomer, 60253-50-1; **16** meta isomer, 351-27-9; **16** para isomer, 351-74-6; **17** para isomer, 352-15-8; **18** para isomer, 1195-45-5; **19** meta isomer, 60253-410; **19** para isomer, 899-26-3; **20** para isomer, 14213-19-5; **21** para isomer, 3296-02-4; **22** para isomer, 51789-00-5; **23** para isomer, 36035-52-6; **24** para isomer, 60253-42-1; **26** para isomer, 1544-68-9; **27** meta isomer, 60253-43-2; **27** para isomer, 724-23-2; **28** para isomer, 35980-24-6; **29** para isomer, 36035-53-7; **30** para isomer, 24075-34-1; **32** para isomer, 3700-34-3; **33** meta isomer, 60253-44-3; **33** para isomer, 60253-45-4; **34** para isomer, 350-46-9; **35** para isomer, 29131-39-3; **36** para isomer, 36035-54-8; **37** para isomer, 60253-46-5; **38** para isomer, 38695-39-5; **39** meta isomer, 57103-74-9; **39** para isomer, 53260-51-8; **40** para isomer, 332-06-9; **42** para isomer, 15851-81-7; **43** para isomer, 1717-35-7; **44** para isomer, 16744-99-3; **45** para isomer, 60252-74-6; **46** para isomer, 60252-75-7; **47** para isomer, 59332-77-3; **48** para isomer, 60252-76-8; **49** para isomer, 60252-77-9; **50** para isomer, 366-75-6; **51** meta isomer, 60252-78-0; **51** para isomer, 38456-65-4; **53** para isomer, 60252-79-1; **54** para isomer, 331-98-6; **55** para isomer, 60252-80-4; **56** para isomer, 459-05-2; **57** para isomer, 6633-22-3; **59a**, 60252-81-5; **59b**, 17350-48-0; **60a**, 60252-82-6; **60b**, 60252-83-7; **60c**, 60252-84-8; **60d**, 60252-85-9.

Supplementary Material Available. The method of preparation and physical data on all new compounds, or compounds not previously well characterized in the literature or where ^{19}F NMR have not been reported (9 pages). Ordering information is given on any current masthead page.

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Reinvestigation of the Thermal Rearrangement of Alkenylidenecyclopropanes

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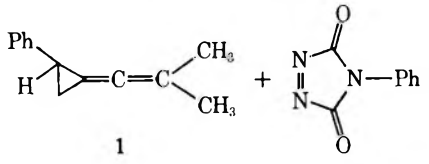
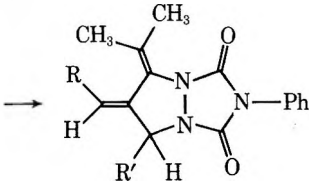
The thermal rearrangement of alkenylidenecyclopropanes has been reinvestigated. It is concluded that the thermal rearrangements occur via perpendicular trimethylenemethane-type diradicals and that the rearrangement is a typical methylenecyclopropane-type rearrangement. Contrary to the previously reported results, enantiomerization and diastereomerization of alkenylidenecyclopropanes is observed, and the activation enthalpies measured in this study are considerably lower than those reported. Whereas aryl-substituted alkenylidenecyclopropanes undergo thermal rearrangement under the more vigorous conditions required for cycloaddition with less reactive dienophiles, alkyl-substituted alkenylidenecyclopropanes rearrange much more slowly, allowing for reaction with the less reactive dienophiles.

In view of the tremendous synthetic utility of the [$_\pi$4 + $_\pi$2] cycloaddition reaction (i.e., the Diels–Alder reaction) for the construction of variously substituted cyclohexenes and the well-known tendency of the cyclopropyl moiety to mimic the carbon–carbon double bond in certain reactions, we embarked on a program designed to evaluate the synthetic utility of cycloaddition reactions of cyclopropane-containing compounds. Although methylenecyclopropanes[1] and vinylcyclopropanes[2] failed to undergo the desired cycloaddition reactions to form five- and seven-membered ring compounds even with the most reactive of the dienophiles, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), alkenylidenecyclopropanes reacted rapidly at 0 °C in the desired manner to form five-membered ring compounds[3] with PTAD.

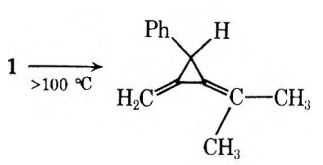


1 PTAD



R = Ph; R′ = H
R = H; R′ = Ph

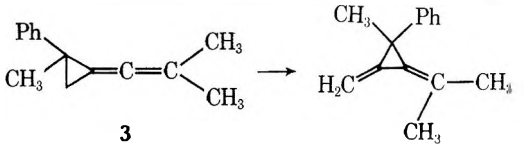
Attempts to react the easily prepared **1** with less reactive dienophiles (maleic anhydride and tetracyanoethylene) at higher temperatures (>100 °C) resulted in the thermal rearrangement of **1** to produce the bisalkylidenecyclopropane **2**.[4]



2

Efforts were temporarily abandoned toward effecting cycloaddition reactions with less reactive dienophiles, and the intimate details of the cycloaddition of alkenylidenecyclopropanes with PTAD were investigated. Theoretical and spectroscopic studies[5] led to an understanding of the nature of the bonding in alkenylidenecyclopropanes and the bonding interactions in the transition state for concerted cycloaddition with PTAD, and the results of a kinetic study gave a value of $\Delta H^{\ddagger}$ for the cycloaddition of **1** with PTAD of 9.6 ± 1.5 kcal/mol.[6]

During the early stages of the later investigations the results of a study of the thermal rearrangement of arylsubstituted alkenylidenecyclopropanes were reported.[7] It was reported that the rearrangement of **3** to **4** occurred with a $\Delta H^{\ddagger}$ of 30.4



3 **4**

kcal/mol. Intuitively, this value seemed far too high in view of our observation that the rearrangement of **1** proceeded at a reasonable rate at ≳100 °C. Furthermore, the difference between the $\Delta H^{\ddagger}$ of 9.6 kcal/mol for cycloaddition of **1** with PTAD and >30.4 kcal/mol for rearrangement of **1** (the methyl group of **3** should lower the $\Delta H^{\ddagger}$ for rearrangement of **3** relative to **1**) provides a rather large "thermodynamic window" between which we should have been able to find a dienophile capable of reacting with **1** with a $\Delta H^{\ddagger} > 9.6$ but <30.4 kcal/mol. Although the thermal rearrangement of the alkenylidenecyclopropanes appeared to be a typical methylenecyclopropane rearrangement, Sadler and Stewart[7] reported that diastereomerization of substituted alkenylidenecyclopropanes did not occur. In view of these unexpected reported aspects of the thermal rearrangements of alkenylidenecyclopropanes it was decided to reinvestigate the rearrangement reaction.

Results

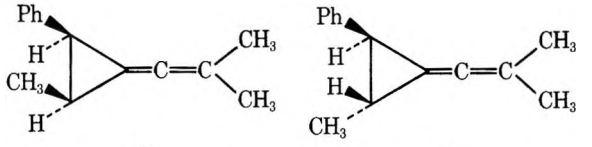
The thermal rearrangements of **1**, **3**, **5**, and **6** were carried out in sealed NMR tubes, the rates of rearrangement being

Table I. Activation Enthalpies for Rearrangement of Alkenylidenecyclopropanes

Compd	$\Delta H^{\ddagger}$, kcal/mol[a]	Compd	$\Delta H^{\ddagger}$, kcal/mol[a]
1	23.0	5	21.5
3	19.6	6	22.6

[a] Values are based on the rates of disappearance of 1, 3, 5, and 6 and do not take into account the contributions from the reverse reaction; however, these contributions are minor.

monitored by integration of the periodically recorded NMR spectra. The rates of rearrangement followed excellent first-

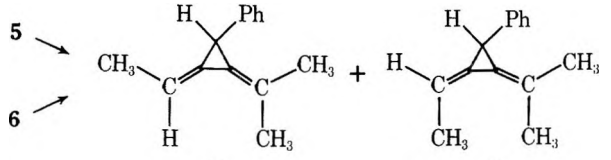


6 5

order kinetis and varied only slightly over a wide range of solvent polarities. The activation enthalpies for rearrangement in hexadeuteriobenzene were determined and found to be ~10 kcal/mol lower than that reported for 3[7,8] (see Table I).

The composition of the thermolysis products derived from the cis and trans compounds 6 and 5 was carefully monitored by NMR. During the thermal rearrangement of 6 a doublet appeared at δ 1.13 (characteristic of the methyl group in 5) which reached a maximum concentration of ~7% and then decreased to zero. Similarly, during the rearrangement of 5, the doublet characteristic of the methyl group in 6 at δ 0.85 increased to 5.7% and then decreased to zero. *This definitely shows that diastereomerization occurs during the thermal rearrangement of alkenylidenecyclopropanes.*

The thermal rearrangements of 5 and 6 result in the formation of mixtures of the *E* and *Z* isomers 7 and 8, the com-



7 8

position of which varies with temperature and starting material (see Table II). The major isomer formed from both 5 and 6 has been assigned structure 8 by Sadler and Stewart[7] based on the observation that the vinyl hydrogen of the minor isomer 7 appears at lower field (δ 5.83) than in the major isomer (δ 5.53), which was attributed to long-range deshielding by the adjacent double bond. Inspection of models, however, indicates that the vinyl hydrogen is not in a strongly deshielding region of the C=C. Of apparently greater importance is the fact that the vinyl hydrogen of 8 resides in a long-range shielding region of the aromatic ring still consistent with the assignment of Sadler and Stewart. The ^{1}H chemical shifts of the vinyl methyl group, however, suggest an opposite assignmment of structures. The ethylidene methyl and the "inside" methyl of the isopropylidene group in the major isomer appear at lower field (δ 2.03 and 1.96, respectively) than in the minor isomer (δ 1.94 and 1.87, respectively), suggesting that minor isomer is 8 in which the higher field shifts of the methyls arises from a steric compression shift. Similar differences in chemical shifts have been observed with the PTAD adducts of alkenylidenecyclopropanes having the partial structures 9 and 10, the methyls in 9 appearing 0.07–0.12 ppm higher field than in 10.[3] (The higher field position of the ethylidene methyl group in 7 can also be attributed to long-range shielding by the aromatic ring. This explanation, however, does not apply to the change in chemical shift of the "inside" methyl of the isopropylidene group.) The ^{13}C NMR

Table II. Composition of Mixtures of 7 and 8 Formed on Pyrolysis of 5 and 6

Temp, °C[a]	% 7 from 5	% 7 from 6
89.0	2.0	37
103.5	9.8	26
118.6	11.7	20

[a] The equilibration of 7 and 8 occurs much more slowly than does the rearrangement of 5 and 6 to 7 and 8.

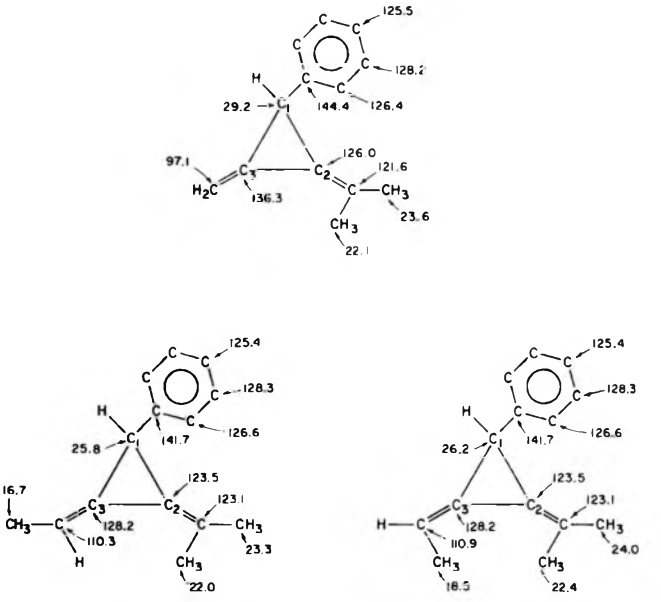
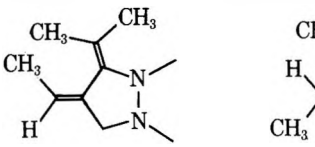


Figure 1. ^{13}C chemical shifts in 2, 7 and 8.



9 10

spectra of the two products show interesting differences (see Figure 1). (Assignment of the resonances to specific carbons is based on an analysis of substituent shift parameters for acyclic dienes.)[9] The ^{13}C shifts of the ipso aromatic carbon, C_1, and the ethylidene methyl all appear at higher field in the minor product (a cis alkene shift effect),[10] suggesting that the minor product is 7.

On further heating, the mixtures of 7 and 8 undergo slow equilibration to a mixture containing 64% of 7 (at 117 °C), the originally minor isomer formed in the rearrangements of 5 and 6. Careful measurement of the nonbonded distances between the ethylidene methyl carbon and C_1 and the aromatic carbons in 7 reveals that these distances are ~0.05 Å *longer* than the distances between the ethylidene methyl carbon and C_2 and the carbons of the isopropylidene group, indicating that 7 should be more thermodynamically stable than 8. Finally, analysis of the steric interactions generated during the ring opening and rotational processes (see later discussion on the mechanism of rearrangement) indicate that 8 should be the kinetically favored product from the rearrangement of both 5 and 6. Thus, except for the ^{1}H chemical shifts of the methyl groups, the data are consistent with the assignment of 8 as the major product formed in the rearrangement of 5 and 6.

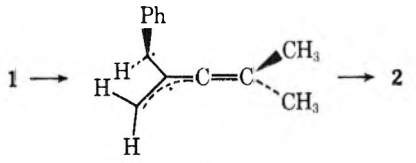
Table III. Rate Constants [a] for the Thermal Rearrangement of 5 and 6

	Cis isomer 6			Trans isomer 5		
Temp, °C	k_{total}	k_{out}	k_{in}	k_{total}	k_{out}	k_{in}
118.6	4.47	3.58	0.89	18.6	16.4	2.18
103.5	1.66	1.23	0.43	4.60	4.15	0.45
89.0	0.40	0.25	0.15	1.37	1.34	0.03

[a] All rate constants × 10^5 (s^{-1}).

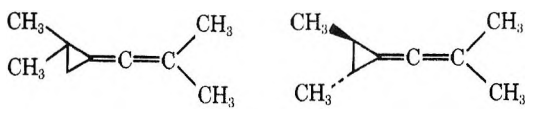
Discussion

Analysis of the thermodynamic data pertaining to the rearrangement of the alkenylidenecyclopropanes indicates that the rearrangement is a typical methylenecyclopropane rearrangement occurring via a perpendicular trimethylenemethane diradical intermediate.[11-14] Subtraction of the methylenecyclopropane strain energy (42)[15] and benzyl radical (−13.5)[16] and allyl radical (−11.6 to −14.0)[17] resonance energies from an average C–C bond dissociation energy (83) plus the resonance energy of the alkenylidenecyclopropane system (3.8 kcal/mol)[5] gives a minimum value for $\Delta H^{\ddagger}$ of 17.3–19.7 kcal/mol for the rearrangement of **1** to **2**. Thus, the application of Hammond's postulate[18] to the rearrangement of **1** indicates that the transition state for rearrangement must occur very late along the reaction coordinate, and that the transition state structure is nearly that present in the perpendicular trimethylenemethane diradical **11**.

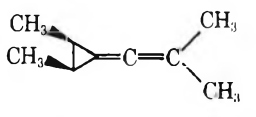


11

Critical to the low enthalpy content of **11** is the benzyl radical portion. If the proposed mechanism of the rearrangement is correct, removal of the phenyl group must result in an elevation of the enthalpy of the diradical and the transition state for its formation by ~12.4 kcal/mol. Consistent with this view is the observation that the methylated compounds **12–14** undergo insignificant isomerization at 140 °C



12 **13**



14

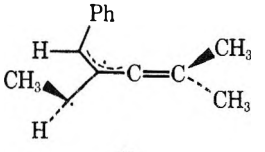
over a period of 24 days. This observation strongly favors a two-step rearrangement over a concerted process in that in a concerted process such a large substituent effect is not anticipated.

The discrimination in formation of **8** vs. **7** as the major product from both **5** and **6** is determined by steric effects arising in the formation of the diradical intermediates **15** and **16** (see Figure 2). With both **5** and **6** the inward rotation of the methyl group attached to C_2 to form diradical **15** is sterically less favorable than outward rotation to form **16**, the inward rotation occurring less rapidly in the cis isomer **6** than in the trans isomer **5** (see partial rates in Table III). It must be noted that there is *no* adverse steric interaction generated in the outward rotation between the methyl on C_2 and the methyl of the isopropylidene group of **15** and **16** because of the perpendicular orientation of the isopropylidene group relative to the plane of the trimethylenemethane portion of the diradical. The slightly less favorable steric interaction between the ethylidene methyl and the "inside" methyl of the isopropylidene group is generated on ring closure of **16** in which the isopropylidene group rotates into the plane of the newly formed three-membered ring. Ring closure of **15** and **16** occurs considerably more rapidly than does the interconversion of **15** and **16** *via* **18**, which would involve the sacrifice of the resonance energy of the allyl radical portions of **15** and **16**, as is evidenced by the considerably different ratios of **15** and **16** formed from **5** and **6** at the same temperatures and the slow rate of interconversion of **7** and **8**.

The slower rate of interconversion of **7** and **8** must be in part due to the greater energy required to cleave a vinyl C–C bond in **7** and **8** relative to the rather weak C_2–C_3 bond in **5** and **6**.[3b] In addition, if the interconversion of **15** and **16** is slow relative to ring closure, the formation of **15** from **7** and **16** from **8** will not result in net interconversion of **7** and **8**. Alternatively, both **7** and **8** could open to form diradical **17** in which ring closure to both **7** or **8** is possible. As with **15** and **16**, the interconversion of **17** with **15** and **16** again must be slow relative to ring closure.

Although the inward rotation of the methyl group in the cis isomer **6** occurs less rapidly than does the *inward* rotation in the trans isomer **5** at higher temperatures, the dominant *outward* rotation of the methyl group occurs more rapidly with the trans than with the cis isomer. This latter result is unexpected in that steric interactions between the phenyl and methyl groups in the cis isomer should result in a higher ground state energy, and hence potentially greater reactivity, than with the trans isomer **5**.[19] Unfortunately, a direct comparison of the ground-state energies of **5** and **6** is not possible as at thermal equilibrium at 117 °C the concentrations of **5** and **6** are below the levels of detection (<0.03% of **6** and <0.05% of **5**). The greater reactivity of the trans isomer **5** toward thermal rearrangement is in contrast to its lesser reactivity than **6** in cycloaddition with PTAD[6] and reaction with trichloroacetic acid.[20] The reason for the greater reactivity of the trans isomer **5**, and the greater discrimination in diradical formation, in thermal rearrangement is not obvious.

The available thermodynamic data allow construction of the qualitatively accurate energy diagram shown in Figure 3. No evidence pertaining to the structure of the transition state for interconversion of **15** and **16**, and hence the $\Delta H^{\ddagger}$ for the interconversion, is available. Assuming that interconversion of **15** and **16** requires the loss of the allyl radical resonance (via diradical **17**), $\Delta H^{\ddagger}$ for this process would be $\gtrsim$11.6–14.0 kcal/mol. However, concomitant rotation of the benzyl radical center would form a cinnamyl-type containing diradical (**18**)



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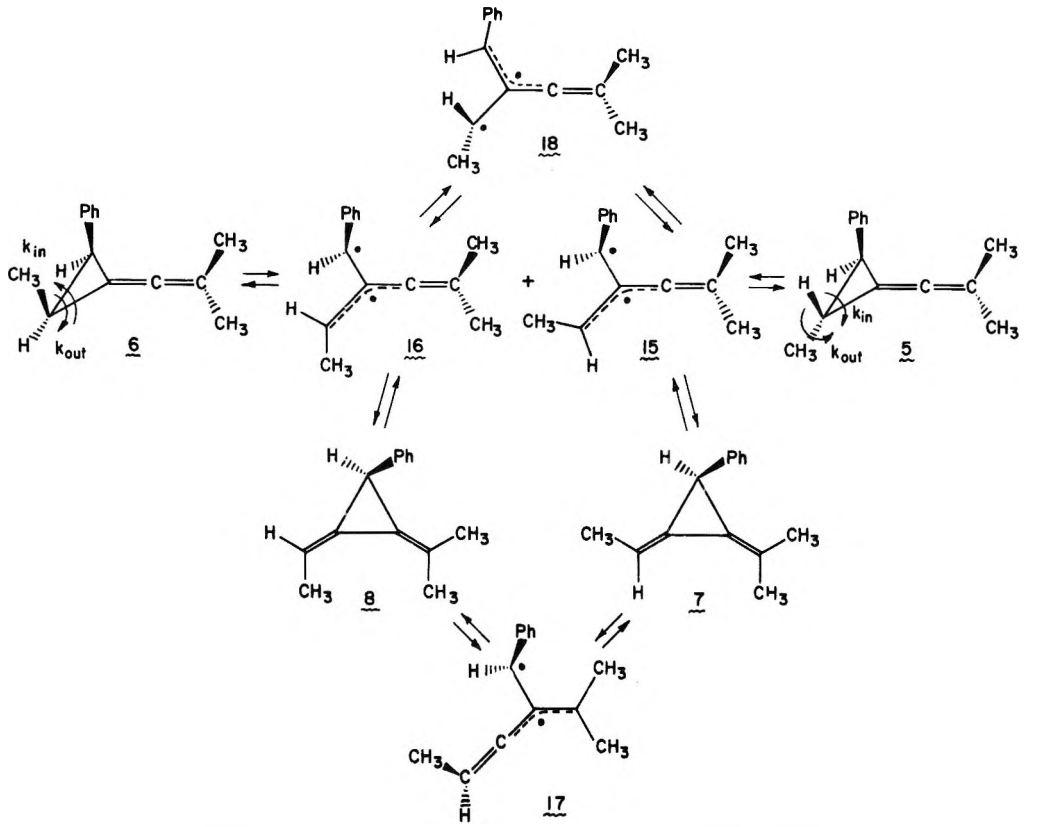

Figure 2. Mechanistic pathway for the thermal rearrangement of **5** and **6** and equilibration of **7** and **8**.

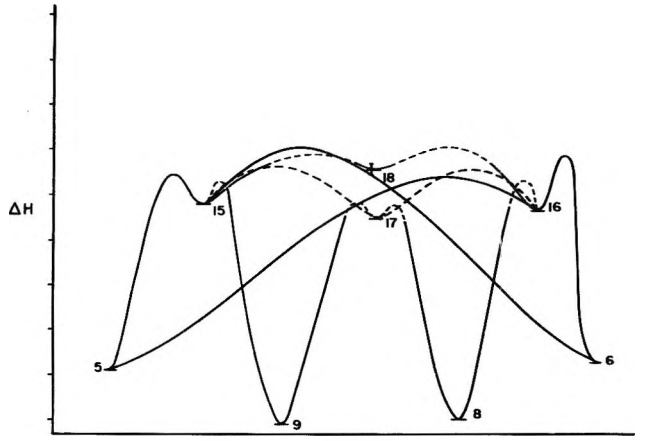

Figure 3. Enthalpy relationships for the thermal rearrangement of **5** and **6** and equilibration of **7** and **8**. Each vertical unit represents 5 kcal/mol. Solid lines represent known energy contours, dashed lines represent unknown energy contours.

which should be lower in enthalpy by ~5 kcal/mol compared to **17**. The energy of diradical **17** should be somewhat lower than either **15** or **16** owing to the additional methyl group attached to the allyl radical portion of **17**. Reversion of **18** to the more stable diradical system represented in **15** and **16** can occur to produce either **15** or **16**, or their enantiomerically related diradicals, in which case loss of optical purity would occur on reversion to **5** and/or **6**. Experiments carried out with optically active **1**[21] indicate that racemization of **1**, and possibly of **2**, does occur at higher temperatures.[22] The optical rotation of a mixture of **1** and **2** formed by partial thermal isomerization of (*R*)-(−)-**1** in benzene at ~120 °C indicates that both **1** and **2** are still optically active,[23] but vapor-phase pyrolysis at temperatures above ~220 °C produces an optically inactive mixture of **1** and **2**. In view of all of the experimental data, it must be concluded that the thermal rearrangements of alkenylidenecyclopropanes occur via a typical methylenecyclopropane rearrangement pathway.

Table IV. First-Order Rate Constants for the Thermal Rearrangement of Alkenylidenecyclopropanes

	$k \times 10^5$, s^{-1} [a]			
Temp, °C	1	3	5	6
89.0	0.09	0.39	1.37	0.40
103.5	0.39	1.13	4.60	1.66
117.0	1.11			
118.6		2.90	13.6	4.47
127.0	1.60			
138.0	3.80			

[a] Rate constants for disappearance of starting material at low conversions.

Experimental Section

Thermal Rearrangement of Alkenylidenecyclopropanes. Samples (100–150 mg) of the alkenylidenecyclopropanes were dissolved in 1.0 ml of hexadeuteriobenzene in NMR tubes. The solutions were triply freeze-degassed and sealed under vacuum. The sample tubes were placed in constant-temperature sand baths, removed periodically, and chilled with ice water, and the NMR spectra recorded and integrated. The data gave excellent first-order kinetic plots. The rate constants are listed in Table IV.

The thermal rearrangement of **1** was also carried out in other solvents at 117 °C as described above giving the rate constants (× 10^6 s^{-1}) 1.1 (CCl_4), 1.3 ($CDCl_3$), 0.9 (CH_3CN), and 1.0 (CD_3SOCD_3).

Thermal Equilibration of 7 and 8. A solution of 150 mg of a mixture of **7** and **8** (18.7% **7**) in 0.75 ml of hexadeuteriobenzene was placed in an NMR tube, triply freeze-degassed, sealed under vacuum, and was heated in a sand bath at 117 °C. The sample was periodically removed and the NMR spectrum was recorded and integrated. The change in composition of the mixture with time was as follows: time in hours (%**7**) 23.5 (29.8); 109 (34.7); 181 (45.0); 373 (51.4); 469 (57.8); 829 (60.9); 1152 (63.0); 2592 (64.1). No **5** or **6** could be detected at the end of the equilibration process.

Registry No.—1, 4544-23-4; 2, 30896-86-7; 3, 40922-91-6; 5, 33530-27-7; 6, 33530-26-6; 7, 40811-43-6; 8, 40811-42-5.

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(23) Attempts to separate **1** and **2** have met with failure and, thus, it has not yet been possible to determine the optical purities of **1** and **2**.

Bridged Polycyclic Compounds. 84. Cationic Rearrangements Accompanying Addition of Acetic Acid to the Cyclopropane Dibenzotricyclo[3.2.2.0^{2,4}]nonadiene[1]

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Acid-catalyzed addition of acetic acid at reflux to 6,8-dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (**1**) gives a mixture of *cis*-8-methyl-7-dibenzobicyclo[2.2.2]octadienyl acetate (**5**), the trans isomer (**6**), and 6,8-dibenzo-2-bicyclo-[3.2.2]nonadienyl acetate (**7**). Low temperature and deuterium-labeling experiments indicate that these products are thermodynamic sinks and that the initial products of addition are undoubtedly *syn*-8-methyl-*exo*-2-dibenzobicyclo[3.2.1]octadienyl acetate (**8**) and 3,6-dibenzo-2-bicyclo[3.2.2]nonadienyl acetate (**24**). The paths which are traversed in the acid-catalyzed rearrangements are explored, and rough rates of isomer interconversions are reported. The experimental results are discussed, with special attention paid to the differences between the isomeric [3.2.2] system and its demethylene analogue, the dibenzobicyclo[2.2.2]- and [3.2.1]octadienyl system.

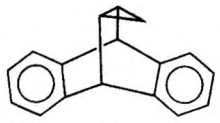
Our interest in the stereochemistries and mechanisms of electrophilic additions to cyclopropanes[2] led us to a study of additions to 6,8-dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (**1**). This cyclopropane offers a variety of paths for ring-opening additions, and, as will be seen below, avails itself of several of these.

Several methods were attempted for the synthesis of **1**. Of these, the Gindig–Cross modification[3] of the Simmons–Smith reaction[4] with **2** gave **1** in about 70% yield. As the synthesis of **2** requires several steps, the following alternative synthesis was somewhat more convenient. Anthracene was condensed with *cis*- or *trans*-1,3-dichloropropene to give **3** or **4**, respectively. Treatment of either isomer with heavily coppered zinc–copper couple (1 g-atom of copper to 6 of zinc) gave **1** in good yield.[5]

When **1** was heated in acetic acid containing 0.1 M perchloric acid and 0.24 M water at 114 °C for 30 min, it reacted completely and gave a mixture containing about 33% of **5**, 22% of **6**, and 45% of **7**. This experiment showed that **1** was reactive, but the conditions are severe enough that it seemed likely that some or all of these products were not those of kinetic control in the ring-opening addition reaction.[7] A reaction run at room temperature with 0.11 M perchloric acid in acetic acid (containing a small amount of acetic anhydride) for 4.5 h gave (^{1}H NMR analysis) about 50% reaction with a ratio of about 5 parts of **8** and **9** to 4 parts of **7**. At this stage neither **5** nor **6** was apparent. The reaction was allowed to continue, with aliquots taken from time to time. After 9 h, a trace of **5** appeared; the amount of **5** grew, after the **1** was consumed, at the expense of **8** and **9**, while the amount of **7** remained constant.

Even after 200 h, no trace of **6** appeared, and **10** and **11**, which may be progenitors of **6** (see below), were also not detected, either in early or late experiments. Compound **12**, which is a possible product of ring opening and which would be stable under these experimental conditions,[8] was also not detected.

At the end of the experiment (200 h), the ratio of **8**:**9** was 33:67. It seemed likely, in view of previous work,[7,9] that the exo isomer **8** was formed first and was converted rapidly in the acid medium to the equilibrium mixture with **9**. This likelihood was increased by a study of the acetolysis of **13** in the presence of sodium acetate, which led, via the Wagner–Meerwein rearrangement common to these ring systems,[9a] to the exo isomer **8**. **8** was found to have a half-life for equilibration with **9** in 0.01 M perchloric acid in acetic acid of a few hours at 41 °C. The half-life for rearrangement of the **8**–**9** mixture, which went cleanly to **5** (no **6** being formed at room temperature), was 135 h at room temperature (25 ± 2 °C) in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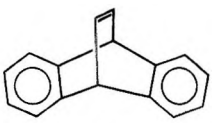
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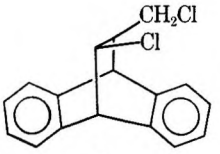

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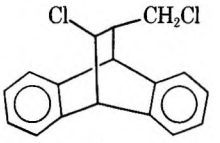

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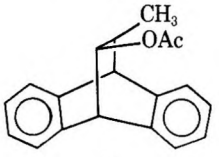

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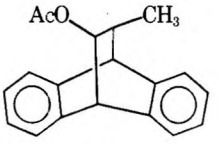

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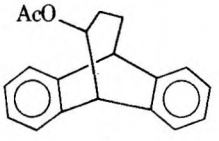

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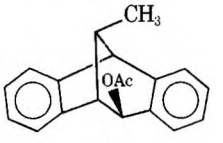

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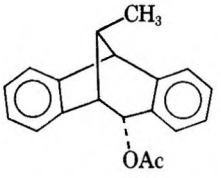

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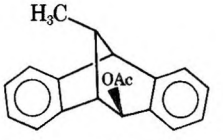

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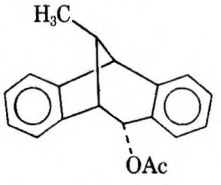

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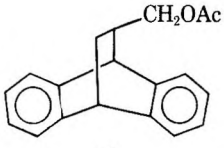

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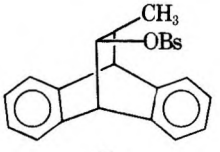

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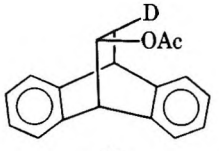

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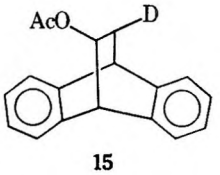

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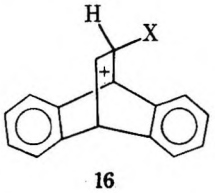

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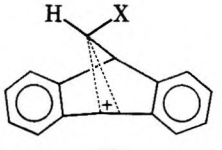

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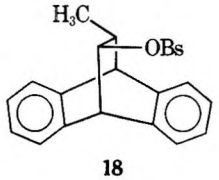

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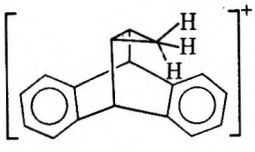

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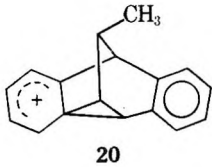

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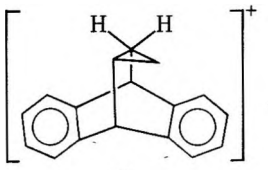
0.1 M perchloric acid in acetic acid containing excess acetic anhydride.

The results suggested that **6**, which was a substantial portion of the product of addition at reflux, arose as a result of acid-catalyzed rearrangement of **5**, and indeed **5** was found to rearrange rapidly with 0.1 M perchloric acid in acetic acid at reflux to mixtures with **6**. The rearrangement of **14** to **15** under severe conditions has been shown recently[7b] to involve the intermediacy of both **16**-*d* and **17**-*d*, and it seems likely that the rearrangement of **5** to **6** similarly involves either **16**-CH_3 or **17**-CH_3 or both.

The fact that the cis [2.2.2]–syn [3.2.1] and trans [2.2.2]–anti [3.2.1] systems maintain their integrities except under severe conditions was also demonstrated by starting with the trans-anti system. Thus acetolysis of **18** gave **10** which epimerized rapidly to a 1:1 mixture with **11** in acid solution and was then transformed to **6** with 0.1 M perchloric acid in dry acetic acid with a half-life of 7 h at room temperature, and without the formation of **5**.

Thus addition of acetic acid to **1** has two modes, one leading to the methylbicyclo[3.2.1] and [2.2.2] systems, which are converted among each other, and one to the [3.2.2] system, which is unrelated to the other set of products. The formation of **8** as the first stable intermediate in one of these systems is consistent with the intervention of the corner-protonated intermediate **19**,[10] whose opening is concerted with migration of the anti benzene ring to give[11] **20**, the precursor of **5**. As perhaps may be expected,[7,9,11] **19** does not suffer external nucleophilic attack to give acetate **6**. The formation of **7** is consistent with the intervention of the alternative corner-protonated intermediate **21**, which might be anticipated to suffer external nucleophilic attack by acetic acid to give **12** (not found) or to give **7**. Alternatively, **21** might open to the cation **22**. Capture of **22** by acetic acid would give **7**. More likely **22** would equilibrate with **23**[12] giving **24**, which, returning through the same set of cations, could give **7**.



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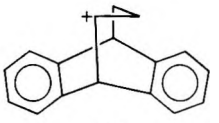

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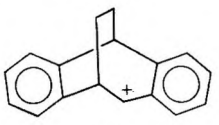

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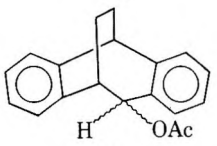

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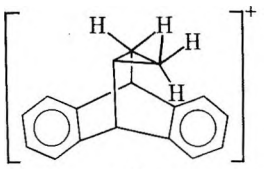
These considerations, plus the possibility[10] that an edge-protonated intermediate **25** was a common precursor to both systems, suggested that we look at the **24**–**7** system and that we study the addition of acetic acid-*O*-*d* to **1** to study the stereochemistry of the addition to give **7**. The ^1H NMR spectrum of the [3.2.2] alcohol **26** makes it convenient to check on the location of deuterium atoms at C-4. The NMR data show that **26** has the conformation indicated, with the hydroxyl group having an equatorial position. Thus the H-1 proton in **26** gives rise to a doublet with J = 2.4 Hz (coupling with the axial H-2 proton), while H-5 gives rise to a doublet of doublets with J = 2.4 and 6.0 Hz (coupling with the two protons on C-4). Similar data are produced with the acetate **7**. Thus the stereochemistry of the C-4 hydrogen atoms can be readily determined.

For a number of reasons we found it more convenient to add normal acetic acid to dideuterio-1 (i.e., **27**) than to add deuterated acetic acid to **1**. Addition of ethyl propiolate-3-*d* to anthracene gave **28**, which, upon reduction with lithium alu-



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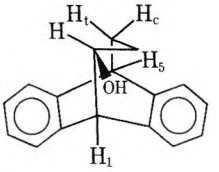

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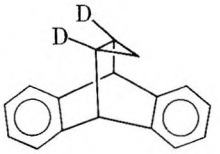

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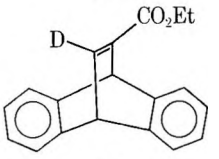

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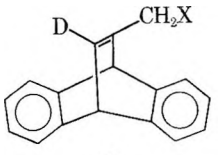
minum hydride–aluminum chloride as described[13] for the protio compound, gave **29**-OH. Treatment with thionyl chloride and tri-*n*-butylamine gave **29**-Cl which, upon acetophenone-sensitized irradiation[14] in acetonitrile, gave **30.** Treatment of **30** with triphenyltin deuteride (azoisobutyronitrile initiation) gave **27.**

27 was treated with 0.1 M perchloric acid in acetic acid at room temperature for 9 h. The resulting acetates were isolated and reduced with $LiAlH_4$ and the [3.2.2] alcohol (**26**-d_2) separated with TLC. ^1H NMR (100-MHz) spectroscopy (see Experimental Section) indicated that equal amounts of four dideuterio compounds resulted. These were **31**-OH, **32**-OH, **33**-OH, and **34**-OH. These results, plus the fact that the rearrangement of **35** to **36** was relatively slow, made it clear that



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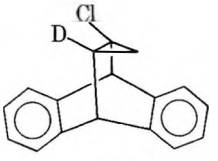

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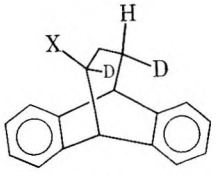

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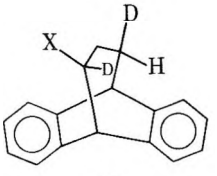

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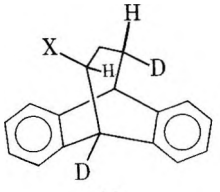

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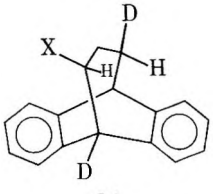

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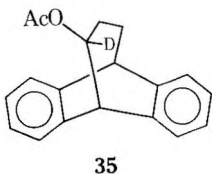

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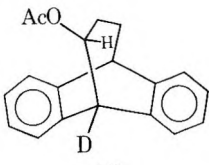
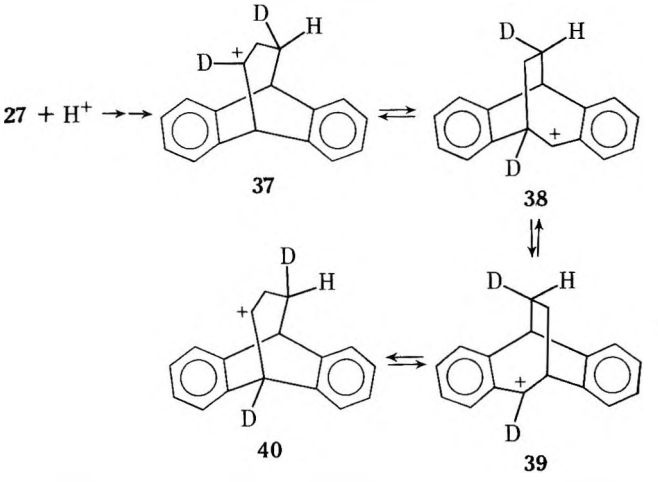


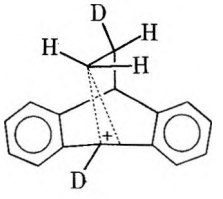
36

nucleophilic attack by solvent on protonated cyclopropane **21** or **25** did not lead directly to **7,** but that instead a more complicated process involving carbenium ions obtained. The fact that equal amounts of **31**-OAc and **32**-OAc, as well as **33**-OAc and **34**-OAc, were produced indicated that we would be unable to learn anything of stereochemical interest about this addition. However, the question of how the reaction proceeded still remained.

A likely rationalization for the production of the four isomers is shown in Scheme I. Ring opening of the protonated cyclopropane species leads to cation **37,**[12] which equilibrates rapidly with its presumably more stable isomer **38.** It is then necessary to assume the rapid migration of the two-carbon saturated bridge to give **39,** via the intermediate or transition state **41,** for the apparent deuterium migration to occur, a reaction which goes only very slowly with a one-carbon bridge (see above and ref 7 and 8), followed by equilibration of **39** with **40.** To learn whether this bridge migration was rapid, we studied the reaction of **42** in 0.1 M perchloric acid in acetic

Scheme I





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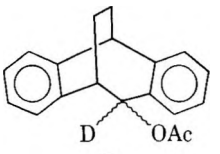

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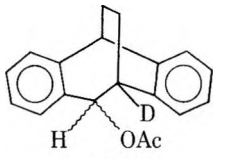

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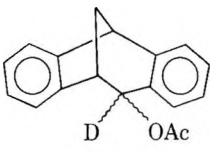
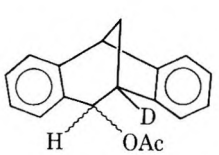


44

acid. Its complete interconversion with **43** occurred before the first NMR scan was taken (5–7 min at 25 °C). The subsequent rearrangement to deuterio-**7** had a half-life of about 50 min at 25 °C, and with no measurable **42** or **43** left at equilibrium. Thus the process outlined in Scheme I, with ions **38** and **39** being captured by acetic acid to give the dideuterio analogues of **42** and **43** and being regenerated from them, and with ions **37** and **40** ultimately being captured to give **31, 32, 33,** and **34**-OAc, is established.[15]

There remains to be discussed the remarkably large difference between the rate of isomerization in the [3.2.2] system, i.e., between **42** and **43** (complete in 0.1 M perchloric acid in acetic acid in <5 min at 25 °C), and that in the [3.2.1] system



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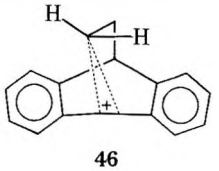

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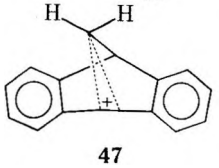

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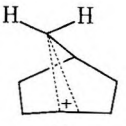

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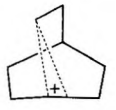
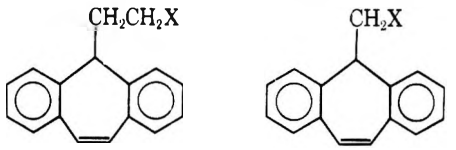


49

(half-life[7] for rearrangement of **44** to **45** under comparable conditions is of the order of 75 h at 85 °C). This must obviously relate to the relative stabilities of the two protonated cyclopropane intermediates or transition states **46** and **47**, which link the two isomeric pairs of cations in the [3.2.2] and [3.2.1] systems, respectively. It has been reported previously[17] that Professor Goering has commented on the difference between ion **47** and the corresponding saturated ion **48**, where the unsaturated ion **47** has serious additional strain associated with the tendency for a flatter system in the dibenzo compound than in the saturated one.

Berson[18] has noted that, in the saturated bicyclo[3.2.2]nonanyl system, rearrangement via **49** occurs substantially less readily (compared with capture) than in the corresponding bicyclo[3.2.1]octanyl system via **48**, and has ascribed this to the additional strain imposed by the extra ring member in the [3.2.2] system vs. that in the smaller system in achieving proper orbital overlap. On extension of the Goering–Berson concept to the flatter dibenzo compounds, the [3.2.1] system does not allow significant overlap without considerable strain, while the additional ring member allows relatively strain-free overlap. Thus the situation is completely reversed from that of the saturated systems.

Consistent with these ideas are some results published by Nenitzescu and co-workers some time ago.[16,19] They reported that the buffered solvolysis of **50**-OTs in acetic acid containing sodium acetate led, via the "π-route" (that is via **46**), to mixtures containing mostly **24**-OAc epimers mixed with some **7**, and with only 9–22% of unrearranged **50**-OAc, while the corresponding analogue **51**-OTs, with one less carbon, gave only 6% of "π-route" products, ring expansion occurring instead. These authors discuss their results in similar, though not identical, terms.



50 **51**

Experimental Section

Except where otherwise mentioned, ^{1}H NMR spectra were taken with a Varian A-60A or A-60 60-MHz spectrometer.

Preparation of *trans*- (4) and *cis*-7-Chloro-8-chloromethyldibenzobicyclo[2.2.2]octadiene (3). A mixture of 35 g (0.19 mol) of anthracene, 110 ml of *trans*-1,3-dichloropropene, and 0.5 g of *p-tert*-butylcatechol was heated in a sealed tube at 195–200 °C for 2 days. After being cooled, the tube was opened and washed with 100 ml of methanol. The solution and washings were combined and the excess dichloropropene and methanol removed by evaporation. The resulting oil was dissolved in 100 ml of benzene, placed on an alumina column (ca. 800 ml of Merck 71707), and eluted with petroleum ether (bp 60–70 °C). Anthracene was eluted first and then the adduct. The solvent was evaporated and the resulting oil was crystallized from ethanol to give 23 g (42%) of **4**: mp 92–92.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 8, aromatic H), 4.39 (d, 2, $J_{1,7} = J_{4,8} = 2.5$ Hz, H-1 and H-4), 3.63 (t, 1, $J_{1,7} = J_{7,8} = 2.5$ Hz, H-7), 3.6–2.7 (septet, 2, CH_2Cl), 2.40 (bm, 1, H-8).

Anal. Calcd for $C_{17}H_{14}Cl_2$: C, 70.61; H, 4.85. Found: C, 70.67; H, 4.99.

The cis adduct **3** was prepared analogously, using *cis*-1,3-dichloropropene: yield 21 g, 40%; mp 176–177 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 8, aromatic H), 4.66 (d, 1, $J_{1,7} = 2$ Hz, H-1), 4.50 (d, 1, $J_{4,8} = 2$ Hz, H-4), 4.44 (dd, 1, $J_{7,8} = 6$ Hz, $J_{1,7} = 2$ Hz, H-7), 2.6–3.8 (septet, 2, CH_2Cl), 2.50 (bm, 1, H-8).

Anal. Calcd for $C_{17}H_{14}Cl_2$: C, 70.61; H, 4.85. Found: C, 70.81; H, 4.63.

Preparation of Dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (1). Powdered analytical grade zinc (38 g) was washed with 2% aqueous copper sulfate until the blue color persisted (about 1 g-atom of copper/6 g-atoms of zinc), then with 50 ml of 95% ethanol, and filtered. A mixture of either dichloride **3** or **4** (1 g, 3.5 mmol), 150 ml of 95% ethanol, and 1.5 g of the zinc–copper couple was heated at reflux with stirring for 48 h, cooled, and filtered. The residue was washed thoroughly with ether. The solvents were evaporated, and the residual oil was dissolved in a minimum amount of chloroform and placed on a silica gel column (ca. 150 ml, 60–200 mesh) and eluted with Skellysolve B. The first fractions contained the pure cyclopropane and later fractions contained small amounts (~5%) of **3** or **4**. Results were similar with both isomers. The solvent was removed by evaporation, and the cyclopropane **1** was fractionally crystallized from acetone: yield 620 mg (80%); mp 176–177 °C. An analytical sample melted at 179–180 °C;[20] ^{1}H NMR ($CDCl_3$) δ 7.10 (m, 8, aromatic H), 4.36 (t, 2, H-1 and H-5), 1.45 (sm, 2, H-2 and H-4), 0.55 (dd, 1 $J_{gem} = 6$ Hz, $J_{2,3} = J_{4,3} = 15$ Hz, exo-H-3), −0.27 (sm, 1, endo-H-3).

Anal.[20] Calcd for $C_{17}H_{14}$: C, 93.53; H, 6.47. Found: C, 93.59; H, 6.62.

Preparation of "Moist" Acetic Acid, 0.1 M in Perchloric Acid. A 1-l. volumetric flask was charged with 9 ml of 70% reagent grade perchloric acid (0.1 mol of perchloric acid and 0.24 mol of water), and filled to the mark with reagent grade acetic acid.

Addition of Acetic Acid to Dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (1) at Reflux. A solution of 200 mg of dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (**1**) in 25 ml of the perchloric acid–moist acetic acid mixture was heated at reflux for 30 min, then cooled, poured into 30 ml of water, and extracted several times with ether. The ether extracts were washed with water and aqueous sodium bicarbonate, dried ($MgSO_4$), and filtered, and the ether was evaporated. Addition and removal by evaporation of carbon tetrachloride three times left a yellow oil free of ether. The product composition was determined by ^{1}H NMR. The *cis*- to *trans*-8-methyl-7-dibenzobicyclo[2.2.2]octadienyl acetate (**5**:**6**) ratio was about 60:40 and the combined percentage of **5** and **6** was 55%. 6,8-Dibenzo-2-bicyclo[3.2.2]nonadienyl acetate (**7**) was the remaining 45%. No peaks due to other products were apparent.

Preparation of *cis*- and *trans*-8-Methyl-7-dibenzobicyclo[2.2.2]octadienyl Acetate (5 and 6) from Anthracene and 1-Propenyl Acetate. A Pyrex tube containing 19.5 g (0.112 mol) of anthracene (98%, Aldrich), 55 g (0.55 mol) of 1-propenyl acetate,[21,22] and 0.5 g of *p-tert*-butylpyrocatechol was sealed and heated at 200–210 °C for 96 h. The tube was cooled and opened and 4.5 g of anthracene removed by filtration. One hundred milliliters of methanol was used to wash the tube and solid. The filtrate and washings were combined and allowed to stand for 2 days at room temperature during which time 8.5 g of 95% pure (as determined by ^{1}H NMR) cis adduct **5** crystallized. The crystals were filtered and the flask was cooled in a freezer at −20 °C for 5 days. A second crop of crystals formed (10.5 g) which was 80% trans acetate **6** (as determined by ^{1}H NMR): total yield, 65%. The cis adduct **1** was recrystallized from aqueous ethanol giving 5.5 g of **5**: mp 122–123 °C; ^{1}H NMR (CCl_4) δ 7.08 (sm, 8, aromatic H), 5.02 (dd, 1, $J_{1,7} = 3$ Hz, $J_{7,8} = 7.0$ Hz, H-7), 4.30 (d, 1, $J_{1,7} = 3$ Hz, H-1), 3.84 (d, 1, $J_{4,8} = 2$ Hz, H-4), 2.20 (m, 1, H-8), 1.76 (s, 3, CH_3COO–), 0.59 (d, 3, $J_{8,9} = 7$ Hz, CH_3–).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.82; H, 6.74.

The crude trans isomer was converted to the alcohol (the procedure follows) and separated on a preparative silica gel plate using 10% ether in benzene to develop the plate. Alternatively, fractional crystallization of the alcohol (80% trans isomer from acetates) from aqueous ethanol was successful, but the yields were rather low. The alcohol was converted to the acetate using acetic anhydride and pyridine. Recrystallization from aqueous ethanol gave pure trans acetate **6**: mp 96.5–97.5 °C; ^{1}H NMR (CCl_4) δ 7.09 (sm, 8, aromatic H), 4.46 (dd, 1, $J_{1,7} = 2.5$ Hz, $J_{7,8} = 3.0$ Hz, H-7), 4.37 (d, 1, $J_{1,7} = 2.5$ Hz, H-1), 3.83 (d, 1, $J_{4,8} = 2.5$ Hz, H-4), 1.82 (s, 3, CH_3COO–), 1.72 (bm, 1, H-8), 0.91 (d, 3, $J_{8,9} = 6.5$ Hz, CH_3–).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.02; H, 6.47.

Preparation of *cis*- and *trans*-8-Methyl-7-dibenzobicyclo[2.2.2]octadienols. Each acetate was converted to the corresponding alcohol with sodium methoxide in methanol at reflux. Recrystallization from aqueous ethanol gave the alcohols as follows.

The cis isomer: mp 145–147 °C; ^{1}H NMR (CCl_4) δ 7.05 (sm, 8, aromatic H), 4.20 (d, 1, $J_{1,7} = 3.5$ Hz, H-1), 4.0 (bm, 1, H-7, not resolved due to OH coupling), 3.81 (d, 1, $J_{4,8} = 2$ Hz, H-4), 3.19 (m, 1, $J_{8,9} = 7$, $J_{4,8} = 2$ Hz, H-8), 0.83 (bd, 1, $J = 11$ Hz, OH), 0.64 (d, 3, $J_{8,9} = 7$ Hz, CH_3–).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.43; H, 7.01.

The trans isomer: mp 114–115.5 °C; ^{1}H NMR (CCl_4) δ 7.08 (sm, 8, aromatic H), 4.09 (d, 1, $J_{1,7} = 3$ Hz, H-1), 3.77 (d, 1, $J_{4,8} = 2.5$ Hz, H-1),

3.32 (dd, 1, $J_{7,8}$ = 3, $J_{1,7}$ = 3 Hz, H-7), 1.39 (sm, 1, H-8), 1.13 (s, 1, OH), 0.82 (d, 3, $J_{8,9}$ = 6.5 Hz, CH_3–).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.14; H, 6.73.

Addition of "Moist" Acetic Acid (0.1 M in Perchloric Acid) to Dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (1) at Room Temperature. A solution of dibenzotricyclo[3.2.2.0^{2,4}]nonadiene (750 mg, 2.7 mmol) in 100 ml of "moist" acetic acid containing 0.1 M perchloric acid and 0.24 M water was allowed to stand at room temperature. Aliquots (20 ml) were taken at various times and worked up in normal fashion. ^{1}H NMR analysis of the crude oils showed no starting material after 150 h. There was no *trans*-8-methyl-7-dibenzobicyclo[2.2.2]octadienyl acetate (**6**) nor anti [3.2.1] acetates (**10** or **11**) visible during the reaction. The presence of *exo*- and *endo*-*syn*-8-methyl-2-dibenzobicyclo[3.2.1]octadienyl acetates (**8** and **9**) was monitored by the appearance of two sets of doublets near δ 6.0. The subsequent rearrangement of **8** and **9** to the cis [2.2.2] acetate **5** as a function of time was apparent. When runs similar to the one described above were made with the water concentration varied, the rate of ring opening was found to be markedly dependent on the amount of water present. Thus, with water molarities of 0.17, 0.24, and 0.46 the percent reaction of **1** after 24 h (as determined by ^{1}H NMR) was 43, 40, and 32, respectively. The rearrangement of the [3.2.1] acetates to cis [2.2.2] acetate was similarly affected, but since the half-lives were approximately 12 times longer than the ring opening the effect appeared magnified.

Preparation of "Dry" Acetic Acid, 0.1 M in Perchloric Acid. In a 1-l. volumetric flask was placed 9 ml of 70% reagent grade perchloric acid (0.1 mol of perchloric acid, and 0.24 mol of water) and 50 ml of reagent grade acetic anhydride, before it was filled to the mark with reagent grade acetic acid. The final solution had about 3 vol % excess acetic anhydride. Titration with potassium acetate, using bromothymol blue indicator, gave a value of 0.108 ± 0.005 M in perchloric acid.

Equilibration of *cis*- and *trans*-8-Methyl-7-dibenzobicyclo[2.2.2]octadienyl Acetates (5 and 6). A two-necked 50-ml round-bottom flask was equipped with a reflux condenser. Twenty milliliters of "dry" acetic acid, 0.108 M in perchloric acid, was added. The solution was heated to reflux, and 200 mg of a mixture of 90% **5** and 10% **6** was added. The solution was heated at reflux for 20 min and half of the solution was withdrawn and worked up in the normal manner. After 60 min the second half of the reaction solution was worked up. ^{1}H NMR analysis of the resultant oils showed a **5** to **6** ratio of 30:70 and 20:80 after 20 and 60 min, respectively.

Preparation of *p*-Bromobenzenesulfonates 13 and 18. A solution of 3.8 g (16 mmol) of *cis*-8-methyl-7-dibenzobicyclo[2.2.2]octadienol, 8.2 g (32 mmol) of *p*-bromobenzenesulfonyl chloride, and 150 ml of dry reagent-grade pyridine was stirred at room temperature for 3 days. The solution was poured into 200 ml of water. The *p*-bromobenzenesulfonate crystallized immediately. The white crystals were filtered and washed with 5% hydrochloric acid (50 ml), 50 ml of water, and 25 ml of cold ether. The *cis*-8-methyl-7-dibenzobicyclo-[2.2.2]octadienyl *p*-bromobenzenesulfonate (**13**) was recrystallized from acetone to give 5.5 g (75%): mp 114–117 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 4 aromatic H's on *p*-bromobenzenesulfonate), 7.18 (sm, 8 benzo protons), 4.97 (dd, 1, $J_{1,7}$ = 3.5, $J_{7,8}$ = 6.5 Hz, H-7), 4.42 (d, 1, $J_{1,7}$ = 3.5 Hz, H-1), 3.96 (d, 1, $J_{1,7}$ = 2 Hz, H-4), 1.60 (bm, 1, H-7), 0.68 (d, 3, $J_{8,9}$ = 7.5 Hz. CH_3–).

Anal. Calcd for $C_{23}H_{19}BrO_3S$: C, 60.67; H, 4.20. Found: C, 60.97; H, 4.06.

The trans isomer was prepared using similar proportions, but it did not crystallize when poured into water. The solution was extracted with ether (3 × 100 ml). The combined ether extracts were washed with 5% hydrochloric acid (2 × 75 ml) and water (2 × 75 ml), dried ($MgSO_4$), and filtered. The ether was evaporated and the crude product was recrystallized from heptane to give **18**: yield 83%; mp 90–100 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 4, aromatic protons on *p*-bromobenzenesulfonate), 7.13 (sm, 8, benzo protons), 4.44 (d, 1, $J_{1,7}$ = 3 Hz, H-1), 4.32 (dd, 1, $J_{1,7}$ = 3, $J_{7,8}$ = 3 Hz, H-7), 3.88 (d, 1, $J_{4,8}$ = 2.5 Hz, H-4), 1.88 (bm, 1, H-8), 0.73 (d, 3, $J_{8,9}$ = 7.5 Hz, CH_3–). An analysis of this compound was not obtained because the compound decomposed on standing at room temperature for several days.

Buffered Acetolyses of *cis*- (13) and *trans*-8-Methyl-7-dibenzobicyclo[2.2.2]octadienyl *p*-Bromobenzenesulfonate (18). A solution of acetic anhydride (4 ml), 8.2 g (0.1 mol) of sodium acetate, 2.37 g (5.2 mmol) of *cis*-8-methyl-7-dibenzobicyclo[2.2.2]octadienyl *p*-bromobenzenesulfonate (**13**), and 96 ml of acetic acid was stirred at room temperature for 12 h. At this time it was noted that all of the **13** had not dissolved, and the temperature was maintained at 60 °C for 3.5 more days. The solution was poured into 50 ml of water, and extracted with ether (3 × 100 ml). The combined ether extracts were washed with cold water and saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered, and evaporated to dryness. The crude yellow oil (1.14 g, 80% yield) was dissolved in ethanol, treated with charcoal, and crystallized by adding water to the cloud point, heating to 80 °C by a steam bath, and slow cooling. The only important product by ^{1}H NMR of the oil was *syn*-8-methyl-*exo*-2-dibenzobicyclo[3.2.1]octadienyl acetate (**8**): mp 109.5–111 °C after recrystallization; ^{1}H NMR (CCl_4) δ 7.25 (sm, 1, benzo proton α to carbon number 3), 7.00 (sm, 7, remaining benzo protons), 5.71 (d, 1, $J_{1,2}$ = 2 Hz, H-2 endo), 3.61 (d, 1, $J_{5,8}$ = 4 Hz, H-5), 3.35 (dd, 1, $J_{1,8}$ = 4 Hz, H-1), 2.75 (bm, 1, H-8 anti), 2.00 (s, 3, CH_3COO–), 1.13 (d, 3, $J_{8,9}$ = 7 Hz, CH_3–).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.95; H, 6.72.

The trans isomer **18** was solvolyzed at room temperature using the same proportions as for the cis isomer. The product, *anti*-8-methyl-*exo*-2-dibenzobicyclo[3.2.1]octadienyl acetate (**10**), was purified by sublimation at 90 °C and 0.5 mm: yield 80%; mp 98.5–100 °C; ^{1}H NMR (CCl_4) δ 7.32 (sm, 1, benzo proton α to carbon number 3), 7.0 (sm, 7, remaining benzo protons), 5.79 (d, 1, $J_{1,2}$ = 2 Hz, H-2 endo), 3.55 (s, 1, H-5), 3.13 (bs, 1, H-1, this is probably a poorly resolved dd), 2.82 (q, $J_{8,9}$ = 6.5 Hz, H-8 anti), 2.02 (s, 3, CH_3COO–), 1.00 (d, 3, CH_3–).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.21; H, 6.64.

Lithium Aluminum Hydride Reduction of *syn*- and *anti*-8-Methyl-2-dibenzobicyclo[3.2.1]octadienyl Acetates (8 and 10) to the Corresponding Alcohols. A solution of 1.14 g (4 mmol) of **8**, 60 ml of anhydrous ether, and 240 mg (6 mmol) of lithium aluminum hydride was stirred at room temperature for 4 hr. Saturated aqueous sodium sulfate was added very slowly until a white granular precipitate was formed. The precipitate was filtered and washed with anhydrous ether. The washings and filtrate were combined and evaporated to dryness. The product, ***syn*-8-*exo*-2-dibenzobicyclo[3.2.1]-octadienol,** was recrystallized from ethanol–water: yield 900 mg (95%); mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 7.15 (sm, 8, aromatic H), 4.54 (d, 1, $J_{1,2}$ = 1.8 Hz, H-2 endo), 3.68 (d, 1, $J_{5,8}$ = 3.5 Hz, H-5), 3.29 (dd, 1, $J_{1,8}$ = 3.5 Hz, H-1), 2.85 (m, 1, H-8 anti), 1.95 (s, 1, –OH), 1.09 (d, 3, $J_{8,9}$ = 7 Hz, CH_3).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.45; H, 7.12.

The reduction of **10** was carried out in a similar manner to give ***anti*-8-methyl-*exo*-2-dibenzobicyclo[3.2.1]octadienol** in 90% yield (after recrystallization from aqueous ethanol): mp 135–138 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (sm, 8, aromatic H), 4.65 (d, 1, $J_{1,2}$ = 2 Hz, H-2 endo), 3.59 (s, 1, H-5), 3.17 (bd, 1, $J_{1,2}$ = 2 Hz, H-1), 2.72 (q, 1, $J_{8,9}$ = 7 Hz, H-8 syn), 2.47 (s, 1, –OH), 1.03 (d, 3, $J_{8,9}$ = 7 Hz, CH_3).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.49; H, 7.04.

Preparation of *syn*- and *anti*-8-Methyl-2-dibenzobicyclo[3.2.1]octadienone. A solution of 50.00 g (0.168 mol) of sodium dichromate dihydrate, 27.5 ml of concentrated sulfuric acid, and water to 250 ml was prepared. A 150-ml round-bottom flask was charged with 1.10 g (4.62 mmol) of *syn*-8-methyl-*exo*-2-dibenzobicyclo[3.2.1]-octadienol, 50 ml of ether, and 5.0 ml of the above aqueous acidic chromic acid solution. The reaction mixture was stirred at room temperature for 24 h. The solution was washed repeatedly with water (6 × 25 ml), dried ($MgSO_4$), filtered, and evaporated to dryness. The product, ***syn*-8-methyl-2-dibenzobicyclo[3.2.1]octadienone,** was recrystallized from aqueous ethanol: yield 770 mg (61%); mp 100–102 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (sm, 1, benzo proton α to C-3), 7.18 (sm, 7, remaining aromatic H), 3.91 (d, 1, $J_{5,8}$ = 5 Hz, H-5), 3.80 (d, 1, $J_{1,8}$ = 4 Hz, H-1), 3.28 (sm, 1, H-8 anti), 1.10 (d, 3, $J_{8,9}$ = 7 Hz, CH_3–).

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.96; H, 5.94.

Similarly, the oxidation of the corresponding anti alcohol gave ***anti*-8-methyl-2-dibenzobicyclo[3.2.1]octadienone** in 60% yield: mp 109–110.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (sm, 1, benzo proton α to C-3), 7.25 (sm, 7, remaining aromatic H), 3.89 (bs, 1, H-1), 3.78 (s, 1, H-5), 3.18 (q, 1, $J_{8,9}$ = 7 Hz, H-8 syn), 1.10 (d, 3, $J_{8,9}$ = 7 Hz, CH_3).

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 86.95; H, 6.02.

Lithium Aluminum Hydride Reduction of *syn*- and *anti*-8-Methyl-2-dibenzobicyclo[3.2.1]octadienones. A solution of 472 mg (2 mmol) of *syn*-8-methyl-2-dibenzobicyclo[3.2.1]octadienone, 30 ml of anhydrous ether, and 40 mg (1 mmol) of lithium aluminum hydride was stirred at room temperature for 30 min. Saturated aqueous sodium sulfate was added very slowly until a white granular precipitate was formed. The mixture was filtered, and the filtered precipitate was washed with additional ether. The washings and filtrate were combined and evaporated to dryness. A ^{1}H NMR spectrum

of the colorless oil (470 mg, yield 95%) showed an exo to endo alcohol ratio of 1:1. The isomers were separated by preparative thin layer chromatography on PF-254 (Brinkmann) silica gel, developed with 10 vol % ether in benzene. The bands were visible under uv light. The upper band contained the endo isomer and was removed and extracted with ether to give 170 mg of ***syn*-8-methyl-*endo*-2-dibenzobicyclo[3.2.1]octadienol,** which after recrystallization from aqueous ethanol melted at 96–97.5 °C: ^{1}H NMR ($CDCl_3$) δ 7.78 (sm, 8, aromatic H's), 4.86 (d, 1, $J_{1,2}$ = 5.5 Hz, H-2 exo) (this proton is frequently broad or a dd with J = 11 due to the slowness of the OH exchange, but addition of D_2O to the sample eliminates the problem), 3.58 (d, 1, $J_{5,8}$ = 4 Hz, H-5), 3.29 (dd, 1, $J_{1,8}$ = $J_{1,2}$ = 5.5 Hz, H-1), 2.93 (bm, 1, H-8 anti), 2.50 (bs, 1, –OH), 1.00 (d, 3, $J_{8,9}$ = 7 Hz, CH_3–).

Similarly, the reduction of *anti*-8-methyl-2-dibenzobicyclo[3.2.1]-octadienone gave exo and endo 4-alcohols in a 25:75 ratio (as determined by ^{1}H NMR) in a 95% yield. ***anti*-8-Methyl-*endo*-2-dibenzobicyclo[3.2.1]octadienol** was recrystallized from aqueous ethanol: mp 121–122.7 °C; ^{1}H NMR ($CDCl_3$) δ 7.16 (sm, 8, aromatic H's), 4.96 (d, 1, $J_{1,2}$ = 5.5 Hz, H-2 exo), 3.55 (s, 1, H-5), 6.68 (d, 1, $J_{1,2}$ = 5.5 Hz, H-1), 2.60 (q, 1, $J_{8,9}$ = 7 Hz, H-8 syn), 1.58 (s, 1, –OH), 1.20 (d, 3, $J_{8,9}$ = 7 Hz, CH_3).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.37; H, 6.99.

This alcohol was converted to the corresponding acetate with acetic anhydride in pyridine. After aqueous extraction of an ether solution and appropriate workup including preparative TLC on silica gel and recrystallization, the ***anti*-8-methyl-*endo*-2-dibenzobicyclo-[3.2.1]octadienyl acetate (11),** mp 95–96 °C, was obtained: ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 8, aromatic H's), 6.25 (d, 1, $J_{1,2}$ = 5.5 Hz, H-2 exo), 3.60 (s, 1, H-5), 3.55 (d, 1, $J_{1,2}$ = 5.5 Hz, H-1), 2.68 (q, 1, $J_{8,9}$ = 7 Hz, H-8 syn), 2.12 (s, 3, CH_3COO–), 1.03 (d, 3, $J_{8,9}$ = 7 Hz, CH_3–).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.71; H, 6.50.

Acid-Catalyzed Equilibration of Exo (8) and Endo (9) Isomers of *syn*-8-Methyl-2-dibenzobicyclo[3.2.1]octadienyl Acetates. Preparation of the Endo Isomer 9. A solution of 500 mg of **8** in 70 ml of 0.1 M perchloric acid in "dry" acetic acid was stirred at room temperature for 30 min. The solution was poured into 75 ml of water and extracted with four 100-ml portions of ether. The ether washings were combined and extracted with aqueous sodium bicarbonate until the washings were basic. The ether layer was treated with charcoal, dried ($MgSO_4$), and evaporated to dryness. The ^{1}H NMR spectrum of the resulting oil showed the **8**:**9** ratio to be 35:65. The oil was fractionally crystallized from aqueous ethanol to give 140 mg of **8**. The mother liquor was concentrated, and **9** crystallized. It was recrystallized from aqueous ethanol to give 100 mg of **9**: mp 129–130 °C; ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 8, aromatic H), 6.16 (d, 1, $J_{1,2}$ = 5 Hz, H-1), 3.68 (d, 1, $J_{5,8}$ = 4 Hz, H-5), 3.53 (dd, 1, $J_{1,2}$ = $J_{1,8}$ = 5 Hz, H-1), 2.95 (sm, 1, H-8 anti), 2.08 (s, 3, CH_3COO–), 1.11 (d, 3, $J_{8,9}$ = 7 Hz, CH_3).

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 82.22; H, 6.63.

6,8-Dibenzo-2-bicyclo[3.2.2]nonadienol (26)[16] has been previously prepared in this laboratory:[23] mp 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 7.23 (sm, 8, aromatic H's), 4.00 (m, 2, H-1 and H-5), 3.80 (bm, 1, H-2), 1.79 (sm, 2, H-4 and cis H-3), 1.50 (s, 1, OH), 1.3–0.7 (bm, 1, trans H-3). The δ 4.00 region was resolved on an HA-100 (100 MHz) spectrometer as follows: the absorbance due to H-1 lies at lower field and is a doublet with $J_{1,2}$ = 2.4 Hz and that of H-5 at about 10 Hz higher field is a doublet of doublets with J_{4c5} = 6 Hz, J_{4t} = 2.4 Hz. The 2-deuterio alcohol[23] **35** had a ^{1}H NMR spectrum differing from that of **26** as follows: δ 4.02 (s, 1, H-1), 3.96 (dd, J = 6, 2.5 Hz), and with no peak at 3.80.

The acetate **7**[16,20] was used for structure verification: ^{1}H NMR ($CDCl_3$) δ 7.10 (sm, 8, aromatic H), 4.72 (sm, 1, H-2), 4.46 (d, 1, $J_{1,2}$ = 2.5 Hz. H-1), 3.82 (dd, $J_{4,5}$ = 2.5, 5 Hz), 2.2–1.0 (bm, 4, H_3 and H_4), 1.88 (s, 3, CH_3COO–).

3,6-Dibenzo-2-bicyclo[3.2.2]nonadienols and their acetates have been prepared previously,[16,20] as has the corresponding ketone.[20] Appropriate data are given below.

3,6-Dibenzo-*exo*-2-bicyclo[3.2.2]nonadienyl Acetate (*exo*-24): colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.10 (sm, 8, aromatic H's), 6.05 (d, 1, $J_{1,2}$ = 5 Hz, H-2 endo), 3.90 (m, 1, H-5), 3.57 (bm, 1, H-1), 2.0 (m, H-8 and H-9), 1.94 (s, 3, CH_3COO–).

***endo*-24:** mp 90–90.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (sm, 8, aromatic H), 6.16 (d, 1, $J_{1,2}$ = 3.5 Hz, H-2 exo), 3.88 (dd, 1, H-5), 3.45 (dd, 1, H-1), 2.5–1.9 (m, 4, H-8 and H-9), 1.94 (s, 3, CH_3COO–).

3,6-Dibenzo-*exo*-2-bicyclo[3.2.2]nonadienol: mp 120–121.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (sm, 8, aromatic H's), 4.94 (d, 1, $J_{1,2}$ = 5 Hz, H-2 endo), 3.87 (m, 1, H-5), 3.30 (m, 1, H-1), 2.6–1.7 (bm, H-8 and H-9), 1.60 (s, 1, –OH).

3,6-Dibenzo-*endo*-2-bicyclo[3.2.2]nonadienol: ^{1}H NMR ($CDCl_3$) δ 7.20 (sm, 8, aromatic H's), 4.76 (d, 1, $J_{1,2}$ = 5 Hz, H-2, exo), 3.93 (dd, 1, H-5), 3.43 (dd, 1, H-1), 2.15–1.85 (m, 4, H-8 and H-9), 1.67 (s, 1, –OH).

3,6-Dibenzo-2-bicyclo[3.2.2]nonadienone: mp 113–114.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (sm, 1, benzo proton α to C-3), 7.25 (sm, 7, aromatic H protons), 4.22 (m, 2, H-1 and H-5), 2.11 (m, H-8 and H-9). Reduction of this ketone with lithium aluminum deuteride (same procedure as given above) gave a 50:50 mixture of exo and endo isomers of 2-deuterio-3,6-dibenzo-2-bicyclo[3.2.2]nonadienols.

Table I. Analysis of Reaction Products from Treatment of 1 with Acetic Acid–Perchloric Acid

Time, h	% 1	% 8 + 9	% 5	% 7
4.5	50	28	0	22
9	25	39	Trace	36
18	5	52	5	41
22	0	50	7	45
30	0	43	12	45
89	0	34	21	45
120	0	30	25	45
167	0	13	42	45

Treatment of 1 with 0.1 M Perchloric Acid in "Dry" Acetic Acid at Room Temperature. A solution of 4.5 g (21 mmol) of **1** in 750 ml of "dry" acetic acid, 0.108 M in perchloric acid, was prepared. Aliquots (25 ml) were withdrawn from time to time, poured into 25 ml of water, and extracted with ether (3 × 50 ml). The ether extracts were combined and washed with cold water (3 × 75 ml), saturated aqueous sodium bicarbonate (3 × 75 ml), and water (2 × 75 ml). The ether layer was dried ($MgSO_4$), filtered, and evaporated to dryness. After several additions and evaporations of carbon tetrachloride, ^{1}H NMR analysis was performed on each residue, based on ^{1}H NMR data from the independently synthesized compounds. These are reported in Table I.

Rough Kinetic Studies. Rates of isomer interconversion or of additions to **1** were measured in NMR tubes by ^{1}H NMR spectroscopy, following the reactions by integrations of absorptions due to the protons α to the acetoxy groups. The temperature of the NMR probe was 41 ± 1 °C, and runs were made either in a constant temperature bath at that temperature or at room temperature (~25 °C). In the latter case, the tubes were kept in the NMR probe for as short a time as possible. Runs were made with approximately 30 mg of material in "dry" acetic acid containing 0.103 M perchloric acid. For the additions and the skeletal rearrangements, reactions were complete, while for the exo–endo isomerizations, appropriate kinetic treatments suitable for equilibria were used.[24] For the rearrangements **8** ⇄ **9** and **10** ⇄ **11**, 0.01 M perchloric acid was used, as reactions were otherwise too fast.

Deuterium Scrambling Studies. A solution of 48 mg (0.20 mmol) of 2-deuterio-6,8-dibenzo-2-bicyclo[3.2.2]nonadienol in 0.3 ml of "dry" acetic acid containing 0.099 M perchloric acid was placed in an NMR tube at 40 °C. The excess acetic anhydride converted the alcohol to the acetate **35** immediately. An initial ^{1}H NMR spectrum was recorded, and the rate of **35** scrambling of the C-2 deuterium to the C-1 position (i.e., to give **36**) was followed at 41 °C. After 4 h there was 8 ± 2% protium at C-2. After 6.5 h there was 13 ± 2% and after 11 h there was 20 ± 2%. A second run was made at 25 ± 2 °C. After 26 h there was 4–5% protium at C-2.

A similar run was made on 2-deuterio-3,6-dibenzo-2-bicyclo[3.2.2]-nonadienol (exo:endo mixture from the lithium aluminum deuteride reduction of the ketone). The alcohol was converted to the acetate **42** immediately. By the time (5–7 min) the first scan was recorded the bridge migration had occurred so that a 50:50 mixture of **42** and **43** was observed. The subsequent rearrangement to deuterio-6,8-dibenzo-2-bicyclo[3.2.2]nonadienol acetates (**35** and **36**) was monitored. The half-life at 41 ± 1 °C was 13 ± 2 min and the half-life at 25 ± 2 °C was 50 ± 5 min.

Preparation of Ethyl Propiolate-*3-d*. A mixture of 10.1 ml (9.8 g, 0.10 mol) of ethyl propiolate (Aldrich Chemical Co.), 100 mg of barium oxide, and 18 ml (20 g, 1.0 mol) of 99.8% deuterium oxide (Mallinckrodt) was placed in a small oven-dried flask and stirred for 24 h at room temperature. ^{1}H NMR analysis of the organic phase showed ~95% deuterium at C-3 (δ 3.0). The layers were separated and the ester salted out of the aqueous layer with sodium chloride. The combined ester layers were treated again with deuterium oxide and

barium oxide for a day, after which no C-3 protons were noted by ^1H NMR. The deuterated ester was dried ($MgSO_4$) and distilled to give 8.4 g (86%) of ethyl propiolate-*3-d*.

Preparation of Ethyl 8-Deuterio-7-dibenzobicyclo[2.2.2]-octatriene Carboxylate (28). A Pyrex tube (15 × 1 in. o.d., 5/32 wall) was washed with deuterium oxide containing 0.5% barium oxide (by weight), then dried at 110 °C for 6 h. The tube was charged with 9.9 g (0.10 mol) of ethyl propiolate-*3-d*, 8.7 g (0.05 mol) of anthracene, 15 ml of "dry" benzene, and 100 mg of *p-tert*-butyldideuteriocatechol (prepared by an exchange reaction). The tube was sealed and heated at 200–210 °C for 4 h. The tube was cooled and opened. Unreacted anthracene (2.5 g, 0.014 mol) precipitated from the solution and was filtered. The filtrate was subjected to distillation at reduced pressure. The distillate contained benzene and ca. 5 g of ethyl propiolate-*3-d* which was recovered and recycled. ^1H NMR analysis of the yellow-orange residue (9.8 g) showed that there was ~4% of anthracene, 10% of ethyl propiolate-*3-d*, and the desired Diels–Alder adduct. The mixture was dissolved in a minimum amount of chloroform and placed on a silica gel column (800 ml of silica gel, 60–200 mesh). The column was eluted with benzene. The first fraction contained 400 mg of anthracene. Subsequent fractions contained ethyl propiolate and the adduct. The ethyl propiolate was removed at 90 °C under reduced pressure. The fractions containing the adduct (8.2 g) were combined and evaporated to dryness. The residue was dissolved in a minimum amount of ethanol and crystallized to give 7.7 g (56%) of **28**. Mass spectral analysis showed 98.5% deuterium incorporation: mp 111–112 °C; ^1H NMR ($CDCl_3$) δ 7.13 (m, 8, aromatic H), 5.70 (s, 1, H-1) 5.23 (s, 1, H-4), H-1 and H-4 shift with concentration ±0.1 ppm, 4.18 (q, 2, CH_3CH_2O–), 1.25 (t, 3, CH_3CH_2O–).

Preparation of 7-Hydroxymethyl-8-deuteriodibenzobicyclo[2.2.2]octatriene (29-OH). A solution of 3.4 g (12 mmol) of **28** in 40 ml of anhydrous ether was added dropwise over a period of 30 min, with stirring, to a solution of 0.80 g (6 mmol) of aluminum chloride, *caution*, and 0.70 g (18 mmol) of lithium aluminum hydride in 150 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 2 h and then worked up as described for the protio analogue.[13,14] The best yields of crystalline product were obtained by dissolving the oil in a minimum amount of ethanol and pouring the solution into an evaporating dish. Evaporation of the solvent at room temperature and atmospheric pressure gave white crystals which were dried in a vacuum desiccator (24 h, aspirator pressure) to give 2.6 g (91%) of **29-OH**. A small amount of material was recrystallized from ethanol for melting point comparison with the undeuterated compound:[13] mp 124–125 °C; ^1H NMR ($CDCl_3$) δ 7.06 (m, 8, aromatic H), 4.98 (bs, 2, H-1 and H-4), 4.13 (s, 2, $-CH_2OH$), 1.70 (bs, 1, –OH).

Preparation of 7-Chloromethyl-8-deuteriodibenzobicyclo[2.2.2]octatriene (29-Cl).[14] To a solution of 1.3 g (5.6 mmol) of **29-OH** and 1.1 g (5.9 mmol) of tri-*n*-butylamine in 175 ml of anhydrous ether, stirred at room temperature, a solution of 0.70 g (5.9 mmol) of thionyl chloride in 40 ml of anhydrous ether was added dropwise over a period of 20 min. After another 1 h, the reaction mixture was poured into 100 ml of cold water in a separatory funnel. Three extractions with 75 ml each of ether were followed by washing of the ether layers several times with dilute hydrochloric acid, water, and saturated aqueous sodium bicarbonate solution. The ethereal solution was dried ($MgSO_4$) and evaporated to dryness. The crude product (1.1 g, 78%) was dissolved in a minimum amount of chloroform and placed on a silica gel column (100 ml of silica gel 60–200 mesh) and eluted with 10 vol % benzene in Skellysolve B (petroleum ether bp 60–70 °C). The solvent was evaporated and the product was recrystallized from Skellysolve B: mp 147–148.5 °C; ^1H NMR ($CDCl_3$) δ 7.13 (m, 8, aromatic H), 5.11 (s, 1, H-1), 5.05 (s, 1, H-4), 4.22 (s, 2, $-CH_2Cl$).

Photorearrangement of 7-Chloromethyl-3-deuteriodibenzobicyclo[2.2.2]octatriene (29-Cl). Preparation of 2-Chloro-4-deuteriodibenzotricyclo[3.2.2.0^{2,4}]nonadiene (30).[14] A quartz tube (7 × 5/16 in o.d.) was charged with 450 mg (1.78 mmol) of **29-Cl**, 0.60 ml of reagent grade acetophenone, and 3.4 ml of spectral quality acetonitrile. The tube was deaerated by bubbling prepurified nitrogen through it for 30 min, stoppered, and irradiated with a 450-W medium-pressure mercury lamp for 48 h. The tube was opened, and the contents were washed into a 125-ml Erlenmeyer flask with acetone. The acetonitrile and acetone were removed at aspirator pressure. The residue was dissolved in a minimum amount of chloroform and placed on a silica gel column (150 ml of silica gel, 60–200 mesh). Elution of the column with 10 vol % benzene in Skellysolve B gave 185 mg (40%) of **30**: mp 115–116.5 °C; ^1H NMR ($CDCl_3$) δ 7.22 (sm, 8, aromatic H), 4.51 (s, 1, H-1), 4.37 (s, 1, H-5), 1.19 (d, 1, J_{gem} = 7 Hz, exo H-3), 0.55 (d, 1, J_{gem} = 7 Hz, endo H-3).

Reduction of 30 to 2,4-Dideuteriodibenzotricyclo[3.2.2.0^{2,4}]nonadiene (27). The experimental procedure described here was developed after several trials. Careful exclusion of water was required to obtain high deuterium incorporation, and all glassware was dried at 110 °C for 4–8 h.

Triphenyltin deuteride was prepared by the method of Kuivila,[25] using lithium aluminum deuteride. It was distilled at 162 °C (0.5 mm) and 12.7 g was dissolved in 6 ml of carefully dried benzene, and stored as such in a freezer. One milliliter of this solution, which was fluid enough to handle in a syringe at room temperature, contained 850 mg (2.5 mmol) of triphenyltin deuteride.

To a test tube containing 300 mg (1.18 mmol) of **30** and 150 mg of azoisobutyronitrile (AIBN), fitted with a stirring bar and a serum stopper, was added 2 ml of the triphenyltin deuteride solution. The tube was deaerated with nitrogen, then held in a 70 °C bath for 6 h. The tube was then cooled, the stopper removed, and an additional 150 mg of AIBN added. The tube was resealed, then 2 ml of the tin deuteride solution and 1 ml of benzene were added. The tube was degassed with nitrogen for 15 min and heated at 70 °C for another 6 h. The tube was opened; the contents were washed into a 50-ml round-bottom flask with acetone, and 5 ml of carbon tetrachloride was added. The solution was heated to 70 °C for 15 min, destroying any remaining triphenyltin deuteride, and the solvents were removed at aspirator pressure. The residue was taken up in about 10 ml of hot chloroform (not all the material went into solution). The mixture was filtered onto a 350-ml silica gel, 60–200 mesh column. An additional 5–7 ml of hot chloroform was used to wash the flask and precipitate. The column was eluted with about 2 l. of petroleum ether (bp 60–70 °C), giving ca. 230 mg (88%) of 2,4-dideuteriodibenzotricyclo[3.2.2.0^{2,4}]nonadiene (**27**). The material was recrystallized from petroleum ether. Mass spectral analysis showed ~2% d_0, ~10% d_1, and ~88% d_2 present: mp 176–177 °C; ^1H NMR ($CDCl_3$) δ 7.17 (sm, 8, aromatic H), 4.36 (s, 2, H-1 and H-5), 0.50 (bd, 1, J_{gem} = 6 Hz, exo H-3), −0.17 (d, 1, J_{gem} = 6 Hz, endo H-3).

Addition of Acetic Acid to 2,4-Dideuteriodibenzotricyclo[3.2.2.0^{2,4}]nonadiene (27). A solution of 500 mg (4.4 mmol) of **27** in 90 ml of "dry" acetic acid, 0.105 M in perchloric acid, was kept at room temperature (25 ± 2 °C) for 9 h (2 half-lives for the reaction with **1**). The solution was then poured into 50 ml of water in a 250-ml separatory funnel. The solution was extracted with 200 ml of pentane. The pentane layer was washed with two 100-ml portions of cold water, two 75-ml portions of saturated aqueous sodium bicarbonate, and twice with water, then dried ($MgSO_4$), filtered, and evaporated to dryness to give 502 mg of product. The ^1H NMR spectrum of the product showed about 25% of **27**. The ^1H NMR spectrum of the crude reaction mixture was quite complex but it was clear that 50% deuterium was at the bridgehead of the [3.2.2] product indicating phenyl migration in the ring opening. The acetates were converted to the alcohols with lithium aluminum hydride, and the [3.2.2] alcohol was separated by preparative thin layer chromatography and submitted for mass spectral analysis and HA-100 ^1H NMR analysis. The deuterium incorporation was 3–4% d_0, 10% d_1, and 87% d_2.

The ^1H NMR spectrum showed[26] that the product contained equal amounts of **31-OH**, **32-OH**, **33-OH**, and **34-OH**. We were able to separate the absorptions due to protons at C-1, C-2, and C-5. The integration of absorption for the C-1 proton was 0.5 H, and the peak was a slightly broadened singlet (this is due to the bridgehead proton in **31-OH** and **32-OH** which is vicinal to a deuterium atom at C-2—the other half of the alcohol mixture has D at C-1—hence the 0.5 intensity). The next higher field peak had an intensity of 1, and had two equal doublets, one a set of exterior peaks, with J = 6–7 Hz, caused by coupling of H-5 with the equatorial (cis to acetoxy) protons at C-4 in **31-OH** and **33-OH**, and the other, a set of interior peaks, with J = 2.4 Hz, due to coupling of H-5 with the axial (trans to acetoxy) proton at C-4 in **32-OH** and **34-OH**. The H-2 proton absorption gives rise to a doublet of doublets (J = 9 and 5 Hz) with the hydrogens at C-3. As the substituent at C-1 is a deuteron when the proton is at C-2, there is no further important coupling. The intensity of this peak was 0.5, and the peak is attributed to the **33-OH–34-OH** equimolar mixture.

Acknowledgment. The authors are indebted to the National Science Foundation for support of this work.

Registry No.—**1**, 30122-20-4; **3**, 59938-53-3; **4**, 59938-54-4; **5**, 59938-55-5; **5** OH analogue, 53483-04-8; **6**, 59938-56-6; **6** OH analogue, 53483-08-2; **7**, 24330-16-3; **8**, 59938-57-7; **8** OH analogue, 59938-58-8; **9**, 59981-06-5; **9** OH analogue, 59981-07-6; **10**, 59981-08-7; **10** OH analogue, 59981-09-8; **11**, 59981-10-1; **11** OH analogue, 59981-11-2; **13**, 59938-59-9; **18**, 59938-60-2; *exo*-**24**, 24332-09-0; *exo*-**24** OH analogue, 23445-14-9; *endo*-**24**, 24332-08-9; *endo*-**24** OH analogue,

23445-15-0; **26**, 23417-00-7; **27**, 59938-61-3; **28**, 59938-62-4; **29**-OH, 59938-63-5; **29**-Cl, 59938-64-6; **30**, 59938-65-7; anthracene, 120-12-7; *trans*-1,3-dichloropropene, 10061-02-6; *cis*-1,3-dichloropropene, 10061-01-5; acetic acid, 64-19-7; *cis*-1-propenyl acetate, 3102-47-4; *trans*-1-propenyl acetate, 1528-10-5; *p*-bromobenzenesulfonyl chloride, 98-58-8; *syn*-8-methyl-2-dibenzobicyclo[3.2.1]octadienone, 59938-66-8; *anti*-8-methyl-2-dibenzobicyclo[3.2.1]octadienone, 59981-12-3; lithium aluminum hydride, 16853-85-3; 3,6-dibenzo-2-bicyclo[3.2.2]nonadienone, 24330-03-8; ethyl propiolate-*3-d*, 59938-67-9.

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Ionic Reactions in Bicyclic Systems. 9. Preparation of Optically Active 1,2-Dimethyl-*exo*-2-norbornyl, 1,2-Dimethyl-*exo*-2-benzonorbornenyl, and 6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl Chloride

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Hydrochlorination of optically active 1-methyl-2-methylenenorbornane (1) in pentane at −78 °C gives active 1,2-dimethyl-*exo*-2-norbornyl chloride (2) with ~27% retention of optical configuration. Under similar conditions active 1-methyl-2-methylenebenzonorbornene (3) gives active 1,2-dimethyl-*exo*-2-benzonorbornenyl chloride (4) (~80% retention) and active 6,7-dimethoxy-1-methyl-2-methylenebenzonorbornene (5) gives 6,7-dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl chloride (6) with about 13% retention of optical configuration.

Recently we reported results of solvolytic studies of optically active 1,2-dimethyl-*exo*-2-norbornyl chloride (**2**)[1] and 1,2-dimethyl-*exo*-2-benzonorbornenyl chloride (**4**).[2] We have also investigated the 6,7-dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl system[3] including the optically active tertiary chloride (6). We now present details of the preparation of these optically active tertiary chlorides.

A possible route to the optically active tertiary chlorides was suggested by the work of Brown and Liu,[4] who observed that under carefully controlled conditions, hydrochlorination of deuterium labeled 1-methyl-2-methylenenorbornane (1) gives **2** with only partial scrambling of the methyl groups. Exposure of the product to hydrogen chloride at 0 or −78 °C results in randomization of the methyl groups (hydrogen chloride catalyzed isomeric Wagner–Meerwein rearrangement[5]). A corollary of that work is that optically active **1** should lead to active **2**; however, **2** racemizes under the conditions of the hydrochlorination.

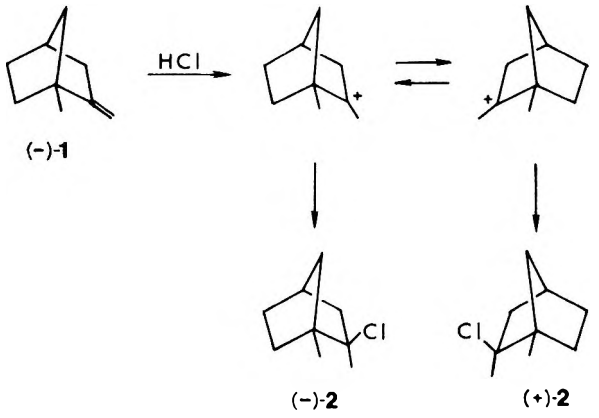
The preparation and determination of absolute configurations and rotations of optically active 1-methyl-2-methylenenorbornane (**1**),[6] 1-methyl-2-methylenebenzonorbornene (**3**),[7] and 6,7-dimethoxy-1-methyl-2-methylenebenzonorbornene (**5**)[8] have been reported elsewhere.[9] Attempts to prepare optically active **2** from active **1** under conditions reported[4] to give minimum scrambling of the methyl groups (hydrochlorination of neat **1**, 0 °C, 1–2 min) were unsuccessful. Hydrogen chloride uptake ceased at about 60% reaction—the remaining liquid **1** was encapsulated by the solid adduct (**2**)—and active chloride could not be separated from the mixture. Evidently, in the earlier work[4b] unreacted **1** in the product did not interfere with NMR analysis of the tertiary chloride. In the present work the additional handling required for separation of pure **2** resulted in racemization.

Hydrochlorination of (−)-**1** in pentane at −78 °C is complete in a few minutes—the reaction is somewhat slower at 0 °C. Removal of the pentane and excess hydrogen chloride under high vacuum at <0 °C gave homogeneous (−)-**2**. The purity of racemic and optically active **2** obtained by this procedure was established by the NMR spectrum, solvolysis equivalent, elemental analysis, and mass spectrum. Efficient

Table I. Retention of Configuration for Hydrochlorination of 1-Methyl-2-methylenenorbornane (1)

(−)-1 $[\alpha]^{30}D^a$	→ (−)-2 →	(−)-1 $[\alpha]^{30}D^a$	% retention
−42.1°		−11.5°	27[b]
−35.7°		−9.2°	26[c]
−34.6°		−2.1°	6[b]
−34.6°		−2.9°	8[c]

[a] Rotations for chloroform solutions. [b] Elimination with 0.1 M 2,6-lutidine in chloroform at 30 °C. [c] Elimination with 0.7 M potassium *tert*-butoxide in dimethyl sulfoxide at 45 °C.



stirring during hydrochlorination, chilling (liquid nitrogen) the reaction container during attachment to a vacuum transfer apparatus, and rapid workup are necessary to avoid extensive racemization.

The tertiary chloride (2) racemizes spontaneously in chloroform at room temperature ($k \sim 4 \times 10^{-3}$ min^{-1}, 30 °C) and reliable rotations could not be determined. The most active samples of (−)-2 had rotations about 3% as large as those of the starting olefin. That the chloride was not contaminated with unreacted (−)-1 was clear from the NMR spectrum, rotary dispersion curves for the two compounds, and complete loss of optical activity during first-order racemization under conditions where active 1 is optically stable.

The optical purity of (−)-2 was determined by reconversion to (−)-1 with either potassium *tert*-butoxide in dimethyl sulfoxide at 45 °C or 2,6-lutidine in chloroform at 30 °C. Results of these experiments are shown in Table I which shows rotations of starting olefin and olefin derived from (−)-2. Both methods for converting (−)-2 to (−)-1 give similar results which suggests that optical configuration is not lost in this transformation. The first two experiments are for the best conditions for obtaining active 2. In these cases (−)-2 was obtained which gave (−)-1 with ~27% of the original optical activity. We believe that the loss of configuration occurs during hydrochlorination. In any case the (−)-2 → (−)-1 correlation gives a lower limit of the optical purity of 2. In the last two experiments in the table less efficient stirring during hydrochlorination led to less active 2 (6–8% retention of configuration).

Hydrochlorination of 1-methyl-2-methylenebenzonorbornene (3) in pentane at −78 °C is complete in 3–7 min (depending on sample size) and (+)-3[7] gives (+)-1,2-dimethyl-*exo*-2-benzonorbornenyl chloride [(+)-4]. The purity of racemic and active samples of 4 was established by the NMR spectrum, solvolysis equivalent, elemental analysis, and mass spectrum. The optical purity of active 4 was determined by reconversion to 3 with potassium *tert*-butoxide in dimethyl sulfoxide at 45 °C. Evidently this is an E2 elimination and

Table II. Rates and Relative Rates of Methanolysis of 2, 4, and 6 at 0 °C

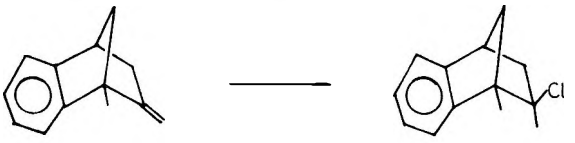
Compd	$10^4 k_t$, min^{-1}	Rel rate
2	85.1[a]	254
4	0.335[b]	1
6	60.8[c]	184

[a] Reference 1. [b] Extrapolated from data at higher temperatures reported in ref 2. [c] Reference 3.

proceeds without loss of optical configuration; independent experiments gave the same ratio of rotations for product and reactant and no loss of optical activity occurs in the absence of base.

The (+)-3 → (+)-4 → (+)-3 sequence resulted in only 20% loss of configuration as compared to >70% loss for the dimethylnorbornyl system (1 → 2 → 1). The tertiary benzonorbornenyl chloride (4) is noticeably more optically stable than the tertiary norbornyl chloride (2) as would be expected from relative rates of ionization. Relative rates of methanolysis of 2, 4, and 6 are shown in Table II.

Hydrochlorination of 3 in pentane shows a more pronounced negative temperature coefficient than hydrochlorination of 1. In contrast to the rapid rate at −78 °C (reaction

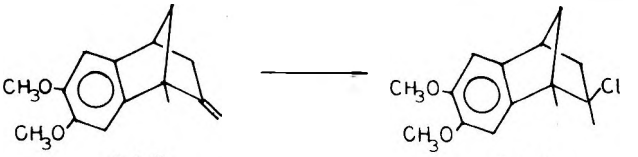


(−)-3 (−)-4

complete in about 4 min), the reaction is <80% complete in 34 min at 25 °C. Hydrogen chloride uptake is pseudo-first-order and $k = 4.4 \times 10^{-2}$ min^{-1}, 25 °C. Evidently the inverse temperature effect results from a change in medium with change in temperature. For 1,2-dimethylcyclopentene in pentane saturated with hydrogen chloride, the hydrogen chloride/olefin molar ratio increases from 1.3 to 0 °C to 6.3 at −78 °C.[10] This suggests that in the present work the medium changes from essentially pentane at 25 °C to largely hydrogen chloride at −78 °C. The large increase in solvent polarity with decrease in temperature is probably the cause of the increase in rate. Also, hydrochlorination may be second or higher order in hydrogen chloride[11] and the increase in hydrogen chloride concentration could also contribute to the temperature effect.

Hydrochlorination of 6,7-dimethoxy-1-methyl-2-methylenebenzonorbornane (5) was complicated by the low solubility of this olefin in pentane at −78 °C. Thus, optimum conditions for maximum retention of configuration for hydrochlorination of 1 and 3 could not be used in this case. Instead, methylene chloride was used—this solvent gives poorer results for the (−)-1 → (−)-2 conversion.

Hydrochlorination of 5 in methylene chloride at −78 °C is complete in about 2 min and (−)-5[8] gives (−)-6 with varying



(−)-5 (−)-6

amounts of retention. As shown in Table II, 6 is more reactive than 4 and nearly as reactive as 2 in methanol at 0 °C. Moreover, the activation energy for methanolysis is lower for 6 (18.5 kcal) than for 2 (21.2 kcal) which indicates that for the tem-

perature range of the hydrochlorination and workup (−78 → 0 °C) the rate of ionization (racemization) is probably at least as high for **6** as for **2**. In the most successful experiment (−)-**5** gave (−)-**6** with 14% retention of optical configuration [established by reconversion to (−)-**5** with potassium *tert*-butoxide in dimethyl sulfoxide]. Recrystallization of (−)-**6** from pentane (<0 °C) resulted in 25% loss of optical activity. Thus, active **6** racemizes spontaneously in nonpolar solvents. The purity of **6** was established by the NMR spectrum, solvolysis equivalent, and elemental analysis.

Experimental Section

Racemic and Optically Active 1,2-Dimethyl-*exo*-2-norbornyl Chloride (2). The tertiary chloride (**2**) was prepared by hydrochlorination of 1-methyl-2-methylenenorbornane (**1**)[6] with an automatic hydrochlorination apparatus described earlier.[4,12] In a typical experiment the apparatus was flushed with nitrogen through the rubber septum in the generator valve and the reaction vessel was cooled to −78 °C (dry ice–acetone). About 2 ml of concentrated hydrogen chloride was added to the concentrated sulfuric acid (100 ml) and the system was flushed and filled with hydrogen chloride. A solution of 1.01 g of **1** in 4.5 ml of pentane was chilled to −78 °C and then injected into the reaction vessel while maintaining vigorous stirring. Hydrogen chloride uptake ceased in 5.5 min. The reaction vessel was removed, rapidly attached to a vacuum transfer apparatus, and chilled with liquid nitrogen. After evacuation to 0.1 mm, the liquid nitrogen was replaced with an ice bath and the hydrogen chloride and pentane vacuum transferred and then the apparatus was filled with dry nitrogen. *dl*-1,2-Dimethyl-*exo*-2-norbornyl chloride (**2**) has mp 120–122 °C; NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.63 (s, 3 H), 0.83–2.75 (m, 9 H); mass spectrum parent peaks *m/e* 160 and 158.

Anal. Calcd for $C_9H_{15}Cl$: C, 68.13; H, 9.53; Cl, 22.34; solvolysis equivalent, 159. Found: C, 68.43; H, 9.70; Cl, 22.06; solvolysis equivalent (60% aqueous methanol), 158.

Optically active **2** was obtained by the same procedure. In a typical experiment 1.01 g of (−)-**1**,[5] $[\alpha]^{30}D$ −42° (*c* 3.5, $CHCl_3$), gave 1.0 g (77%) of (−)-1,2-dimethyl-*exo*-2-norbornyl chloride [(−)-**2**], $[\alpha]^{30}D$ −0.197° (*c* 7.63, $CHCl_3$). Optically active chloride was prepared shortly before use[1] and stored under nitrogen at −25 °C. All spectral properties of active **2** were indistinguishable from those of racemic material.

Racemic and Optically Active 1,2-Dimethyl-*exo*-2-benzonorbornenyl Chloride (4). This tertiary chloride was prepared from 1-methyl-2-methylenebenzonorbornene (**3**)[7] by the procedure described above for the **1** → **2** transformation except that during the vacuum transfer the temperature rose from −78 °C to room temperature instead of from −78 to 0 °C. *dl*-1,2-Dimethyl-*exo*-2-benzonorbornenyl chloride (**4**) has mp 48–50 °C; NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.58 (s, 3 H), 1.67–1.95 (m, 2 H), 2.30–2.92 (m, 2 H), 3.10–3.27 (m, 1 H), 7.02 (s, 4 H); mass spectrum parent peaks *m/e* 206 and 208.

Anal. Calcd for $C_{13}H_{15}Cl$: C, 75.54; H, 7.31; Cl, 17.15. Found: C, 75.63; H, 7.36; Cl, 17.25.

Hydrochlorination of a 0.4-g sample of **3** in 1.6 ml of pentane at −78 °C was complete in 3 min. At 25 °C the hydrogen chloride uptake is pseudo first order and only 78% complete in 34 min. The amount of reaction was determined by NMR analysis ($CDCl_3$) of the reaction mixture using the methylene proton signals in **3** (δ 4.70 and 4.90) and the 2-methyl signal in **4** (δ 1.58).

Hydrochlorination of (+)-1-methyl-2-methylenebenzonorbornene [(+)-**3**],[7] $[\alpha]^{30}D$ 198° (*c* 2.72, $CHCl_3$), by the above method (−78 °C) gave (+)-1,2-dimethyl-*exo*-2-benzonorbornenyl chloride [(+)-**4**], $[\alpha]^{30}D$ 42.9° (*c* 3.74, $CHCl_3$). Spectral properties were the same as for racemic material.

Racemic and Optically Active 6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl Chloride (6). 6,7-Dimethoxy-1-methyl-2-methylenebenzonorbornene (**5**)[8] was converted to **6** by hydrochlorination by the method described above for the **1** → **2** conversion except that the solvent was methylene chloride instead of pentane. Hydrochlorination of a 1.15-g sample of **5** at −78 °C was complete in 2 min. *dl*-6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl chloride (**6**) has mp 47–49 °C; NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.65 (s, 3 H), 1.69–2.15 (m, 2 H), 2.39–2.80 (m, 2 H), 3.05–3.20 (m, 1 H), 3.79 (s, 6 H), 6.62 (d, 2 H).

Anal. Calcd for $C_{15}H_{19}O_2Cl$: C, 67.54; H, 7.18. Found: C, 67.73; H, 7.20.

Hydrochlorination of (−)-**5**,[8] $[\alpha]^{25}D$ −143° (*c* 1.5, $CHCl_3$), gave (−)-**6**, $[\alpha]^{25}D$ −3.03° (*c* 1.1, $CHCl_3$). Spectral properties of (−)-**6** were the same as for racemic **6**. In the experiment which gave the most active (−)-**6** the above (−)-**5** gave (−)-**6**, $[\alpha]^{25}D$ −4.04°. From absolute rotations for **5** and **6** (see below) it can be determined that this corresponds to about 14% retention of configuration.

Dehydrochlorination of (+)-1,2-Dimethyl-*exo*-2-benzonorbornenyl Chloride [(+)-4]. In a typical experiment 0.25 g (1.21 mmol) of (+)-**4**, $[\alpha]^{30}D$ 42.9° (*c* 2.7, $CHCl_3$), derived from (+)-**3**, $[\alpha]^{30}D$ 198.2° (*c* 2.7, $CHCl_3$), was dissolved in 80 ml of dimethyl sulfoxide containing 5.2 g (4.6 mmol) of potassium *tert*-butoxide. The solution was held at 45 °C for 1 h and then poured into 300 ml of water. The resulting solution was extracted with pentane, the extract dried ($MgSO_4$), and the solvent removed with a rotary evaporator. Purification by preparative GC (20 ft, 30% Carbowax 20M on Chromosorb P at 200 °C) gave (+)-**3**, $[\alpha]^{30}D$ 159.3° (*c* 4.01, $CHCl_3$). This is 80% retention of configuration for the (+)-**3** → (+)-**4** → (+)-**3** sequence. The absolute rotation for **3** is 315° ($CHCl_3$).[7] From these data a lower limit of 42.9° × (315/159) = 85° can be determined for the absolute rotation of **4**.

In a duplicate experiment similar results were obtained, i.e., 80% retention for (+)-**3** → (+)-**4** → (+)-**3**.

A solution of (+)-**4** in dimethyl sulfoxide was placed in a 1-dm polarimeter tube thermostated at 45 °C. During 40 min α_{365} changed from −3.081° to −3.140°. This shows that the chloride does not racemize under these conditions. The small increase in rotation may be due to slight elimination to form more active **3**.

A solution of 406 mg (0.239 mmol) of (+)-**3**, $[\alpha]^{30}D$ 198.2° (*c* 2.72, $CHCl_3$), in dimethyl sulfoxide containing 52 mg (0.46 mmol) of potassium *tert*-butoxide was placed in a 1-dm polarimeter tube thermostated at 45 °C. There was no change in the observed rotation of 8.691° over a period of 65 min. This shows that **3** is optically stable under the conditions of the (+)-**4** → (+)-**3** conversion.

Dehydrochlorination of (−)-1,2-Dimethyl-*exo*-2-norbornyl Chloride [(−)-2]. To determine the minimum value for retention of optical configuration for the (−)-**1** → (−)-**2** transformation the active tertiary chloride [(−)-**2**] was reconverted to (−)-**1** as described above for the (+)-**4** → (+)-**3** conversion. In a typical experiment 0.25 g (1.58 mmol) of (−)-**2**, derived from (−)-**1**, $[\alpha]^{30}D$ −35.7° (*c* 1.64, $CHCl_3$), was dissolved in 30 ml of dimethyl sulfoxide that contained 2.50 g (22 mmol) of potassium *tert*-butoxide. The solution was warmed to 45 °C for 15 min and then poured into 200 ml of ice water. Workup and isolation by preparative GC as described in the preceding section gave (−)-**1**, $[\alpha]^{30}D$ −9.18° (*c* 2.06, $CHCl_3$). Thus, hydrochlorination of **1** proceeds with at least 26% retention of configuration.

In another experiment 0.46 g (3 mmol) of (−)-**2**, $[\alpha]^{30}D$ 0.197° (*c* 3.50, $CHCl_3$), derived from (−)-**1**, $[\alpha]^{30}D$ −34.6°, was dissolved in 25 ml of chloroform containing 2.52 g (24 mmol) of 2,6-lutidine. The resulting solution was kept at 30 °C for 11 h. The change in rotation in a 1-dm tube was α_{365}[30] 0.030° → 0.610° and the final rotation was constant. The solution was treated with 8.0 g (56 mmol) of methyl iodide for 24 h at 30 °C to quaternize the lutidine and then the solution was extracted with water, dried ($MgSO_4$), and concentrated with a fractionating column. Analytical GC showed the product to be 71% **1** and 29% 1,2-dimethyl-2-norbornene. Preparative GC (20% Ucon Polar IB-550-X on Chromosorb W at 120 °C) gave (−)-**1**, $[\alpha]^{30}D$ −11.5°. This corresponds to 27% retention for the (−)-**1** → (−)-**2** → (−)-**1** sequence.

Dehydrochlorination of (−)-6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornyl Chloride [(−)-6]. Dehydrochlorination of (−)-**6**, $[\alpha]^{25}D$ −1.48° (*c* 1.0, $CHCl_3$), in dimethyl sulfoxide as described above for the **4** → **3** transformation gave (−)-**5**, $[\alpha]^{25}D$ −7.3°. Control experiments showed that **5** is optically stable under these conditions. From the absolute rotation for **5**, $[\alpha]^{25}D$ 291°, it can be determined that the absolute rotation for **6** is about 1.48° × 291/7.3 = 59°.

Acknowledgment. This work was supported by the National Science Foundation (MPS 76-15879) and the Air Force Office of Scientific Research (AFOSR-71-1974).

Registry No.—(±)-**1**, 60338-54-7; (−)-**1**, 18366-95-5; (±)-**2**, 60338-55-8; (−)-**2**, 35733-52-9; (±)-**3**, 35001-33-3; (+)-**3**, 34993-32-3; (±)-**4**, 60383-65-5; (+)-**4**, 60383-66-6; (±)-**5**, 54576-25-9; (−)-**5**, 54630-87-4; (±)-**6**, 60338-56-9; (−)-**6**, 60383-67-7.

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Structure of the o-Aminophenol–Adipoin Condensation Product

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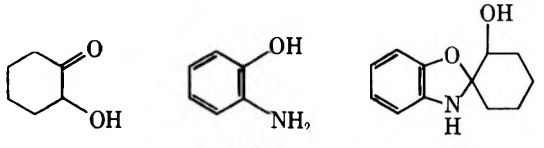
The thermal condensation product from adipoin and o-aminophenol is found to be 1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (8). This structure, which corrects an assignment in the earlier literature, is based on spectral data, chemical transformations, and a single crystal x-ray crystallographic study of 8 HI.

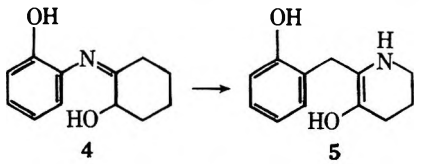
While studying the reactions of adipoin (1) with aromatic amines, Cummins and Tomlinson[1] found that heating 1 with *o*-aminophenol (2) at 135 °C produced a condensation product, $C_{12}H_{15}O_2N$, mp 171 °C, in unspecified yield. The spirocyclic structure 3 was tentatively assigned to this substance based largely on its infrared spectrum which displayed O–H



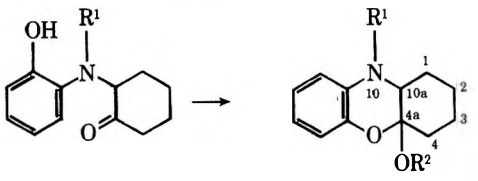
1 2 3

and N–H but no C=O absorption. Our interest in spirocyclic systems prompted us to repeat this preparation so that the properties of the product might be explored. In our hands, heating an intimate mixture of 1 (as the dimer[2]) and 2 under nitrogen for 5 min gave the expected product in 57% yield. Its melting point and infrared spectrum were compatible with the reported data and it could be recrystallized unchanged from aqueous alkali in further agreement with the observations of Cummins and Tomlinson. However the NMR spectrum (in Me_2SO-d_6) of this condensation product ruled out the assigned structure 3 by failing to show a signal in the δ 3.5–4.0 region for the carbinol proton of a secondary alcohol.

At this point, an alternative formulation for the condensation product came to mind by very simple mechanistic reasoning. Initial reaction between 1 and 2 to give the Schiff base 4, followed by successive proton shifts, would lead via enol 5 to the phenolic ketone 6; the corresponding hemiketal structure 8 is compatible with all reported properties of Cummins and Tomlinson's condensation product and explains our failure to find a signal for a carbinol proton in its NMR spectrum. The formulation of this product as 1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (8) accounts for the observation of a 1 H multiplet at δ 3.0 (–NCHCH$_2$–) and the absence of any other signals (excluding exchangeable protons) in the region δ 2.5–6.8. The revised structure is further supported by the properties of several transformation products.



4 5



6, R^1 = H
7, R^1 = Ac

8, R^1 = R^2 = H
9, R^1 = Ac; R^2 = H
10, R^1 = Ac; R^2 = Ac
11, R^1 = $CH_2C_6H_5$; R^2 = H

Brief heating with acetic anhydride at its boiling point (137 °C) converted 8 to the *N*-acetyl derivative 9, mp 162–163.5 °C, whose infrared spectrum showed distinct hydroxyl and amide absorption as well as a weak carbonyl band at 1705 cm^{-1} reflecting a small fraction of the open form 7 in equilibrium with 9. The 10a proton of 9 appeared as a four-line signal (X part of an ABX system) centered at δ 5.2. This 2 δ downfield shift on acetylation presumably reflects the diamagnetic anisotropy as well as the inductive effect of the acetyl substituent. Treatment of 9 with acetic anhydride at 90 °C in the presence of *p*-toluenesulfonic acid as catalyst provided the *O,N*-diacetyl derivative 10, mp 126–127.5 °C, which showed bands in the infrared at both the amide and ester carbonyl stretching frequencies. Formation of the tertiary acetate presumably occurred by an alkyl–oxygen cleavage mechanism.

Alkylation of 8 with benzyl bromide yielded the noncrystalline 10-benzylhexahydrophenoxazine 11 which showed appropriate spectral characteristics; its NMR spectrum exhibited the nonequivalent benzylic protons as a widely separated ($\Delta\delta$ 0.36 ppm) AB quartet reflecting the proximity of nearby chiral centers.

The o-aminophenol–adipoin condensation product 8 was partly converted to a trideuterio derivative (46.5% d_3, 26.6% d_2) by heating a sample under reflux with NaOD in D_2O followed by H_2O washing of the product. Incorporation of one deuterium at C-10a and two at C-4, expected if 8 is in rapid equilibrium with 6, is supported by the disappearance of appropriate proton signals in the NMR spectrum of 8-d_3 and its *N*-acetyl derivative.

Final support for the assigned structures was obtained by single-crystal x-ray crystallographic methods. Compound 8

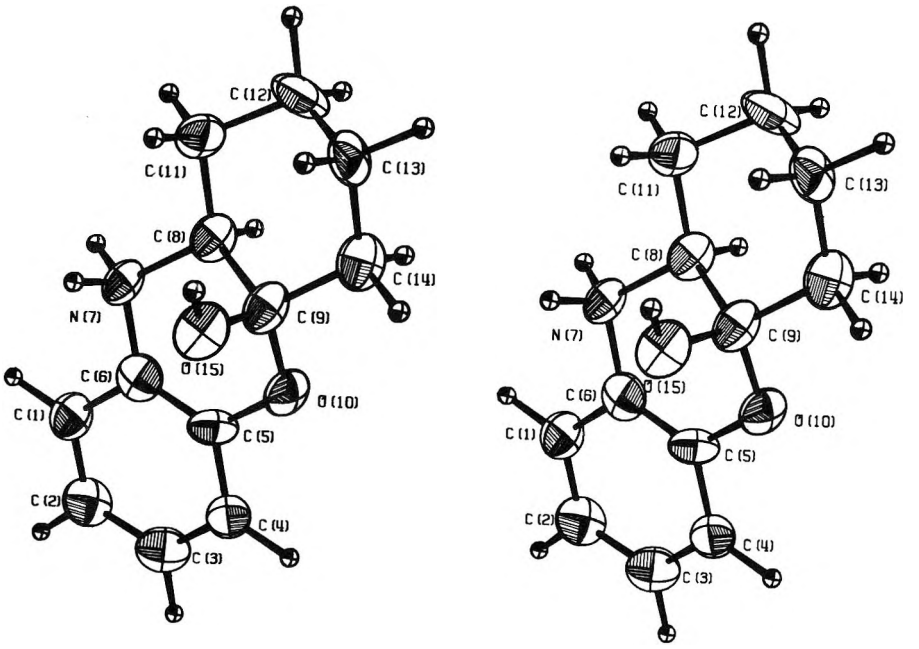
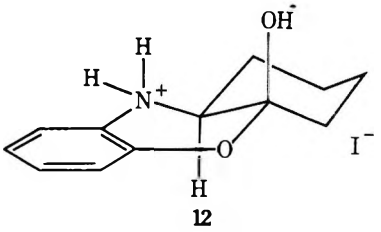


Figure 1. Stereoview of the hexahydrophenoxazine molecule.

gave a hydriodide which, by slow cooling of an aqueous 2-propanol solution, provided crystals suitable for x-ray analysis. Based on the crystallographic data given below, the crystal structure of 8 HI may be depicted as **12**, which reveals that the



12

tricyclic structure includes a trans fusion between the nonaromatic rings. Bond angles and bond lengths did not differ appreciably from the expected values.

The crystals were found to be of the monoclinic space group Cc with a = 17.834 (9), b = 8.831 (3), c = 10.534 (5) Å, β = 129.85 (3)°. The density was measured by flotation as 1.75 g/cm^3. Based on four molecules per unit cell, the calculated density was 1.737 g/cm^3. Because the molecule did not contain a center of symmetry or a twofold axis, space group $C2/c$ was eliminated. A 1-Å data set (maximum sin θ/λ = 0.5) was collected on a Syntex $P\bar{1}$ diffractometer using molybdenum radiation (λ = 0.71069 Å). The diffractometer was equipped with an incident beam monochromator. All diffraction data were collected at room temperature.

All crystallographic calculations were facilitated by the CRYM system.[3] A trial structure was obtained using conventional Patterson and Fourier techniques. This trial structure refined routinely to a final R index ($R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$) of 0.028. The final cycles of full matrix least squares contained all nonhydrogen coordinates, anisotropic temperature factors, and scale factor in one matrix. No corrections were made for absorption (μ = 25.3 cm^{-1}) or secondary extinction. Hydrogen positions were calculated wherever possible. The hydroxyl hydrogen was located by difference Fourier techniques. While the hydrogen parameters were added to the structure factor calculations during the final stages of refinement, they were not refined. A final difference Fourier revealed no missing or misplaced electron density. A stereoview of the molecule is given in Figure 1. Other pertinent crystallographic data will appear in the microfilm edition.

Experimental Section

Microanalyses were performed by Galbraith Laboratories, Inc., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C. Melting points were determined on a Thomas hot-stage mounted on a Bausch and Lomb microscope and are uncorrected. Infrared (ir) spectra were recorded on a Beckman Acculab 1 or Beckman 33 spectrophotometer. Ultraviolet (uv) spectra were measured on a Perkin-Elmer 202 instrument. Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Associates HA-100 instrument, and chemical shifts are given in parts per million (δ) downfield from an internal tetramethylsilane standard except where noted. The abbreviations s, d, t, q, m, and br stand for singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectra (MS) were determined on AEI MS 12 instrument. The abbreviation M$^+$ refers to the molecular ion. Analytical thin layer chromatography (TLC) was done on ICN silica gel F-254 and F-254/366 plates. Preparative thin layer chromatography was performed using Merck silica gel F-254 (20 × 20 cm × 2 mm thick) plates. Column chromatography employed Woelm alumina activity II or Bio-Sil A (100–200 mesh) silica gel.

1,2,3,4,4a,10a-Hexahydro-4a-hydroxyphenoxazine (8). Samples of 2-hydroxycyclohexanone (5.54 g, 48.6 mmol) and o-aminophenol (5.86 g, 53.8 mmol) were ground to an intimate mixture in a mortar and pestle, then heated in a flask under nitrogen at 129–130 °C for 5 min during which the mixture melted and then solidified. The product was taken up in hot ethanol, filtered through a cotton plug, and allowed to cool, giving 5.68 g (57%) of a beige, crystalline solid, mp 164–166 °C. Upon recrystallization from 80:20 ethyl acetate–n-hexane, colorless plates were obtained: mp 166.5–167.5 °C (lit.[1] 171 °C); ir 3580, 3480, 3390, 1610, 1590 cm^{-1}; uv max (CH_3OH) 208.5 nm (ϵ 29 300), 244.5 (7150), 295 (3810); max (0.0375 M NaOH in CH_3OH) 215.5 (11 400), 244 (5970), 295 (3060); NMR (Me_2SO-d_6 with external Me_4Si) δ 1.3–2.1 [br m, 8, -$(CH_2)_4$-], 3.0 (m, 1, NCH), 3.5 (br s, 1.4, OH), 5.7 (br s, 0.3, NH), 6.6 (m, 4, aromatic); MS m/e 205 (M$^+$).

1,2,3,4,4a,10a-Hexahydro-4a-hydroxyphenoxazine Hydriodide (8 HI). A sample of 8 (102 mg, 0.5 mmol) was dissolved in 2-propanol (3.0 ml) to which hydriodic acid (47% aqueous, 0.10 ml) had been added. Overnight cooling to 4 °C afforded 27.5 mg (17%) of colorless prisms, mp 169.5–171.5 °C with decomposition.

Anal. Calcd for $C_{12}H_{15}NO_2$·HI: C, 43.26; H, 4.84; N, 4.20. Found: C, 43.04; H, 4.51; N, 3.60, 3.81.

10-Acetyl-1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (9). A sample of 8 (2.03 g, 9.9 mmol) was dissolved in 10 ml of acetic anhydride and heated at 141–142 °C for 5 min. Solvent was removed under vacuum in the presence of added Celite to increase the surface area. Chloroform was added to the residue, Celite was removed by filtration, and the filtrate was concentrated under vacuum. The amorphous residue crystallized from ether (10 ml) giving 2.04 g (83%) of beige needles, mp 162–163.5 °C. Recrystallization from methylene chloride and n-hexane gave a colorless product: mp 164–165.5 °C; ir

($CHCl_3$) 3580, 3210, 1705, (weak), 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.7 [br m, 8, $-(CH_2)_4-$], 2.20 (s, 3, $NCOCH_3$), 5.19 (X part of ABX system, $J_{AX} + J_{BX}$ = 19 Hz, 1, $NCHCH_2$), 6.8–7.1 (br m, 4, aromatic), 9.24 (s, 1, OH); MS *m/e* 247 (M^+).

Anal. Calcd for $C_{14}H_{17}NO_3$: C,68.00; H, 6.93; N, 5.66. Found: C, 68.12; H, 6.87; N, 5.77.

4a-Acetoxy-10-acetyl-1,2,3,4,4a,10a-hexahydrophenoxazine (10). A sample of **9** (243 mg, 0.99 mmol) and *p*-toluenesulfonic acid (18 mg, dried by removal of water as a benzene azeotrope) were heated in 3.0 ml of acetic anhydride for 5 min at 80–90 °C. Solvent was removed in a manner similar to the method used in preparation of **9**. Preparative thin layer chromatography (silica gel, 20% EtOAc/$CHCl_3$, one development, R_f 0.49) gave 190 mg (66.4%) of colorless needles, mp 121–126 °C. Recrystallization from 50% ethanol–water gave colorless prisms: mp 126–127.5 °C; ir ($CHCl_3$) 1745, 1661 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.4 (br m, 8, aliphatic), 1.88 (s, 3, $NCOCH_3$), 2.26 (s, 3, $OCOCH_3$), 2.66 (br m, 1, NCH), 7.0 (m, 4, aromatic); MS *m/e* 289 (M^+).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N. 4.84. Found: C, 66.32; H, 6.92; N, 4.71.

10-Benzyl-1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (11). A solution of 8 (254 mg, 1.24 mmol) and benzyl bromide (1.0 ml) in 10 ml of acetone was heated under reflux with potassium carbonate (343 mg) for 13.5 h. After removal of solvent, the residue was partitioned between benzene and water. The organic phase was washed with water until neutral and the dried ($MgSO_4$) solution was filtered and concentrated. The residue was redissolved in benzene and filtered through an 8-cm column of alumina II. Removal of solvent afforded 150 mg (41%) of a colorless oil which appeared pure by TLC (R_f 0.40 on silica gel with chloroform): ir ($CHCl_3$) 3490, 2935, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.0–1.8 (m, 7, aliphatic), 2.20 [m, 1, $-OC(OH)CH-$], 2.97 (m, 1, NCH), 3.64 (s, 1, OH), 4.18 and 4.54 (calculated shifts from AB quartet for benzylic protons), 6.8 (m, 4, aromatic), 7.3 (s, 5, aromatic); MS *m/e* 295 (M^+), 91 (tropylium).

4,4,10a-Trideuterio-1,2,3,4,4a,10a-hexahydro-4a-hydroxyphenoxazine (8-d_3). A sample of 8 (341 mg, 1.66 mmol) was added to a solution of sodium metal (0.2 g) in 10.0 ml of deuterium oxide and heated at reflux under nitrogen for 2 h. The reaction mixture was cooled to 10 °C, neutralized with glacial acetic acid, and extracted with 25 ml of chloroform. The organic phase was washed twice with water, dried ($MgSO_4$), and filtered through a column of silica gel (5 g) to remove traces of a polar contaminant. Removal of solvent gave 256 mg (74%) of a beige solid, mp 161–164 °C. Upon recrystallization from ethyl acetate and *n*-hexane, 128 mg of light pink crystals, mp 169–170 °C, were obtained: MS (14 eV) 4.4% d_5 (210), 13.9% d_4 (209), 46.5% d_3 (208), 26.6% d_2 (207), 4.7% d_1 (206), 3.9% d_0 (205).

4a-Acetyl-4,4,10a-trideuterio-1,2,3,4,4a,10a-hexahydrophenoxazine (9-d_3). A sample of 8-d_3 (111 mg, 0.53 mmol) was acetylated as for the undeuterated compound giving 71 mg (54%) of a pink, crystalline solid: mp 176–178.5 °C; NMR ($CDCl_3$) δ 1.0–2.2 [br m, 6, $-(CH_2)_3-$], 2.20 (s, 3, $NCOCH_3$), 6.8–7.1 (br m, 4, aromatic), 9.25 (s, 1, OH); MS (7 eV deuterated vs. 20 eV undeuterated) 8.5% d_4 (251), 51% d_3 (250), 32.5% d_2 (249), 5% d_1 (248), 3% d_0 (247).

Registry No.—**1**, 533-60-8; **2**, 95-55-6; **8**, 60349-94-2; 8 HI, 60349-95-3; 8-d_3, 60349-96-4; **9**, 60349-97-5; **9**-d_3, 60349-98-6; **10**, 60349-99-7; **11**, 60350-00-7; acetic anhydride, 108-24-7; benzyl bromide, 100-39-0.

Supplementary Material Available. The following crystallographic data: coordinates and anisotropic temperature factors for nonhydrogen atoms, distances, and angles (1 page). Ordering information is given on any current masthead page.

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Notes

An Improved Synthesis of Sulfamoyl Chlorides

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Sulfamoyl chlorides are important intermediates in the synthesis of sulfamate esters and unsymmetrical sulfamides. These latter compounds are useful in the synthesis of azo compounds[1] as well as certain biologically active chemicals.[2] Although many processes have been published for the synthesis of alkyl sulfamoyl chlorides,[3] only one method of preparation[4,5] is frequently cited as being useful on a laboratory scale.[6] This involves direct treatment of an amine hydrochloride with sulfuryl chloride either with[5] or without[4] a Lewis acid catalyst. The method is limited to simple alkyl amines[4,5] and is often characterized by long reaction times,[4,5] large excesses of reagent,[4,5] and low yields.[4] In addition, this procedure precludes the synthesis of those compounds bearing functionality sensitive to sulfuryl chloride. Aryl and alkenyl sulfamoyl chlorides are thus unobtainable by this route.[5]

In view of the above limitations we have developed an alternative synthesis which not only provides for the facile preparation of simple alkyl sulfamoyl chlorides, but also allows, for the first time, synthesis of monoaryl sulfamoyl chlorides.

In 1953 Bieber reported that treatment of isocyanates with an excess of neat, anhydrous sulfuric acid resulted in evolution of carbon dioxide and concomitant formation of the corresponding sulfamic acid.[7] On a preparative scale this reaction has been rendered more convenient by use of a highly polar solvent such as nitromethane and 1 equiv of fuming sulfuric acid. The reaction is instantaneous and the product precipitates as a crystalline solid. Filtration and recrystallization (if necessary) affords pure sulfamic acids in good to excellent yields. (See Table I.)

These acids are then slurried in benzene and treated with phosphorus pentachloride. Gentle warming initiates a vigorous reaction which produces the sulfamoyl chlorides as well as phosphorus oxychloride and hydrogen chloride.[8] After concentration the product may be purified by distillation or crystallization, although in most cases removal of the final traces of phosphorus oxychloride at high vacuum provides a product adequate for continued use.

$$RNCO + H_2SO_4 \cdot SO_3 \rightarrow RNHSO_3H$$

$$RNHSO_3H + PCl_5 \rightarrow RNHSO_2Cl$$

While the above method is effective for simple alkyl compounds, there are certain cases (e.g., R = *tert*-butyl and phenyl, entries 6 and 7 in Table I) where the use of fuming sulfuric acid is precluded. An alternate procedure is then effective. The salt of the sulfamic acid may be prepared by treatment of chlorosulfonic acid with an excess of the corresponding

Table I[a]

Entry	Sulfamic acid (salt)	Registry no.	% yield	Sulfamoyl chloride	Ref	% yield	Registry no.
1	CH_3NHSO_3H	4112-03-2	58	CH_3NHSO_2Cl	5	84	10438-96-7
2	$C_2H_5NHSO_3H$	4626-94-2	86	$C_2H_5NHSO_2Cl$	4	89	16548-07-5
3	n-$C_4H_9NHSO_3H$	39085-61-5	65	n-$C_4H_9NHSO_2Cl$	4	65	10305-43-8
4	i-$C_3H_7NHSO_3H$	42065-76-9	65	i-$C_3H_7NHSO_2Cl$	8	94	26118-67-2
5				c-$C_6H_{11}NHSO_2Cl$[b]	5	65	10314-35-9
6	t-$C_4H_9NHSO_3^- \cdot H_3N^+$-$t$-$C_4H_9$	60260-48-2	c	t-$C_4H_9NHSO_2Cl$	g	34[d]	33581-95-2
7				$C_6H_5NHSO_2Cl$[e]		f	60260-49-3

[a] All compounds had boiling points consistent with those in the literature, or satisfactory elemental analysis. Ed. [b] Starting sulfamic acid commercially available. [c] The salt was not isolated. [d] Yield based on starting amine. [e] From the sodium salt of phenylsulfamic acid; see ref 9. [f] Simple workup provided 90% material recovery. Attempts to purify further were attended by considerable decomposition. Immediate use of this crude material afforded adequate yields of products. [g] W. L Matier, W. T. Comer, and D. Deitchman, *J. Med. Chem.*, **15**, 538 (1972).

amine.[9] Treatment of a benzene slurry of these salts with PCl_5 as described above provides the desired compounds.[10]

$$3RNH_2 + ClSO_3H \rightarrow RNHSO_3^- \cdot H_3N^+R$$

$$RNHSO_3^- \cdot H_3N^+R \xrightarrow{PCl_5} RNHSO_2Cl$$

The previously unreported phenylsulfamoyl chloride thus obtained had limited stability. Bulb-to-bulb distillation of the crude reaction mixture resulted in considerable decomposition but did afford a product which recrystallized from carbon disulfide to afford an analytical sample. Treatment of the crude reaction mixture with excess isopropylamine provided *N*-isopropyl-*N'*-phenylsulfamide, identical with the product obtained from aniline and isopropylsulfamoyl chloride. Allowing the crude acid chloride to stand for any length of time resulted in significantly lower yields of products.

In summary, the method described above provides a synthesis of sulfamoyl chlorides that is fast, efficient, economical, and uncomplicated by side reactions. The starting materials are readily available and the conditions employed are quite mild, thereby allowing synthesis of more functionally diverse compounds than was previously possible.

Experimental Section[11]

General Procedure for the Preparation of Sulfamic Acids.[7] To a stirred solution of 100 g of 15% fuming sulfuric acid in 250 ml of nitromethane was added dropwise 1 mol of the appropriate isocyanate. An ice bath maintained the temperature at 25–30 °C. After addition the resulting suspension was refluxed for 0.5 h, then cooled and filtered. The collected crystalline acid was washed with ether and air dried.

General Procedure for the Preparation of Sulfamoyl Chlorides. To a stirred suspension of 1 molar equiv of the appropriate sulfamic acid in a suitable amount of benzene was added 1 molar equiv of phosphorus pentachloride. After gentle warming initiated a vigorous reaction, an ice bath was used to control the rate of reaction. After gas evolution had ceased the resulting solution was refluxed for 0.5 h, cooled, and concentrated in vacuo. Distillation at reduced pressure afforded the product.

***N*-*tert*-Butylsulfamoyl Chloride.** To a stirred solution of 43.8 g (0.6 mol) of *tert*-butylamine in 500 ml of methylene chloride, cooled to 0 °C in an ice/salt bath, was cautiously added 23.3 g (0.2 mol) of chlorosulfonic acid. After addition was complete, the resulting suspension was stirred for 0.5 h at room temperature and then filtered. The collected solids were air dried, then slurried in a convenient amount of benzene and treated with 41.6 g (0.2 mol) of phosphorus pentachloride. After the mildly exothermic reaction subsided, the solution was refluxed for 1 h. After cooling the mixture was filtered, and the filtrate was concentrated in vacuo. Distillation afforded the product as a colorless oil which crystallized on standing, bp 76–78 °C (0.6 mm).

***N*-Phenylsulfamoyl Chloride.** A slurry of 14.95 g (0.077 mol) of sodium *N*-phenylsulfamate and 15.95 g (0.077 mol) of phosphorus pentachloride in 250 ml of benzene was refluxed for 21 h. After cooling, the reaction mixture was cooled and filtered. The filtrate was concentrated in vacuo to afford 13.8 g (94%) of a crude yellow oil. A 1-g portion of this oil was subjected to evaporative bulb-to-bulb distillation (0.05 mm, oven temperature 110 °C) and provided 0.42 g of a yellow solid. Recrystallization from CS_2 gave pale yellow crystals, mp 69–70 °C.

Anal. Calcd for $C_6H_6ClNO_2S$: C, 37.60; H, 3.16; N, 7.31. Found: C, 37.82; H, 3.25; N, 7.41.

Registry No.—RNCO (R = CH_3), 624-83-9; RNCO (R = C_2H_5), 109-90-0; RNCO (R = n-C_4H_9), 111-36-4; RNCO (R = i-C_3H_7), 1795-48-8; cyclohexylsulfamic acid, 100-88-9; sodium phenylsulfamate, 15790-84-8; sulfuric acid, 7664-93-9; phosphorus pentachloride, 10026-13-8; *tert*-butylamine, 75-64-9; chlorosulfonic acid, 7790-94-5.

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(8) A report of a conceptually similar transformation has been made: G. Hamprecht, D. Mangold, and K. Koenig, German Patent 2 164 176 (1973). Although PCl_5 was included in a long list of similar reagents alleged to effect this type of conversion, emphasis was given to the fact that thionyl chloride was the reagent of choice. In our hands this reagent was of little or no value.
(9) L. F. Audrieth and M. Sveda, *J. Org. Chem.*, 9, 89 (1944).
(10) This transformation parallels the synthesis of sulfonyl chlorides: R. Adams and C. S. Marvel, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 394.
(11) Melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on Varian T-60 and EM-360 spectrometers. Combustion analyses were performed by Atlantic Microlabs.

Ortho Lithiation of Thiobenzamides

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Access to ortho-substituted derivatives of benzoic acids, in particular to those bearing one or more additional ring substituents, has been rather limited and was largely based on oxidative degradation, or Sandmeyer-type reactions of the

Table I

Registry no.	Starting thioamide	Lithiation conditions	Electrophile[c]	Product[d]	R	Yield, % (isolated)	Mp, °C
60253-29-4	**1a**	−45 to 10 °C	$(C_6H_5S)_2$	**3**	SC_6H_5	90.6	112–115
	1a	−45 to 10 °C	*t*-BuNCO	**4**	CONH-*t*-Bu	61	178–179
	1a	−45 to 10 °C	DMF	**5**	(CHO)[a]	76.5	175–178
	1a	−45 to 10 °C	CH_3CHO	**6 (9)**	$HOC(—)HCH_3$	68[b]	94–96[b]
5310-14-5	**1b**	0 °C, 4 h	$(CH_3)_3SiCl$	**7**	$Si(CH_3)_3$	48.5	121–123
32872-35-8	**1c**	25 °C, 8.5 h	$(CH_3S)_2$	**8**	SCH_3	77.6	79–81

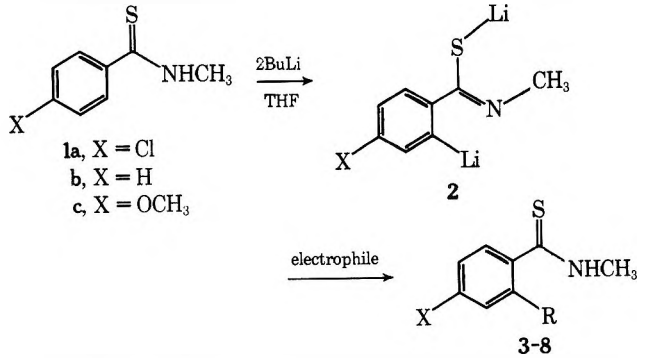
[a] This compound exists exclusively as the cyclic tautomer **5**. [b] Compound isolated as phthalide **9**. [c] Registry no. are, respectively, 882-33-7, 1609-86-5, 68-12-2, 75-07-0, 75-77-4, 624-92-0. [d] Registry no. are, respectively, 96-32-2, 60253-31-8, 60253-32-9, 60253-33-0 (60253-34-1), 60253-35-2, 60253-36-3.

appropriate anthranilic acids. With the discovery that certain derivatives of aromatic carboxylic acids, such as benzamides[1,2] and aryloxazolines,[3,4] can be lithiated directly in their ortho position, a useful, reliable, and simple new method for the regiospecific introduction of virtually any substituent became available.

In the search for new ortho-directing groups which would be more easily amenable to further transformation, ideally without the need to protect other functionalities, our attention turned to thioamides. In particular, the secondary thioamides and lactams are known to serve as excellent precursors for the subsequent elaboration to β-keto or β-enamino ketone systems via sulfur extrusion.[5] Although the ortho metalation of numerous benzamides and arylsulfonamides[6] has been studied extensively, the analogous reaction with *N*-alkylthio benzamides has hitherto not been reported.

Although thioamides are generally prepared by sulfurization of the corresponding amides, we find it more convenient to treat the appropriate aryllithium reagent with methyl isothiocyanate. Thioamides **1a–c** and **10** are obtained in 40–60% yield.

As expected, the dilithiation of *N*-methylthiobenzamides (**1a–c**) with 2 equiv of *n*-BuLi in tetrahydrofuran proceeds quite readily to produce **2** which, after reaction with appropriate electrophiles, gives access to a variety of ortho-substituted derivatives, as indicated in Table I. The effect of para substituents on the ease of metalation parallels quite closely the observations made with regular benzamides, i.e., the rate increases in the following order: $OCH_3 < H < Cl$. Analogous to the results in the lithiation of *p*-methoxy-*N*-methylbenzamide,[7] metalation of **1c** was found to occur exclusively ortho to the thiocarboxamide function.

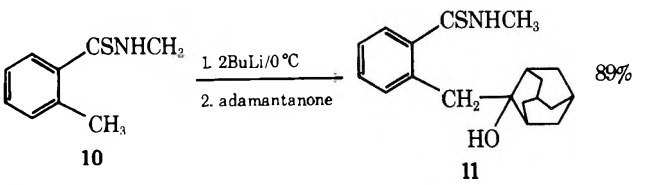


1a, X = Cl
b, X = H
c, X = OCH_3

2

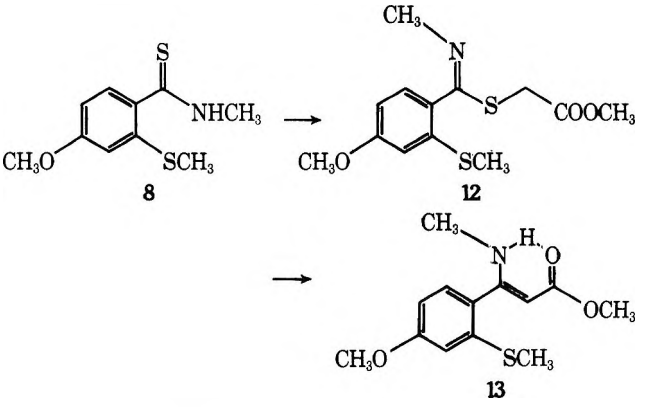
3-8

The lithiation of the *N*-methylthio-*o*-toluamide **10** proceeds rapidly to give, by analogy with the *o*-toluamides,[8,9] the deep red benzylic anion which reacts with adamantanone to give the carbinol **11** in high yield.



10 **11**

To illustrate the potential for further transformation, the thioamide **8** was alkylated with methyl bromoacetate. The crude product **12** of this reaction was then directly desulfurized[5] with triphenylphosphine to give the enamino ester **13**.



8 **12** **13**

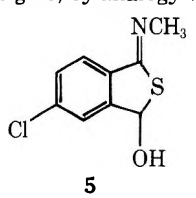
Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); ir spectra on a Perkin-Elmer 521; mass spectra on a AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 using Me_4Si as internal standard. The following abbreviations are used: (b) broad, (w) weak, (ex) exchangeable with D_2O, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet.

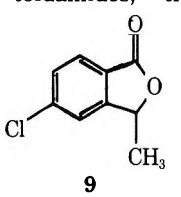
4-Chloro-*N*-methyl-2-phenylthiothiobenzamide (3). A solution of 2.8 g (15 mmol) of thioamide **1a** in 40 ml of dry THF was cooled to −45 °C under N_2. Then 20 ml (32 mmol) of a 1.6 *m* solution of *n*-BuLi in hexane was added dropwise. The reaction mixture was stirred at room temperature until the internal temperature reached 10 °C. It was then recooled to −70 °C, and a solution of 3.5 g (15 mmol) of phenyl disulfide in 15 ml of THF added. The mixture was stirred for 18 h at 25 °C, quenched with water, washed with brine, and dried over Na_2SO_4. The residue from the organic layer crystallized from ether to give 3.99 g (90.6%) of compound **3**: mp 112–115 °C; ir (CH_2Cl_2) 3386, 1565, 1510, 1340 cm^{-1}; NMR ($CDCl_3$) δ 3.21 (d, 3 H), 7.00–7.58 (m, 8 H), 7.87 (b, 1 H, ex).

Anal. Calcd for $C_{14}H_{12}ClNS_2$: C, 57.23; H, 4.12; N, 4.77. Found: C, 57.49; H, 4.11; N, 4.68.

***N*-(*tert*-Butyl)-3-chloro-6-(*N*-methylthiocarbamoyl)benzamide (4).** A solution of 2.8 g (15 mmol) of thioamide **1a** in 50 ml of dry THF was cooled to −50 °C and 20 ml of a 1.6 *m* solution of *n*-BuLi/hexane was added. The mixture was allowed to reach 10 °C and was cooled again to −70 °C, then 1.7 g of *t*-BuNCO in 5 ml was added and the reaction mixture was stirred at ambient temperature overnight. After diluting with ether and washing with water and brine, the



5



9

organic layer was evaporated. The residue was crystallized from AcOEt/hexane to give 2.6 g (61%) of product **4**: mp 178–179 °C; ir (Nujol) 3250, 3180, 1635, 1545, 1530 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 9 H), 3.33 (d, J = 5 Hz, 3 H/singlet after exchange), 6.5 (s, ex, 1 H), 7.0 (s, broad, 1 H), 7.35 (s, broad, 2 H).

Anal. Calcd for $C_{13}H_{17}ClN_2OS$: C, 54.83; H, 6.02; N, 9.83. Found: C, 54.94; H, 6.07; N, 9.56.

6-Chloro-1,3-dihydro-3-methyliminobenzo[*c*]thiophen-1-ol (5). A solution of 2.8 g (15 mmol) of thioamide **1a** in THF was lithiated as described for **3**. After cooling to −70 °C, 5.48 g (75 mmol) of dimethylformamide was added and the reaction mixture stirred to room temperature for 18 h. The reaction mixture was quenched with water, washed with NaH_2PO_4 buffer, and dried over Na_2SO_4. Evaporation of the organic layer gave a residue that crystallized from ether/hexane, 2.45 g (76.5% yield) of compound **5**: mp 175–178 °C; ir (Nujol) 3230, 1585, 1303, 820 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) δ 3.38 (s, 3 H), 5.82 (s, 1 H), 6.80 (b, 1 H, ex), 7.33–7.91 (m, 3 H); MS m/e 213 (M^+).

Anal. Calcd for C_9H_8ClNOS: C, 50.59; H, 3.87; N, 6.57. Found: C, 50.64; H, 3.83; N, 6.42.

5-Chloro-3-methylphthalide (9). A solution of 2.8 g (15 mmol) of thioamide **1a** in THF was lithiated as described for **3**. After cooling to −70 °C, a solution of 750 mg (17 mmol) of acetaldehyde in 5 ml of THF was added. After stirring at room temperature for 18 h the mixture was quenched with water, washed with brine, and dried over Na_2SO_4. The residue from the organic layer, 3.5 g of compound **6**, was an oil: NMR ($CDCl_3$) δ 1.28 (d, 3 H), 3.1 (s, 3 H), 4.65–5.1 (m, 1 H), 7.02–7.68 (m, 3 H), 8.8 (b, 1 H, ex). It was dissolved in 25 ml of ethanol and 15 ml of 5.0 N HCl and refluxed for 24 h. The reaction mixture was evaporated and the residue partitioned between brine and ether. The residual oil from the ether layer crystallized from ether–hexane to give 1.86 g (68%) of compound **9**: mp 94–96 °C; ir (CH_2Cl_2) 1765, 1620, 1055 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (d, 3 H), 5.57 (q, 1 H), 7.40–8.0 (m, 3 H).

Anal. Calcd for $C_9H_7ClO_2$: C, 59.20; H, 3.86. Found: C, 59.07; H, 4.11.

4-Methoxy-2-methylthio-*N*-methylthiobenzamide (8). A solution of 1.36 g (7.5 mmol) of thioamide **1c** in 20 ml of dry THF was cooled in an ice bath under N_2. Then 10 ml (16 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise and stirred for 8.5 h at room temperature. The reaction mixture was recooled in an ice bath and 800 mg (8.5 mmol) of methyl disulfide added. The mixture was stirred at 25 °C for 18 h, quenched with water, washed with brine, dried, and evaporated to give an oil residue. Crystallization from ether gave compound **8**: 1.32 g (77.6%); mp 79–81 °C; ir (CH_2Cl_2) 3395, 1592, 1351, 1040 cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.29 (d, 3 H), 3.81 (s, 3 H), 6.58–7.66 (m, 3 H), 7.95 (b, 1 H, ex).

Anal. Calcd for $C_{10}H_{13}NOS_2$: C, 52.86; H, 5.77; N, 6.17. Found: C, 53.06; H, 5.76; N, 6.14.

***N*-Methyl-2-trimethylsilylthiobenzamide (7).** A solution of 1.13 g (7.5 mmol) of thioamide **1b** in 20 ml of dry THF was cooled in an ice bath under N_2. Then 10 ml (16 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise. After stirring for 4.0 h at 0 °C the reaction mixture was cooled to −70 °C and 920 mg (8.5 mmol) of chlorotrimethylsilane added. The mixture was stirred for 18 h at 25 °C, quenched with water, washed with brine, dried, and evaporated to give a crystalline residue. Recrystallization from ether–hexane gave 640 mg (48.5%) of compound **7**: mp 121–123 °C; ir (CH_2Cl_2) 3375, 1508, 1340, 828 cm^{-1}; NMR ($CDCl_3$) δ 0.30 (s, 9 H), 3.24 (d, 3 H), 7.25–7.70 (m, 4 H), 8.15 (b, 1 H, ex).

Anal. Calcd for $C_{11}H_{17}NSSi$: C, 59.14; H, 7.67; N, 6.27. Found: C, 59.06; H, 7.93; N, 6.23.

***o*-[(2-Hydroxy-2-adamantanyl)methyl]-*N*-methylthiobenzamide (11).** A solution of 1.24 g (7.5 mmol) of thioamide **10** in 20 ml of dry THF was cooled in an ice bath under N_2. Then 10 ml (16 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise. After 15 min at 0 °C, a solution of 1.2 g (8 mmol) of 2-adamantanone in 5 ml of THF was added. After 18 h at 25 °C the reaction mixture was quenched with water, washed with brine, dried, and evaporated to give a crystalline residue. Recrystallization from ether gave 2.11 g (89.4%) of compound **11**: mp 172–175 °C; ir (Nujol) 3370, 3190, 1555, 755 cm^{-1}; NMR ($CDCl_3$) δ 1.40–2.35 (m, 14 H), 2.98 (s, 2 H), 3.20 (d, 3 H), 6.82–7.81 (m, 5 H; 1 H, ex), 9.95 (b, 1 H, ex).

Anal. Calcd for $C_{19}H_{25}NOS$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.55; H, 7.93; N, 4.27.

***N*-Methylthio-o-toluamide (10).** A solution of o-tolyllithium was prepared from 17.1 g (0.1 mol) of o-bromotoluene and 1.4 g of lithium wire in 75 ml of ether. This solution was then cooled to −78 °C, diluted with 75 ml of dry THF, and then a solution of 7.3 g (0.1 mol) of methyl isothiocyanate in 10 ml of THF was added at once. The cold bath was removed and the reaction mixture stirred at ambient temperature for 4 h. Workup with cold water, then brine, provided 13.0 g of a dark oil which was crystallized from ether to give 6.1 g of **10**, mp 76–78 °C.

Anal. Calcd for $C_9H_{11}NS$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.83; H, 6.78; N, 8.19.

The thioamides **1a–c** were prepared analogously.

4-Methoxy-β-methylamino-2-methylthiocinnamic Acid Methyl Ester (13). A solution of 500 mg (2.2 mmol) of thioamide **8** in 10 ml of dry THF was cooled to −70 °C under N_2. Then 1.5 ml (2.4 mmol) of a 1.6 m solution of n-BuLi in hexane was added dropwise. After 15 min, a solution of 340 mg (2.2 mmol) of methyl bromoacetate in 2 ml of THF was added. The mixture was stirred for 18 h at 25 °C, quenched with water, washed with $NaHCO_3$ solution (twice) and brine, dried, and evaporated to give 590 mg of compound **12**: NMR ($CDCl_3$) δ 2.42 (s, 3 H), 3.03 (s, 3 H), 3.32–3.88 (m, 2 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 6.50–7.35 (m, 3 H). To a solution of this residue in 20 ml of xylene, 2.07 g (7.89 mmol) of triphenylphosphine was added and refluxed for 24 h. The solvent was evaporated and the residue chromatographed over 15 g of silica gel set in hexane. Compound **13**, 160 mg (31%) of a solid, was eluted with benzene. Recrystallization from ether afforded the analytical sample: mp 100–102 °C; ir (CH_2Cl_2) 3300, 1645, 1595, 1170 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (s, 3 H), 2.67 (d, 3 H), 3.65 (s, 3 H), 3.82 (s, 3 H), 4.52 (s, 1 H), 6.57–7.29 (m, 3 H), 8.50 (b, 1 H, ex); MS m/e 267 (M^+); uv (CH_3OH) 216 nm (ε 20 870), 293 (19 740).

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.65; H, 6.33; N, 4.91.

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Registry No.—**10**, 60253-37-4; **11**, 60253-38-5; **12**, 60253-39-6; **13**, 60253-40-9; 2-adamantanone, 700-58-3; o-tolyllithium, 6699-93-0; methyl isothiocyanate, 556-61-6; methyl bromoacetate, 590-97-6.

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The Chemistry of Carbanions. 29. The Nature of the Enolate Formed by Addition of Lithium Dimethylcuprate to Enones[1]

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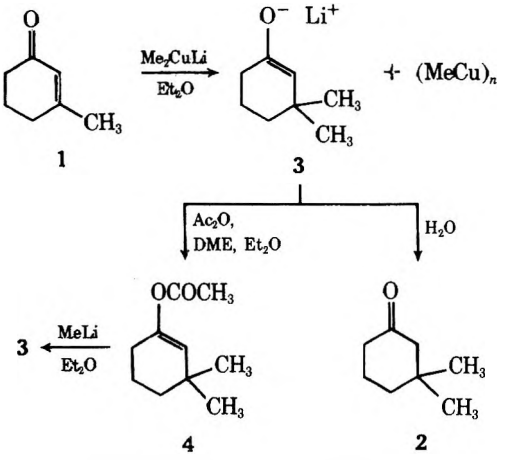
The conjugate addition of lithium diorganocuprates to α,β-unsaturated carbonyl compounds[2] produces, prior to hydrolysis, an intermediate with the properties of a metal enolate. Thus, reaction of this intermediate with Ac_2O yields an enol acetate,[3] reaction with Me_3SiCl yields a trimethylsilyl enol ether,[4] and reaction with a $ClPO(OEt)_2$ yields an enol phosphate.[5] Furthermore, this reaction intermediate reacts with carbonyl compounds to give aldol products,[6] with Michael acceptors to form Michael adducts,[7] and with reactive alkyl halides to form alkylated ketones.[4b,8] This reaction intermediate has been variously formulated as a lithium enolate,[2b] a copper(I) enolate,[7,8a,b] or as a species with the copper

bound either to the α carbon atom or to both the oxygen atom and the C=C of the enolate.[3b]

Several observations led us to believe that these reaction intermediates were best formulated as lithium enolates rather than copper derivatives. The addition of 1 equiv of the *soluble* copper(I) derivative $(n\text{-}Bu_2S)_2CuI$ to a solution of the enolate $PhC(OLi)=CH_2$ did not alter the reactivity of this enolate in a Michael reaction.[9] Also, the addition of 1 equiv of the same *soluble* copper(I) derivative did not alter the ^1H NMR spectrum of the lithium enolate $PhC(OLi)=CHCl$.[10] Furthermore, in typical reactions of lithium dialkylcuprates (e.g., Me_2CuLi) with enones, the reaction is accompanied by precipitation of the *insoluble* alkylcopper(I) derivative [e.g., $(MeCu)_n$] suggesting that the copper does not remain in solution with the intermediate enolate. However, all of the above observations leave some ambiguity about the nature of the reaction intermediate and yet this reaction intermediate is attaining increasing importance as a synthetic intermediate.[3-8] Consequently, it was clearly desirable to provide unambiguous information concerning this intermediate.

To provide this information in a typical reaction, the enone 1 was added to an Et_2O solution containing 1 equiv of Me_2CuLi. The resulting slurry was centrifuged to separate about 75% of the reaction mixture, a colorless, supernatant liquid, from the lower portion of the reaction mixture which contained all the yellow $(MeCu)_n$ precipitate. Analysis of aliquots of each portion of the reaction mixture indicated that more than 99% of all the copper employed in the reaction was in the lower portion containing the $(MeCu)_n$ precipitate. A second aliquot of the supernatant solution exhibited ^{13}C NMR absorption corresponding to an Et_2O solution of a lithium enolate.[11] After the remaining supernatant solution had been hydrolyzed, the amount of ketone 2 isolated corresponded to a 66% yield of this product from the supernatant solution.



In another experiment, the total reaction mixture from the enone 1 and Me_2CuLi was added to excess Ac_2O to form the expected[3] enol acetate 4 in 76% yield. Reaction of this enol acetate 4 with an ethereal solution containing 2 equiv of MeLi afforded an Et_2O solution of the lithium enolate 3 whose ^{13}C NMR spectrum corresponded to the spectrum of the solution obtained from the cuprate reaction. Therefore, it is clear that conjugate addition of ethereal Me_2CuLi to the enone 1 forms the lithium enolate 3 and not some other intermediate in which the enolate is associated with a copper(I) species. It is very probable that the same conclusion applies to any conjugate addition of a cuprate reagent R_2CuLi that yields a soluble metal enolate along with an insoluble RCu product. Even in cases where the organocopper product RCu remains in the reaction solution, our earlier NMR and reactivity studies[9,10] offer no evidence to support the view that lithium enolates interact with soluble copper(I) species to form copper(I) enolates.

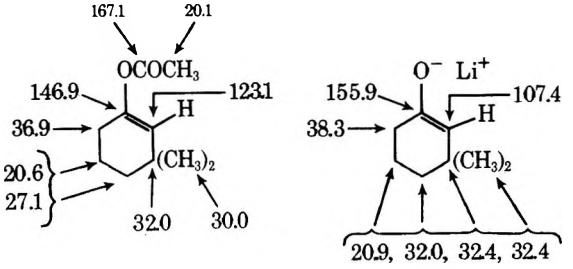
Experimental Section[12]

Preparation of the Enol Acetate 4 and the Lithium Enolate 3. After a solution of Me_2CuLi, prepared from 9.64 g (46.9 mmol) of Me_2SCuBr in 25 ml of Me_2S and 53 ml of an Et_2O solution containing 93.8 mmol of halide-free MeLi, had been stirred at 27 °C for 5 min, a solution of 3.93 g (35.8 mmol) of the enone 1 in 12 ml of Et_2O was added dropwise and with stirring during 10 min. The resulting mixture [containing solid $(MeCu)_n$] was stirred for 20 min and then added with stirring to a solution of 18.3 g (179 mmol) of freshly distilled Ac_2O in 35 ml of DME. After the resulting slurry had been stirred at 27 °C for 30 min, it was partitioned between pentane and saturated aqueous $NaHCO_3$ and the organic phase was separated, dried, and concentrated. After an aliquot of the crude product had been mixed with a known weight of *t*-BuPh, analysis (GLC, Carbowax 20M on Chromosorb P) indicated the presence of *t*-BuPh (retention time 3.8 min) and the enol acetate 4 (8.8 min, calculated yield 96%); neither the enone 1 (16.5 min) nor the ketone 2 (6.5 min) was detected in the GLC analysis. Distillation of the crude product separated 4.54 g (75.5%) of the enol acetate 4 as a colorless liquid: bp 35–37 °C (0.4 mm); $n^{25}D$ 1.4500; ir (CCl_4) 1754 (ester C=O) and 1689 cm^{-1} (C=C); uv (95% EtOH), end absorption with ϵ 1580 at 210 nm; NMR (CCl_4) δ 5.05 (1 H, broad, vinyl CH), 1.2–2.3 (9 H, m, aliphatic CH including a CH_3CO singlet at 1.99), and 1.02 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 168 (M^+, 5), 126 (12), 111 (100), 55 (13), 43 (30), and 41 (11).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.38; H, 9.58.

To obtain an authentic sample of the enolate 3, 678 mg (4.04 mmol) of the enol acetate 4 was added, dropwise and with stirring, to 5.02 ml of a cold (10 °C) Et_2O solution containing 8.88 mmol of halide-free MeLi. After the resulting pale yellow solution had been stirred at 20 °C for 5 min, a 2.3-ml aliquot was mixed with 0.2 ml of Me_4Si and 0.2 ml of C_6D_6 (to provide a "lock" signal) and the natural abundance ^{13}C NMR signal was determined. For comparison the natural abundance ^{13}C NMR spectrum of the enol acetate 4 was also determined in Et_2O containing Me_4Si and C_6D_6. These ^{13}C NMR spectra (assignments consistent with off-resonance decoupling measurements and previous[11] analogous measurements) are summarized in the following structures. The ^{13}C NMR spectrum of the enolate 3 also exhibited a peak at 35.0 ppm attributable[11] to the Me groups of *t*-BuOLi; the second ^{13}C NMR signal for this material was not resolved from the Et_2O peak at 65.8 ppm.

It will be noted that the chemical shift difference ($\Delta\delta$) between the α-carbon atoms of the enol acetate 4 and the lithium enolate 3 in an Et_2O solution is 15.7 ppm, a value considerably smaller than the $\Delta\delta$ values (21.5–25.5 ppm) observed for similar lithium enolates in DME or THF solution.[11]



Reaction of the Enone 1 with Me_2CuLi. To 5.00 g (24.3 mmol) of Me_2SCuBr was added, dropwise with stirring and cooling to 18–20 °C, 27.5 ml of an Et_2O solution containing 48.7 mmol of halide-free MeLi. The enone 1 (2.55 g or 23.2 mmol) was added to this solution of Me_2CuLi dropwise and with stirring during 15 min. The reaction mixture, from which yellow $(MeCu)_n$ began to precipitate within a few seconds after addition of the enone began, was stirred at 20–25 °C for 20 min and then centrifuged. The colorless supernatant solution (23.2 ml) was separated and the residue [a mixture of solid $(MeCu)_n$ and the remaining reaction solution] was quenched in dilute aqueous HNO_3. Analysis of an aliquot of this aqueous solution by electrodeposition indicated the total copper content of the residue to be 24.3 mg-atoms. Three 1.00-ml aliquots of the supernatant solution were each quenched in dilute aqueous HNO_3 and then analyzed by electrodeposition; from these analyses, the copper content of the total supernatant solution was found to be 0.047 mg-atom. A 2.00-ml aliquot of the supernatant solution was mixed with 0.2 ml of C_6D_6 and 0.2 ml of Me_4Si in order to determine the ^{13}C NMR spectrum. This spectrum exhibited peaks corresponding to Et_2O (15.4 and 65.8 ppm), Me_2S (17.9 ppm), and to the previously described enolate 3. The positions of the "carbonyl" carbon and α-carbon ^{13}C signals of this en-

olate (156.2 and 105.4 ppm) differed slightly from the spectrum of the enolate 3 described above, reflecting the facts that the concentrations of the two solutions were different and that one solution contained an equimolar amount of *t*-BuOLi while the other solution contained equimolar amounts of LiBr and Me_2S. However, in all other respects, the two enolate ^{13}C NMR spectra were the same.

The remaining 18.2-ml aliquot of the supernatant liquid was partitioned between aqueous $NaHCO_3$ and pentane. After the organic layer had been dried and concentrated, distillation of the residual liquid separated 1.51 g (corresponding to a 66% yield of ketone 2 in the supernatant solution) of the pure (GLC) ketone 2 as a colorless liquid, bp 47–49 °C (5 mm), $n^{25}D$ 1.4454 [lit.[13] bp 74–74.5 °C (16 mm), $n^{25}D$ 1.4458], that was identified with an authentic sample[13] by comparison of ir and NMR spectra.

Registry No.—1, 1193-18-6; 2, 2978-19-3; 3, 57074-02-9; 4, 54200-64-5; Me_2CuLi, 15681-48-8.

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(1) This research has been supported by Public Health Service Grant 9-RO1-GM-20197 from the National Institute of General Medical Sciences. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.
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(12) All boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Perkin-Elmer Model 202 recording spectrophotometer. The ^1H NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the ^{13}C NMR spectra were determined at 25 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.
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Organocopper Intermediates. Synthesis of 2-Isoxazoline *N*-Oxides and Cyclopropanes

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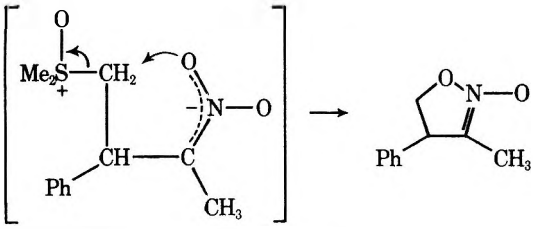
We had as a synthetic objective the preparation of the cyclopropane derived from β-methyl-β-nitrostyrene. Since palladium-catalyzed cyclopropanation has been effective for olefins bearing electron-withdrawing groups, this route was evaluated.[2] Upon treatment of the styrene with diazomethane and palladium nitrate, 60% of the starting material was recovered and there was no evidence of cyclopropane formation. An alternative route, employing a Me_2SO-derived ylide, was then investigated. Treatment of β-methyl-β-nitrostyrene with dimethylsulfoxonium methylide led to the immediate precipitation of an amorphous solid.[3,4] Noting that a transient red color appeared during this reaction and that electron transfer processes often display this behavior,[5] it was considered that the electron-donating characteristics of the ylide might be altered by complexation with copper.[6] Thus, the ylide was prepared in the usual fashion and a copper halide was then added. In dimethylformamide (DMF), with copper(I) iodide, the reagent was red-brown; in methyl sulfoxide (Me_2SO) the same halide resulted in an intense orange-pink color.[7] Because of greater solubility, Me_2SO was typically employed as the solvent. Upon addition of the styrene to the ylide–copper complex no precipitate was formed and after 2 h the products were isolated and purified. Instead of finding the cyclopropane, we identified the product as a 2-isoxazoline



N-oxide. A likely intermediate in its formation is the ylide adduct, which O-alkylates instead of closing to form the cyclopropane.[8] To determine the generality of this reaction, other unsaturated compounds were treated with copper–ylide complexes (Table I).

The reaction has greater significance as a synthetic approach to 2-isoxazoline *N*-oxides than to cyclopropanes. The cyclopropanation yield from benzalacetophenone is comparable to that reported from the ylide without the use of copper.[3] By contrast, there is no cyclopropanation of ethyl cinnamate in the presence of the copper reagent.[3b,c] The yields from the α,β-unsaturated ester and ketones are lower than those obtained using (dimethylamino)methyloxosulfonium methylide.[3d]

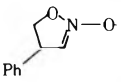
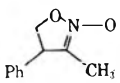
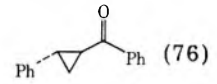
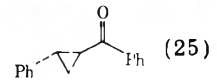
The experimental results are consistent with the relationship between product formation and polarographic reduction potential reported initially by House.[9] In this study, compounds having reduction potentials less negative than −1.8 V vs. SCE react with the ylide–copper complex whereas compounds with reduction potentials more negative than −1.8 V vs. SCE are recovered unchanged. Thus, the utility of this reaction lies in those applications in which derivatives are desired of compounds having low reduction potentials.

Experimental Section

Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 710 infrared spectrometer. Proton magnetic resonance spectra were recorded on a Varian A-60A spectrometer using Me_4Si as the internal standard. The carbon-13 magnetic spectra were obtained with a Varian CFT-20. The mass spectrum was recorded on a Perkin-Elmer RMU7, ionizing voltage 70 and 10 eV.

3-Methyl-4-phenyl-2-isoxazoline *N*-Oxide. To 250 ml of dry deoxygenated (N_2) DMF were added 12.8 g (58.2 mmol) of trimethylsulfoxonium iodide and 2.6 g (50% in oil, 55 mmol) of sodium hydride. After stirring for 2 h, 3.00 g (15.8 mmol) of copper(I) iodide was added. Upon stirring for 0.5 h, during which the color changed from gray to red-brown, the solution was cooled in an ice bath and 8.00 g (49.2 mmol) of β-methyl-β-nitrostyrene dissolved in 60 ml of DMF was added dropwise over the course of 20 min. After addition was complete, the ice bath was removed. After stirring for 2 h, ice water was added, the organic products were extracted with methylene chloride, and 6.4 g (74%) of crude 3-methyl-4-phenyl-2-isoxazoline *N*-oxide was isolated, mp 45–54 °C. Recrystallization from anhydrous ethanol resulted in 5.6 g (64%) of the purified product: mp 63–64 °C; NMR (CCl_4) δ 1.82 (d, 3 H, CH_3), 4.12–4.93 (m, 3 H, CH and CH_2),

Table I. Reactions of the Dimethylsulfoxonium Methylide–Copper(I) Complex with Olefins[a]

Registry no.	Entry	Compd	$E_{1/2}$, V vs. SCE	Product (%)	Registry no.
102-96-5	1	$PhCH{=}CHNO_2$	−0.58[b]	 (71)	60239-08-9
705-60-2	2	$PhCH{=}C(CH_3)NO_2$	−0.64[b]	 (64)	60239-09-0
5292-53-5	3	$PhCH{=}C(CO_2Et)_2$	−0.78[c]	Polymer	
1885-38-7	4	PhCH=CHCN	−1.36[d]	Polymer	
94-41-7	5	PhCH=CHCOPh	−1.41[e]	 (76)	1145-92-2
	6	PhCH=CHCOPh	−1.41[e]	 (25)	
103-36-6	7	$PhCH{=}CHCO_2Et$	−1.81[e]	(80% recovered)	
930-68-7	8		−2.07[f]	(65% recovered)	

[a] All but experiment 6, which employed the copper(I) complex of triphenylphosphonium methylide. [b] R. F. Silver and H. L. Holmes, *Can. J. Chem.*, 44, 1031 (1966). [c] M. Bargain, *C. R. Acad. Sci.*, 255, 1948 (1962). [d] I. G. Sevast'yanova and A. P. Tomilov, *Zh. Obshch. Khim.*, 33, 2815 (1963). [e] H. O. House and J. Umen, *J. Am. Chem. Soc.*, 94, 5495 (1972). [f] For 5-methyl-2-cyclohexen-1-one, ref e.

7.40 (s, 5 H, aryl); ^{13}C NMR ($CDCl_3$, 5000 transients, norm decoupling) 137.54, 128.97, 128.04, 127.19, 114.81, (quaternary), 70.45 (methylene), 52.09 (methine), and 10.29 ppm (methyl); ir (CCl_4) 1640 cm^{-1} (C=N); MS (70 eV) *m/e* (rel intensity) 160 (13), 159 (100), 158 (15), 131 (56), 130 (60), 116 (33), 105 (8), 104 (15), 103 (39), 102 (6), 90 (18), 89 (17), 77 (15), 63 (34), 51 (18); (10eV) 159.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21; N, 7.91. Found: C, 67.98; H, 6.34; N, 7.81.

4-Phenyl-2-isoxazoline *N*-Oxide. The procedure was the same as that reported above except that 7.00 g (47.0 mmol) of β-nitrostyrene was added. Isolation eventuated in 6.4 g (83%) of crude oil. Elution from a silica gel column with absolute ethanol gave 5.5 g (71%) of pure 4-phenyl-2-isoxazoline *N*-oxide: NMR ($CDCl_3$) δ 2.92 (d, 3 H, CH and CH_2), 7.12–7.61 (m, 5 H, aryl), 8.08 (bs, 1 H, vinyl); ir ($CHCl_3$), 1660 cm^{-1} (C=N).

Cinnamonitrile. To 25 ml of dry deoxygenated DMF were added 1.30 g (5.82 mmol) of trimethylsulfoxonium iodide and 0.26 g (50% in oil, 5.5 mmol) of sodium hydride. Upon stirring for 0.5 h, 0.30 g (1.6 mmol) of copper(I) iodide was added. After stirring for 0.5 h, 0.71 g (5.5 mmol) of cinnamonitrile was added. A precipitate appeared within 5 min. After stirring for 2 h, water was added and an amorphous solid, 0.75 g, separated, having an ir band at 2340 cm^{-1} (CN). The aqueous portion was extracted several times with ether, and the combined ether portions were washed with water, dried, and evaporated to leave a smear of product.

Benzylidenediethyl Malonate. The reaction was performed analogous to the description of the cinnamonitrile experiment. An amorphous solid was isolated.

***trans*-1-Benzoyl-2-phenylcyclopropane (from Dimethylsulfoxonium Methylide).** To 90 ml of dry, deoxgenated (N_2) methyl sulfoxide were added 6.4 g (29.1 mmol) of trimethylsulfoxonium iodide and 1.4 g (50% in oil, 29.1 mmol) of sodium hydride. After stirring for 2 h, 1.50 g (7.9 mmol) of copper iodide was added. After 1 h, 5.1 g (24.5 mmol) of benzalacetophenone was added; 13 h later workup resulted in 4.9 g (91%) of crude *trans*-1-benzoyl-2-phenylcyclopropane. Purification by column chromatography from silica gel, eluting with chloroform-petroleum ether, resulted in the isolation of 4.1 g (76%) of the product whose data were identical with literature data:[3d] ir (film) 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.1–8.3 (m, 10, aryl), 2.45–3.50 (m, 2, COH and CH), 1.20–2.00 (m, 2, CH_2).

***trans*-1-Benzoyl-2-phenylcyclopropane (from Triphenylphosphonium Methylide).** To 90 ml of dry, deoxgenated methyl sulfoxide were added 85.4 g (21.0 mmol) of methyltriphenylphosphonium iodide and 9.2 ml (2.4 M, 22 mmol) of *n*-butyllithium. After stirring for 5 min, 3.80 g (20.0 mmol) of copper(I) iodide was added. After 1 h, 4.16 g (20.0 mmol) of benzalacetophenone was added. Upon stirring for 1.5 h, workup gave 3.8 g of product containing 25% of the cyclopropane.

Ethyl Cinnamate. To 150 ml of dry, deoxygenated methyl sulfoxide was added 6.4 g (29.1 mmol) of trimethylsulfoxonium iodide and 1.4 g (50%, 20.1 mmol) of sodium hydride. After stirring for 2 h, 1.50 g (7.9 mmol) of copper iodide was added. After 1 h, 4.65 g (26.4 mmol) of ethyl cinnamate was added. After 21 h, there was no indication of reaction by TLC. Workup eventuated in the recovery of 3.8 g (80%) of ethyl cinnamate.

Acknowledgments. We wish to thank Drs. Stan Smith and John Layton for the carbon-13 spectrum of 3-methyl-4-phenyl-2-isoxazoline *N*-oxide and Ms. Penny Purdue for its mass spectrum.

Registry No.—Dimethylsulfoxonium methylide–copper(I) complex, 60260-29-9; triphenylphosphonium methylide–copper(I) complex, 60260-30-2; trimethylsulfoxonium iodide, 2181-42-2; copper(I) iodide, 7681-65-4; methyltriphenylphosphonium iodide, 2065-66-9.

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E. P. Kohler and S. F. Darling, *ibid.*, **52**, 1174 (1930); E. P. Kohler and G. R. Barrett, *ibid.*, **46**, 2105 (1924); L. I. Smith, *Chem. Rev.*, **23**, 193 (1938); A. T. Nelsen and T. G. Archibald, *Tetrahedron Lett.*, 3375 (1968); V. A. Tartakovskii, B. G. Gribov, I. A. Savost'yanova, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1644 (1965).

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Tin–Copper Couple. A New Reagent for Selective Debromination of Activated Dibromides

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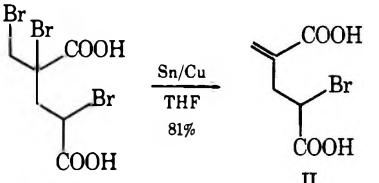
We wished to prepare the α-methylene-γ-bromoglutaric acid II. Attempts to accomplish this from the known[1] γ-methyleneglutamic acid by diazotization in the presence of sodium bromide[2] were frustrated by persistent lactone formation. As an alternative, the selective debromination of the tribromide I was explored. The latter is readily prepared by Hell–Volhard–Zelinsky bromination of α-methyleneglutaryl chloride.



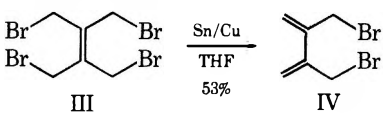
I II

Of the many possible reagents appropriate for the reductive removal of vicinal dibromides,[3] zinc–copper couple[4] was chosen for this purpose. Tetrahydrofuran was used as solvent in order to avoid lactone formation to whatever extent possible.

Attempts to carry out the desired reduction with zinc–copper couple led in every case to substantial overreduction, with production of starting α-methyleneglutaric acid (60%). A lesser amount (40%) of the desired monobromide II was also observed. It seemed reasonable to suppose, since tin has a lower reduction potential than zinc, that improved selectivity might be realized if the reduction could be induced to proceed with tin[5] instead of with zinc.

We have found that the bromoglutarate II can be prepared in 81% yield (recrystallized) from the tribromide I using tin–copper couple in tetrahydrofuran. In the total crude product approximately 3% of the fully reduced α-methyleneglutaric acid can be detected by NMR.[9] This impurity is readily removed by one crystallization from chloroform–ethyl acetate. An interesting feature of this reduction is the requirement of only 0.5 mol of tin–copper couple for complete reaction. This facet has not been explored further. However, it appears that Sn(II) is also sufficiently reactive to promote elimination of such active dibromides and that a further refinement in selectivity might be realized using the latter as a reagent.

Tin–copper couple reacts very slowly, if at all, with 1,2-dibromoethane. On this limited basis, it appears that unactivated dibromides will be relatively unreactive toward this reagent. By contrast, the tin–copper reagent quite effectively reduced tetrakis(bromomethyl)ethylene (III) to the labile dibromide IV.[6]



III IV

Because of its simplicity and ready availability, the tin–copper couple reagent may serve, in favorable instances, as an alternative to electrochemical reduction as it is used to select among several readily reduced functional groups.

Experimental Section

α-Methyleneglutaryl Chloride.[7] α-Methyleneglutaric acid (5.76 g, 0.04 mol) was carefully mixed with phosphorus pentachloride (18.35 g, 0.09 mol) in a round-bottom flask. A vigorous reaction began immediately, and the reaction mixture became liquid. When the initial exothermic part of the reaction had subsided, the mixture was heated at 110–115 °C for 15 min. Phosphorus oxychloride was removed by distillation under aspirator vacuum. The liquid remaining was distilled through a 14-cm Vigreux column yielding 6.15 g (85%), bp 84–86 °C (2 mm), of a colorless liquid: infrared (neat) 5.59 and 5.78 μ; NMR (CCl_4) one-proton vinyl singlet at δ 6.6, one-proton vinyl singlet at δ 6.2, and two two-proton aliphatic multiplets at δ 3.2 and 2.8.

α-Bromomethyl-α,γ-dibromoglutaric Acid (I). Dry bromine (5.65 ml, 0.11 mol) was added dropwise to α-methyleneglutaryl chloride (9.05 g, 0.05 mol) with stirring at room temperature. When the addition was complete (ca. 30 min), the reaction mixture was heated in an oil bath at 80–85 °C for 14 h. The reaction mixture was allowed to cool to room temperature, then transferred to a large watchglass for slow hydrolysis in the air. After 36 h a solid mass was formed. It was collected and washed with 15 ml of chloroform yielding 5.85 g (71%) of the desired tribromo diacid I, mp 148–152 °C. One crystallization from a mixture of chloroform–ethyl acetate (2:1) yielded 5.52 g (67%) of white solid, mp 153–155 °C. The melting point was not improved by further crystallization. Infrared (KBr) 5.81 μ; NMR (acetone-d_6) two-proton broad singlet at δ 9.7, one-proton quartet (H_γ, $J_{\beta\gamma}$ = 4.4, $J_{\beta'\gamma}$ = 7 Hz) at δ 4.67, two-proton bromomethyl singlet at δ 4.25, one-proton quartet (H_β, $J_{\beta\gamma}$ = 7, $J_{\beta\beta'}$ = 17 Hz) at δ 3.57, and a one-proton quartet ($H_{\beta'}$, $J_{\beta'\gamma}$ = 4.4, $J_{\beta\beta'}$ = 17 Hz) at δ 2.78. At 250 MHz the singlet at δ 4.25 is split further into an AB quartet (J = 12 Hz).

Anal. Calcd for $C_6H_7O_4Br_3$: C, 18.81; H, 1.82; Br, 62.63. Found: C, 19.04; H, 1.90; Br, 62.58.

Tin–Copper Couple. The procedure of Le Goff,[4] developed for the preparation of zinc–copper couple, was followed. Thirty mesh granular tin (3.5 g, 0.0295 mol, Mallinckrodt) was added to a hot solution of cupric acetate monohydrate (0.050 g, 0.0025 mol) in acetic acid (25 ml). The mixture was stirred and shaken until the blue color of the cupric acetate was no longer evident (ca. 3 min). The acetic acid was decanted and the reddish tin–copper couple washed with two 15-ml portions of acetic acid followed by three 20-ml portions of ether. The tin–copper couple was used freshly prepared and was kept covered with ether.

α-Methylene-γ-bromoglutaric Acid (II). A solution of α-bromomethyl-α,γ-dibromoglutaric acid (I, 3.83 g, 0.01 mol) in dry tetrahydrofuran (6 ml), freshly distilled from $LiAlH_4$, was stirred magnetically with freshly prepared tin–copper couple (0.590 g, 0.005 mol) for 1 h. The precipitated tin bromide was removed by filtration and washed with carbon tetrachloride. Removal of the solvent from the filtrate and addition of chloroform to the concentrate afforded 1.92 g (86%) of white, crystalline α-methylene-γ-bromoglutaric acid (II), mp 133–136 °C. Crystallization from a 2:1 mixture of chloroform–ethyl acetate yielded 1.80 g (81%) of the pure bromo acid II: mp 136–137 °C; infrared (KBr) 5.81, 5.92, and 6.13 μ; NMR (acetone-d_6) two-proton, broad carboxylic acid singlet at δ 8.83, one-proton vinyl singlet at δ 6.33, one-proton vinyl doublet (J = 1 Hz) at δ 5.83, one-proton bromomethylene triplet (H_γ, $J_{\beta\gamma}$ = $J_{\beta'\gamma}$ = 7 Hz) at δ 4.60, allylic one-proton quartet (H_β, $J_{\beta\beta'}$ = 14, $J_{\beta\gamma}$ = 7 Hz) at δ 3.25, and allylic one-proton quartet ($H_{\beta'}$, $J_{\beta\beta'}$ = 14, $J_{\beta'\gamma}$ = 7 Hz) at γ 2.83. The NMR spectrum of the total crude product shows approximately 3% of the fully reduced α-methyleneglutaric acid, which is easily removed in the crystallization step.

Anal. Calcd for $C_6H_7O_4Br$: C, 32.30; H, 3.14; Br, 35.84. Found: C, 32.41; H, 3.28; Br, 35.67.

2,3-Bis(bromomethyl)-1,3-butadiene (IV). Tetrakis(bromomethyl)ethylene (III) was prepared according to Cope and Kagan,[8] NMR ($CDCl_3$) singlet at δ 4.18. A solution of the tetrabromide III (50 g, 0.125 mol) in 300 ml of tetrahydrofuran was stirred for 48 h in the refrigerator (4 °C) with 250 g (2.106 mol) of freshly prepared tin–copper couple. The progress of the reaction was conveniently followed in the same solvent using NMR. The bromomethyl protons of IV are

shifted to slightly higher field than those of the starting material III. When the reaction was judged to be complete, it was filtered and the solvent was removed on the rotary evaporator at room temperature. The resulting yellow solid was triturated repeatedly with six 50-ml portions of ether yielding 25 g of solid after evaporation of the ether. This substance was then triturated several times with *n*-pentane with very brief heating on the steam bath each time, followed by filtration. Evaporation of the combined filtrates yielded 22 g of a solid. A white fibrous substance was removed in the filtration step. Finally, the product was dissolved in *n*-pentane with gentle warming and allowed to crystallize overnight in the freezer (−20 °C) yielding 16 g of slightly tan, crystalline dibromide IV, mp 57–58 °C (resolidifies to a fibrous gel soon after melting). The dibromide IV exhibits a very clean NMR spectrum ($CDCl_3$): two-proton vinyl singlet at δ 6.03, two-proton vinyl singlet at δ 5.97, and four-proton bromomethyl singlet at δ 4.15.

Acknowledgment. This work was generously supported by the Institute for General Medical Sciences of the National Institutes of Health through Grant GM 19906 01.

Registry No.—I, 60239-16-9; II, 60239-17-0; III, 30432-16-7; IV, 18214-55-6; α-methyleneglutaryl chloride, 32287-80-2; α-methyleneglutaric acid, 3621-79-2; Sn/Cu, 12735-84-1.

References and Notes

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(3) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 1307.
(4) E. Le Goff, *J. Org. Chem.*, **29**, 2048 (1964).
(5) Selective reduction of 2,6-dibromo-1-naphthol to 6-bromo-1-naphthol using mossy tin and hydrobromic acid has been reported by C. F. Koelsch, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 132. See M. Fieser and L. F. Fieser, "Reagents for Organic Synthesis", Vol. 2, Wiley, New York, N.Y., 1969, p 414.
(6) G. B. Butler and R. M. Ottenrite, *Tetrahedron Lett.*, 4873 (1967); Y. Gaoni, *ibid.*, 2361 (1973).
(7) Cf. the procedure of H. Feuer and S. M. Pier, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 554, for itaconyl chloride.
(8) A. C. Cope and F. Kagan, *J. Am. Chem. Soc.*, **80**, 5499 (1958).
(9) Use of copper powder alone (tetrahydrofuran, 12 h, 25 °C) yielded a small amount of the desired bromide II (5%) together with a comparable amount of unwanted lactone. The bulk of the material was unreacted tribromide I. The reaction was only marginally improved at 60 °C.

Substitution and Elimination Reactions of Steroid Tertiary C-17 Trifluoroacetates

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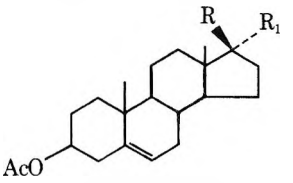
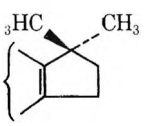
Although solvolytic reactions in the steroid field are of long established synthetic and mechanistic interest,[1] the use of a tertiary trifluoroacetoxy substituent as a leaving group has received relatively little attention. Just and Di Tullio reported briefly that the ethanolysis of 3α-methylcholest-5-en-3β-yl trifluoroacetate (**5**) resulted merely in the recovery of the starting 3β-alcohol (**5a**).[2] Work in other fields suggested, nevertheless, that tertiary trifluoroacetates react in uncatalyzed (neutral) hydrolyses by an alkyl–oxygen fission path or a mechanism which involves both SN and $B_{Ac}2$ routes.[3] Prompted by these results we have examined the solvolytic behavior of 17α-methylandrost-5-ene-3β,17β-diol 3-acetate 17-trifluoroacetate (**1**)[4] and its epimer at C-17 (**1a**), both readily available from the corresponding tertiary alcohols **1b** and **1c**.

Results and Discussion

When **1** and **1a** were solvolyzed in refluxing methanol in the presence of sodium acetate, the following major products were formed. The less polar fractions after chromatography consisted essentially of 17,17-dimethyl-18-norandrosta-5,13-dien-3β-yl acetate (**2**)[5] and a mixture of 17-methyleneandrost-5-en-3β-yl acetate (**3**)[6] and 17-methylandrosta-5,16-dien-3β-yl acetate (**4**)[7] which could not be separated. The other products were, in order of elution, the 17α-methoxy-17β-methylandrost-5-en-3β-yl acetate (**1d**), and (from **1** only) the 17β-alcohol **1b**.[8]





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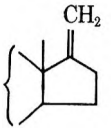
1, R = $OCOCF_3$; R_1 = CH_3
1a, R = CH_3; R_1 = $OCOCF_3$
b, R = OH; R_1 = CH_3
c, R = CH_3; R_1 = OH
d, R = CH_3; R_1 = OCH_3
e, R = CH_3; R_1 = OC_2H_5
f, R = CH_3; R_1 = N_3
g, R = CH_3; R_1 = $NHCOCH_3$



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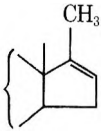

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The structure of the methyl ether **1d** was deduced on the basis of analytical and spectral data and by comparison of the C-5 saturated analogue[9] with an authentic sample.[10]

In Table I the yields of the products resulting from the two methanolyses are compared. The enhancement of the elimination path for the quasi-axial 17α-trifluoroacetate **1a** has analogy in the solvolyses of several secondary sulfonate esters.[11] The major product **4** should derive from a rapid trans quasi-diaxial elimination with the 16β proton. In both cases the unrearranged elimination products are accompanied by the rearranged Δ^{13} olefin **2**, which is the usual product from a C-17 carbonium ion.[5] The replacement reaction by alkyl–oxygen fission, though proceeding by unimolecular heterolysis (SN1),[12] leads, whatever the substrate, to the 17α-methoxy derivative **1d**, a result which probably depends on the steric opposition of the 13-methyl group to β-attack by the solvent.

Methanolysis of **1** in the absence of a buffer gave the expected enhancement of the rearranged Δ^{13} olefin **2** at the expense of the 17β-alcohol **1b** (only traces).

Turning next to the solvolysis in ethanol, the 17α-ethoxy derivative **1e**[13] was obtained in 11% yield from **1** in the presence of sodium acetate, together with the usual elimination products (52% yield), and the 17β-alcohol **1b** (25% yield).

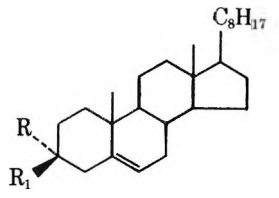
This result differed considerably from that reported by Just and Di Tullio for **5**[2] but a reexamination of the ethanolysis of **5** showed that, in addition to a 78% yield of the starting alcohol **5a**, only an 8% yield of a hydrocarbon mixture containing both 3-methylcholesta-3,5-diene (**6**)[14] and 3-methylenecholest-5-ene (**7**)[14] and a 9% yield of 3β-ethoxy-3α-methylcholest-5-ene (**5b**)[14] were formed.

As to the aprotic solvents, when dimethyl sulfoxide was used, in the presence of sodium acetate, the decomposition of **1** and **1a** to the elimination products strongly preponderated, as can be seen from Table I. For **1**, the olefin composition observed appears to minimize the possible intervention of a preliminary SN2 substitution of the trifluoroacetoxy group by the solvent (which is more nucleophilic than AcO^- anion) to give an axial *O*-alkyl sulfonium salt,[15] since this would

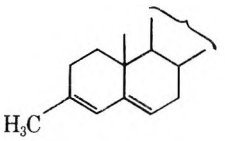
Table I. Percentages[a] of the Products Obtained by Solvolysis of 1 and 1a

Product	MeOH + AcONa[b] 1[c]	MeOH + AcONa[b] 1a	MeOH + LiN_3, 1	MeOH, 1	Me_2SO + AcONa 1	Me_2SO + AcONa 1a	Me_2SO + AcONa (+2% H_2O), 1	Me_2SO + NaN_3, 1
2	10	13	14	33	12	4		7
3	16.5	21	20	15	42	34	28	44
4	6.5	46	8	10	24	62		25
1b	42		28		6		63	
1c					9		9	10.5
1d	21	9	22	16				
1f			8					13

[a] The yields of **2**, **1b**, **1c**, **1d**, and **1f** are calculated from weights of chromatographic fractions; those of **3** and **4** are inferred from the ^1H NMR spectra of their mixtures. [b] Medium. [c] Substrate.



5, R = CH_3; R_1 = $OCOCF_3$
5a, R = CH_3; R_1 = OH
b, R = CH_3; R_1 = OC_2H_5



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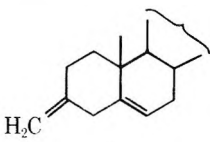

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produce more **4** than was actually obtained. The alcohols that occurred in low yield among the solvolytic products of **1** should arise from hydrolysis of such intermediate species during workup or, alternatively, from adventitious water present in the reaction mixture. In fact, since the solvolysis of **1** in Me_2SO + AcONa in the presence of 2% water raised the yield of **1b** to 63%, while leaving that of **1c** practically unaffected, the latter process should be the more effective for the 17β-alcohol and the former for the 17α-alcohol.

As expected, the solvolysis of **1** in Me_2SO in the presence of the more powerful nucleophile sodium azide gave, in addition to **2**, **3**, **4**, and **1c**, the 17α-azido-17β-methylandrost-5-en-3β-yl acetate (**1f**) in 13% yield. The 17α configuration of the azide group was inferred from both mechanistic considerations (mechanism SN2 is predominant in dipolar aprotic solvents)[12] and the following data. The 13β-methyl group in the ^1H NMR spectrum of **1f** resonates at a value (0.75 ppm) consistent with those of all the compounds of the 17α series (**1a**, **1c**, **1d**, and **1e**) (0.68–0.77 ppm), while the corresponding signal of the compounds of the 17β series (**1** and **1b**) exhibit a distinct downfield shift. Furthermore, **1f** was reduced with lithium aluminum hydride[16] and the crude amine was acetylated to give a 17-acetamido derivative **1g** of retained configuration which is different from the known 17β-acetamido-17α-methylandrost-5-en-3β-yl acetate.[17] A similar amount of **1f** resulted when the solvolysis was carried out in hexamethylphosphoric triamide (HMPT), as indicated by the comparable intensities of the asymmetric azide stretching band at 2100 cm^{-1} in the ir spectrum of each crude reaction residue.

Finally, treatment of **1** with lithium azide in refluxing methanol resulted in a limited competition between azide ion and methanol since only an 8% yield of **1f** was obtained against the 22% yield of the methoxy derivative **1d**.

In conclusion, we have found that solvolysis of tertiary trifluoroacetates is useful for nucleophilic substitution at tertiary centers but, as expected, the yields are strongly limited by concurrent eliminations. The latter are not specific and give merely mixtures "for the balance between E1 and E2 can be very delicately poised in tertiary structures" [18] and, in addition, the syn-coplanar mode of E2 elimination in cyclopentyl rings may be only moderately less favorable than the anti reaction.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are not corrected. Rotations were taken with a Schmidt-Haensch polarimeter (1-dm cell) in 1% $CHCl_3$ solutions. Where appropriate, identities of compounds were confirmed by comparison of ir spectra (KBr disks; Perkin-Elmer 521 grating spectrophotometer). ^1H NMR spectra were measured for solutions in $CDCl_3$ (Me_4Si as internal standard) with a Varian HA-100 spectrometer. Column chromatographies were carried out with deactivated (grade II) Woelm neutral alumina. Dimethyl sulfoxide and hexamethylphosphoric triamide were refluxed over calcium hydride and distilled in vacuo; methanol and ethanol were dried by treatment with magnesium.

17α-Methylandrost-5-ene-3β,17-diol 3-Acetate 17-Trifluoroacetate (1). 17α-Methylandrost-5-ene-3β,17-diol 3-acetate (**1b**, 1.00 g, 2.9 mmol) and trifluoroacetic anhydride (1.5 ml) in dry pyridine (7 ml) were set aside at room temperature for 3 h, then poured slowly into 85 ml of cold aqueous 15% HCl, with stirring. The yellow precipitate was filtered and dissolved in ether and the extracts washed with water until neutral. After drying (Na_2SO_4), the ether was evaporated and the residue (1.31 g) crystallized twice from methanol (0.72 g): mp 118–120 °C; $[\alpha]_D$ −65°; ir CF_3COO 1770 cm^{-1}; ^1H NMR δ 0.91 (3 H, s, 13-Me), 1.05 (3 H, s, 10-Me), 1.51 (3 H, s, 17α-Me), 2.00 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 5.4 ppm (1 H, m, C-6 H).

Anal. Calcd for $C_{24}H_{33}F_3O_4$ (442.5): C, 65.14; H, 7.51; F, 12.88. Found: C, 65.42; H, 7.65; F, 12.73.

17β-Methylandrost-5-ene-3β,17-diol 3-Acetate 17-Trifluoroacetate (1a). This was prepared in the same manner as above from 17α-alcohol **1c** and crystallized from *n*-hexane: mp 95–96 °C; $[\alpha]_D$ −109°; ir CF_3COO 1770 cm^{-1}; ^1H NMR δ 0.77 (3 H, s, 13-Me), 1.06 (3 H, s, 10-Me), 1.57 (3 H, s, 17β-Me), 2.05 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 5.4 ppm (1 H, m, C-6 H).

Anal. Calcd for $C_{24}H_{33}F_3O_4$ (442.5): C, 65.14; H, 7.51; F, 12.88. Found: C, 65.01; H, 7.52; F, 12.54.

Solvolysis of 17β-Trifluoroacetate 1 in Methanol in the Presence of Sodium Acetate. A stirred solution of **1** (4.42 g, 10 mmol) in 125 ml of methanol was refluxed for 32 h[19] in the presence of sodium acetate (4.10 g, 50 mmol). Part of the methanol was distilled and water was added to the mixture. The product was extracted with ether, and the extract washed with water and dried over Na_2SO_4. The residue (3.51 g) was chromatographed over 210 g of alumina. Elution with *n*-hexane–benzene (7:3) gave 17,17-dimethyl-18-norandrosta-5,13-dien-3β-yl acetate (**2**, 0.35 g, 10%), identical with an authentic sample,[5] followed by a mixture of 17-methyleneandrost-5-en-3β-yl acetate (**3**)[6] and 17-methylandrosta-5,16-dien-3β-yl acetate (**4**,[7] 0.81 g, 23%). Elution with benzene gave **17α-methoxy-17β-methylandrost-5-en-3β-yl acetate (1d,** 0.73 g, 21%): mp 130–131 °C (from *n*-hexane); $[\alpha]_D$ −90°; ^{1}NMR δ 0.71 (3 H, s, 13-Me), 1.05 (3 H, s, 10-Me), 1.11 (3 H, s, 17β-Me), 2.03 (3 H, s, 3β-OAc), 3.18 (3 H, s, 17α-OCH_3), 4.6 (1 H, m, 3α-H), 5.4 ppm (1 H, m, C-6 H).

Anal. Calcd for $C_{23}H_{36}O_3$ (360.5): C, 76.62; H, 10.07. Found: C, 76.65; H, 10.12.

Finally, elution with benzene–ether (9:1) gave 17α-methylandrost-5-ene-3β,17-diol 3-acetate (**1b**, 1.47 g, 42%), mp 177–179 °C (from AcOEt).

Repetition of the procedure on **17α-methyl-5α-androstane-3β,17-diol 3-acetate 17-trifluoroacetate** [mp 107–108.5 °C (from methanol); $[\alpha]_D$ −7.5°; ir CF_3COO 1770 cm^{-1}] resulted in the formation of 17α-methoxy-17β-methyl-5α-androstan-3β-yl acetate (23%): mp 94–94.5 °C (from methanol); $[\alpha]_D$ −24°; identical with an authentic sample.[10]

In the same manner were carried out the solvolyses of **1a** in MeOH in the presence of sodium acetate and of **1** in MeOH alone and in 0.92 M anhydrous methanolic lithium azide.[20]

Solvolysis of 17β-Trifluoroacetate 1 in Ethanol in the Presence of Sodium Acetate. Treatment of **1** (1.74 g, 3.9 mmol) with AcONa (1.62 g, 19.5 mmol) in EtOH (50 ml) in the above manner gave, after chromatography of the residue (1.36 g) on alumina, **17α-ethoxy-17β-methylandrost-5-en-3β-yl acetate (1e)** (147 mg, 11%): mp 96–97 °C (from MeOH); $[\alpha]_D$ −90°; ^1H NMR δ 0.68 (3 H, s, 13-Me), 1.04 (3 H, s, 10-Me), 1.10 (3 H, s, 17β-Me), 1.11 (3 H, t, J = 7 Hz, CH_3CH_2O–), 2.03 (3 H, s, 3β-OAc), 3.34 (2 H, q, J = 7 Hz, CH_3CH_2O–), 4.6 (1 H, m, 3α-H), 5.4 ppm (1 H, m, C-6 H).

Anal. Calcd for $C_{24}H_{38}O_3$ (374.5): C, 76.93; H, 10.26. Found: C, 76.93; H, 10.23.

Solvolysis of 17β-Trifluoroacetate 1 in Me_2SO in the Presence of NaN_3. **1** (4.4 g, 10 mmol) in Me_2SO (120 ml) containing NaN_3 (6.6 g, 100 mmol) was heated at 80 °C with stirring for 24 h.[21] The mixture was cooled and water was added. The product was isolated with ether, washed with water, and dried over Na_2SO_4. Evaporation of the ether gave 3.2 g of an oily residue which was chromatographed on alumina (192 g). Elution with n-hexane–benzene (7:3) gave **2** (0.23 g, 7%) followed by **3** + **4** (1.6 g), by a mixture of **3**, **4**, and **1f** (0.81 g), and by pure **17α-azido-17β-methylandrost-5-en-3β-yl acetate (1f)** (0.20 g): mp 138–139 °C (from n-hexane); $[\alpha]_D$ −109°; ir N_3 2100 cm^{-1}; ^1H NMR δ 0.75 (3 H, s, 13-Me), 1.05 (3 H, s, 10-Me), 1.29 (3 H, s, 17β-Me), 2.02 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 5.4 ppm (1 H, m, C-6 H).

Anal. Calcd for $C_{22}H_{33}N_3O_2$ (371.5): C, 71.22; H, 8.95; N, 11.33. Found: C, 71.03; H, 8.92; N, 11.29.

Elution with benzene–ether (9:1) gave 0.33 g of predominantly **1c**, mp 156–158 °C (from acetone), identical with an authentic sample[8] (trace amounts of **1b** were present). Repeated chromatographies of the mixture of **3**, **4**, and **1f** (0.81 g) on alumina as above gave more pure **1f** (0.21 g, total yield 13%) in addition to 0.6 g of **3** + **4** (total yield 69%).

In the same manner were carried out solvolyses of **1** and **1a** in Me_2SO + AcONa.

17α-Acetamido-17β-methylandrost-5-en-3β-yl Acetate (1g). To 0.2 g of $LiAlH_4$ in 10 ml of dry ether was added 0.2 g (0.54 mmol) of **1f** in 10 ml of dry ether. The mixture was stirred at room temperature for 5 h, and excess $LiAlH_4$ decomposed with AcOEt and water. The mixture was filtered and the filtrate washed with water. The ether was evaporated after drying and the crude amino derivative obtained [0.17 g, ir 3670 and 3600 (NH_2) and 3440 cm^{-1} (OH)] was directly acetylated (Ac_2O–pyridine) to give 0.21 g of 17α-acetamido-17β-methylandrost-5-en-3β-yl acetate (**1g**): mp 155–156 °C (from isopropyl ether); $[\alpha]_D$ −96°; ir 3450 (NH), 1720 (3β-OAc), and 1665 cm^{-1} (acetamido); ^1H NMR δ 0.76 (3 H, s, 13-Me), 1.04 (3 H, s, 10-Me), 1.40 (3 H, s, 17β-Me), 1.92 (3 H, s, $NHCOCH_3$), 2.01 (3 H, s, 3β-OAc), 4.6 (1 H, m, 3α-H), 5.4 (2 H, m, C-6 H and NH).

Anal. Calcd for $C_{24}H_{37}NO_3$ (387.5): C, 74.38; H, 9.62; N, 3.61. Found: C, 74.18; H, 9.49; N, 3.46.

Registry No.—1, 474-34-0; **1a**, 60282-52-2; **1b**, 33854-98-7; **1c**, 3090-73-1; **1d**, 60282-53-3; **1e**, 60282-54-4; **1f**, 60282-55-5; **1g**, 60282-56-6; trifluoroacetic anhydride, 407-25-0; 17α-methyl-5α-androstane-3β,17-diol 3-acetate 17-trifluoroacetate, 60282-57-7; 17α-methoxy-17β-methyl-5α-androstan-3β-yl acetate, 60282-58-8.

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Resolution of Anomeric Ethyl 2-Amino-2-deoxy-D-glucopyranoside by Cation-Exchange Chromatography, and Its N-Acylation with Carboxylic Anhydrides

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Ethyl 2-acetamido-2-deoxy-β-D-glucopyranoside is found in some microorganisms[1] and has a growth-promoting activity (the bifidus activity) for *Lactobacillus bifidus* var. *pennsylvanicus*.[2,3] The bifidus activity is found in the β anomer only, but the α anomer is inactive.[2,3] Little is known about the structural specificity of the *N*-acyl group for the bifidus activity.[4] Therefore, a modification of the *N*-acyl group is of significance from these points of view. The bifidus activity was originally observed with oligosaccharides[5] and glycopeptides[5,6] present in human milk.

The anomeric mixtures are generally produced in the course of the preparation of glycosides by the Fischer method,[7a] and the anomeric resolution is one of the important tasks. In the past, the resolution of anomeric hexosaminides in a preparative scale has been performed by differential solubilities in various solvents[7b] or, more recently, by anion-exchange chromatography utilizing the difference in acidities of the glycoside bonds.[8]

The present paper reports a novel and facile method for the anomeric resolution of ethyl 2-amino-2-deoxy-D-glucopyranoside by cation-exchange chromatography utilizing the difference in basicities of the amino groups, and the preparation of some novel *N*-acyl derivatives by N-acylation with carboxylic anhydrides.

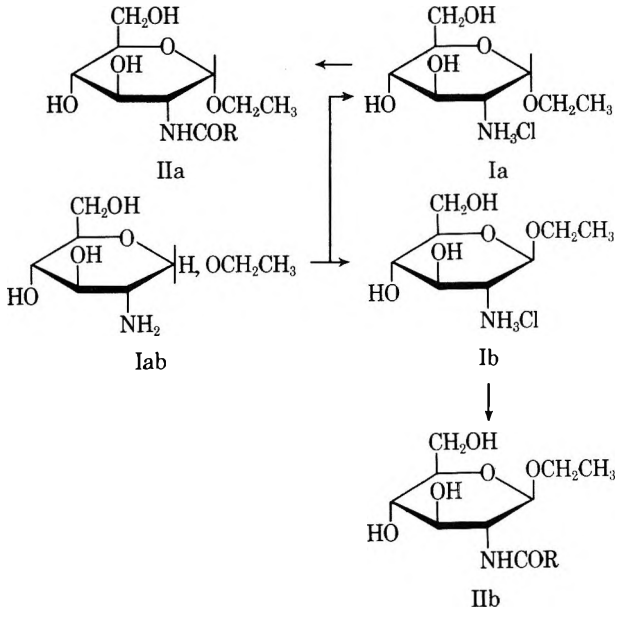
Results and Discussion

The anomeric ethyl 2-acetamido-2-deoxy-D-glucopyranoside was N-deacetylated with 1.0–6.0 N NaOH in a boiling water bath for 1–5 h. The extent of N-deacetylation was analyzed by the ninhydrin reaction and by an amino acid analyzer. The maximum yield (42.6% Ia and 39.8% Ib) was obtained by treating with 2.0 N NaOH in a boiling water bath for 3 h, and the reaction with 6.0 N $Ba(HO)_2$ under these conditions afforded 35.0% Ia and 24.1% Ib. Product degradation occurred with 3.0–6.0 N NaOH in the reaction for 4 h and longer, and N-deacetylation was incomplete in the reactions with 1.0 N NaoH for 1 h and shorter. The degradation was evident by the detection of a strong NH_3 peak by the amino acid analyzer.

Table I. Ethyl 2-Acylamino-2-deoxy-D-glucopyranosides Prepared by the Reaction of Fatty Acid Anhydrides[f]

Acylamino group[a]	Anomeric configuration	Mp, °C	$[\alpha]^{20}D$, deg	Yield, %	Registry no.
Propionyl	α	162–166	+134 (c 0.5, water)	54.0	32469-95-7
	β	172	−17.8 (c 0.45, methanol)	58.0	32469-96-8
Butyryl	α	169–171	+100 (c 0.46, water)	57.0	60538-24-1
	β	169–172	−42.6 (c 0.68, water)[b]	93.0	60538-25-2
Caproyl	α	172–174	+107 (c 0.44, water)	56.0	60538-26-3
	β	173–175	−10.2 (c 0.44, water)	n.d.[c]	60538-27-4
Capryloyl	α	160–163	+134 (c 0.73, methanol)	83.6	60538-28-5
	β	191–193	−17.7 (c 0.62, methanol)	54.0	60538-29-6
Caprinoyl	α	163–164	+116 (c 0.83, methanol)	64.0	60538-30-9
	β	203–205	−14.1 (c 1.1, methanol)	n.d.	60538-31-0
Lauroyl	α	159–163	+110 (c 0.53, methanol)	92.3	60538-32-1
	β	206–208	−13.9 (c 0.96, methanol)	88.0	60538-33-2
Myristoyl	α	167–169	+70.5 (c 0.53, methanol)	60.0	60538-34-3
	β	205–207	−16.6 (c 0.96, methanol)	73.0	60538-35-4
Palmitoyl	α	160–163	+78.8 (c 0.8, methanol)	68.6	60538-36-5
	β	200–203	−13.0 (c 1.0, methanol)[e]	87.7	60538-37-6
Stearoyl	α	130–133	+60.0 (c 0.5, methanol)[d]	87.7	60538-38-7
	β	202–205	−18.6 (c 1.0, methanol)[e]	84.0	60538-39-8

[a] The reaction of ethyl 2-amino-2-deoxy-β-D-glucopyranoside with acetic anhydride by the present procedure produced ethyl 2-acetamido-2-deoxy-β-D-glucopyranoside (76%): mp 177–180 °C; $[\alpha]^{20}D$ −41.0° (c 1.0, water) [lit.[13] mp 178–180 °C; $[\alpha]^{20}D$ −42.5° (water)]. [b] $[\alpha]^{23}D$ −17.4° (c 1.1, methanol). [c] Not determined. [d] Measured at 33 °C because of its slight solubility in methanol at 20 °C. [e] Measured at ~50 °C because of its slight solubility in methanol at 20 °C. [f] All C, H, and N analyses of the compounds listed in the table were within 0.5% of theoretical.



A portion of the anomeric ethyl 2-amino-2-deoxy-D-glucopyranoside (Iab) was analyzed on the amino acid analyzer, and it showed the presence of two components: R_{NH_3} 0.56 (the α anomer) and 0.47 (the β anomer).[9] The anomers (Iab) resolved clearly on a column of Amberlite CG 120 (H^+) eluted with 0.3 N HCl, and this elution pattern in a preparative scale was essentially similar to that in the amino acid analyzer.

Each amino group of the anomeric hexosaminides has a unique basicity.[9] This is due to an anomeric effect associated with the dipole–dipole interaction of aglycons.[10] The α anomer ($K_a = 1.95 \times 10^{-8}$) of 2-amino-2-deoxy-D-glucose is more basic than the β anomer ($K_a = 5.3 \times 10^{-8}$).[11] The difference in basicity is utilized in the present study for the anomeric resolution of Iab in a preparative scale by cation-exchange chromatography.

Each of Ia and Ib was converted to the free base by the addition of sodium methoxide (1.0 molar equiv to hexosaminide) in methanol, and its N-acylation was performed with carboxylic anhydride (1.2 molar equiv) by our procedure as reported previously.[12] The *N*-acyl derivatives (IIa and IIb) were isolated in 54–93% yields (Table I). IIa and IIb are soluble in methanol but insoluble in petroleum ether (bp 30–70 °C) and ethyl ether. *N*-Acyl derivatives of the lower member of fatty acids (C_2–C_6) are soluble in water but those of the higher member of fatty acids (C_8–C_{18}) are slightly soluble or almost insoluble in water. The α anomer of the *N*-palmitoyl derivative is very soluble in methanol at room temperature but the β anomer is slightly soluble in this solvent. Both the α and β anomers of the *N*-stearoyl derivative are slightly soluble in methanol. The β anomer of the *N*-benzoyl derivative is soluble in water but the α anomer is insoluble. IIa and IIb are expected to be active in the bifidus assay. All of these products are novel, but the *N*-acetyl derivative has been reported.[13]

All the *N*-acyl derivatives isolated show strong ir absorptions at ~1650 (C=O in *N*-acyl) and ~1540 (N–H in *N*-acyl) and at 2920–2850 cm^{-1} (C–H in fatty acid), but these products show the disappearance of ir absorptions at ~1750 (C=O in *O*-acyl) and ~1240 cm^{-1} (C–O in *O*-acyl).

A weak ir absorption at ~855 cm^{-1} appears in all the α-D anomers, and that at ~870 cm^{-1} appears in all the β-D anomers.[14] Furthermore, the anomeric configuration is confirmed by their specific rotations (Table I). The *N*-propionyl, butyryl, and caproyl derivatives of anomerically pure ethyl 2-amino-2-deoxy-D-glucopyranoside show H-1 of the α anomer at δ 4.85–4.86 ppm as a doublet with $J_{1,2}$ = 3.0 Hz, H-1 of the β anomer at δ 4.54–4.68 ppm as a doublet with $J_{1,2}$ = 10.0–11.0 Hz, and the corresponding *N*-acyl protons in the NMR spectra.

Table I summarizes the melting points, specific rotations, yields, and elemental analysis of both the pure anomers.

Experimental Section

Melting points were measured on a Yanagimoto SP-2 apparatus and are uncorrected. NMR spectra were recorded at 60 MHz on a Hitachi R-24 spectrometer in D_2O using sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate as an internal standard, and ir spectra on a Hitachi 215 grating spectrometer (KBr). Specific rotations were recorded in methanol using a cell of path length 1.0 cm on a Yanagimoto OR-50 automatic polarimeter.

The anomeric mixture of ethyl 2-amino-2-deoxy-D-glucopyranoside was analyzed with a Hitachi KLA-2 amino acid analyzer as reported previously.[9]

Elemental analysis was performed at the Elemental Analysis Center of Kyoto University, Kyoto.

Ethyl 2-Amino-2-deoxy-D-glucopyranoside (Iab). The anomeric mixture of ethyl 2-acetamido-2-deoxy-D-glucopyranoside was prepared by refluxing 2-acetamido-2-deoxy-D-glucose in the presence of dry IRA 120 (H^+) resin in anhydrous ethanol for 5 h. The anomeric mixture (500 mg), $[\alpha]^{23}D$ +35.7° (c 1.02, water), was dissolved in 10 ml of 2.0 N NaOH and the solution was kept in a boiling water bath for 3 h. After cooling to room temperature, the reaction mixture was neutralized with 2.0 N HCl and diluted with distilled water to ~150 ml.

Ethyl 2-Amino-2-deoxy-α-D-glucopyranoside (Ia) and Ethyl 2-Amino-2-deoxy-β-D-glucopyranoside (Ib). The diluted solution of **Iab** obtained above was applied to a column (2.7 × 52 cm) of Amberlite CG 120 (H^+). The column was eluted with 0.3 N HCl at a flow rate of 30 ml/h, and fractions of 7.0 g each were collected. A screening test was carried out by the ninhydrin reaction. Each of the peaks was combined and concentrated in vacuo to dryness. Crystallization was performed from a mixture of water, ethanol, and ethyl ether, and two recrystallizations from the same solvent. Ethyl 2-amino-2-deoxy-α-D-glucopyranoside hydrochloride (Ia) was isolated from fractions 139–157, yield 213 mg (42.6%): mp 199–203 °C; $[\alpha]^{23}D$ +135° (c 0.48, water) [lit.[15] mp 197–198 °C; $[\alpha]^{19}D$ +129.2° (c 0.4, water)]. The β anomer (Ib) was isolated from fractions 123–135, yield 199 mg (39.8%): mp 227–228.5 °C; $[\alpha]^{24}D$ −18.7° (c 0.48, water) [lit.[16] mp 213–214 °C; $[\alpha]D$ −27.8° (water)].

Ethyl 2-Acylamino-2-deoxy-α-D-glucopyranosides (IIa) and Ethyl 2-Acylamino-2-deoxy-β-D-glucopyranosides (IIb). Each of Ia and Ib (72.9 mg each) was placed in 0.5 ml of anhydrous methanol involving 7 mg of Na. Upon gentle swirling, NaCl separated and was removed by filtration and washed with 0.5 ml of anhydrous methanol. An amount of carboxylic anhydride (1.2 molar equiv to Ia or Ib) was added at room temperature with stirring. In the case of the anhydride of the fatty acids higher than C_{12}, an additional 2.0 ml of methanol was added to the mixture and the mixture was warmed at ~60 °C for a few seconds. The mixture was allowed to stand at room temperature overnight, and ethyl ether and petroleum ether (bp 30–70 °C) were added. The mixture was kept in a refrigerator to give crystals, and two recrystallizations were performed from ethanol, ethyl ether, and petroleum ether. It was essential for analysis to remove a trace of NaCl contaminated through the recrystallizations. The crystalls were filtered, washed with ethyl ether, and dried over P_2O_5 in vacuo at 100 °C for 2 h. Table I shows the anomerically pure *N*-acyl derivatives thus prepared in the reaction with the anhydrides of fatty acids.

Ethyl 2-Benzamido-2-deoxy-α-D-glucopyranoside. The above procedure was applied to the preparation of the title compound by using benzoic anhydride, yield 93.2%: mp 199–202 °C; $[\alpha]^{20}D$ +85.4° (c 0.48, methanol); ir (KBr) 3500–3300 (OH, NH), 1630 (C=O in *N*-benzoyl), 1540 (N–H in *N*-benzoyl), 1140–1030 (C–O–C), 850 cm^{-1} (the α-D configuration).

Anal. Calcd for $C_{15}H_{21}O_6N$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.63; H, 7.00; N, 4.40.

Ethyl 2-Benzamido-2-deoxy-β-D-glucopyranoside. The same procedure was applied to prepare the title compound, yield 55%: mp 192–195 °C; $[\alpha]^{21}D$ −40.3° (c 0.62, water); λ_{max} (water) 230 nm (ε 6400); ir (KBr) 3450–3250 (OH, NH), 1630 (C=O in *N*-benzoyl), 1550 (N–H in *N*-benzoyl), 1070–1020 (C–O–C), 870 cm^{-1} (the β-D configuration); NMR (D_2O) δ 1.05 (t, 3 protons, CH_3), 3.72 (q, 2 protons, CH_2), 4.65 (d, 1 proton, $J_{1,2}$ = 7.0 Hz, H-1), 7.55 ppm (m, 5 protons, phenyl).

Anal. Calcd for $C_{15}H_{21}O_6N$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.77; H, 7.08; N, 4.54.

Registry No.—Ia, 57120-95-3; Ib, 6835-60-5; ethyl 2-benzamido-2-deoxy-α-D-glucopyranoside, 60538-40-1; benzoic anhydirde, 93-97-0; ethyl 2-benzamido-2-deoxy-β-D-glucopyranoside, 60538-41-2; propionic anhydride, 123-62-6; butyric anhydride, 106-31-0; caproic anhydride, 2051-49-2; caprylic anhydride, 623-66-5; capric anhydride, 2082-76-0; lauric anhydride, 645-66-9; myristic anhydride, 626-29-9; palmitic anhydride, 623-65-4; stearic anhydride, 638-08-4.

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Selectivity in the Reduction of Enantiomers of Hexahelicene in an Optically Active Solvent

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The reduction of aromatic molecules to their anions by alkali metals is now a well-established chemical process. Soon after the identification of the reduction products as anions it was recognized that interactions involving the anions, the solvent, and the alkali metal counterions play an important part in the behavior of the systems. It has also been recognized for a long time that interactions between chiral solvents and solutes produce a variety of observable effects such as induced optical activity in nonchiral solutes and selective formation of enantiomers of chiral products in chemical reactions. Examples of the latter phenomena are provided by Wright's observations that reductions carried out in one of the enantiomers of dimethoxybutane are selective among the enantiomers of chiral products.[1-4]

In this note I describe experiments which were intended to isolate some features of solvent–anion interaction through a study of the selective reduction to their mononegative anions of the enantiomers of hexahelicene in the optically active solvent (+)-2,3-dimethoxybutane (DMB). Because of the stability of the anions of hexahelicene and the enormous rotation and circular dichroism of neutral hexahelicene the system is ideal for the observation of small effects. The reactions were followed by recording the circular dichroism spectra of a solution of hexahelicene in the optically active solvent subsequent to successive reductions by a potassium mirror. The standard high vacuum methods for handling solutions of radical anions were used. The apparatus was fitted with two quartz optical cells, one with a 0.10-mm light path, the other with a 1.00-mm path. Either cell could be inserted into the light beam of a Jasco J-20 spectropolarimeter. Readings were as reproducible on removal and reinsertion of the cells as they were on successive recordings during which the cells were not removed. For the experiments with the optically active solvent, the shorter light path was used in order to minimize contributions in the 300–350-nm region of the tail of the ultraviolet circular dichroism peak of DMB.

A solution of "racemic" hexahelicene in DMB (absorbance at λ_{max} 310 nm in the 0.1-mm cell of 0.45, concentration approximately 10^{-3} M) exhibited ellipticity at 322 nm of $+0.5 \times 10^{-3}$ degrees. This small peak is reproducible to less than 0.2×10^{-3} degrees. It arises not from a difference of interaction of DMB with the enantiomers of hexahelicene but rather from the fact that the starting material was not perfectly racemic. A solution of the starting material in benzene exhibited the same circular dichroism as in DMB.[5]

After the first brief contact of the above solution with a potassium mirror, the ellipticity at 322 nm changed sign becoming -1.3×10^{-3} degrees. After the second contact with the potassium mirror the ellipticity became -3.5×10^{-3} degrees. After a third contact the peak diminished to 0.8×10^{-3} degrees, and disappeared after a fourth contact. The shape of the peak was the same as that of resolved neutral hexahelicene. (The mononegative anion does not exhibit a circular dichroism peak at 322 nm.) No changes with time of the properties of the solution were observed during each interval of about 1 h between reductions.

In the early stages of the reduction only neutral molecule and mononegative ions are present.[6] The appearance of the circular dichroism peak of neutral (−) hexahelicene must result from a selective reduction of the (+) enantiomer. The effect is remarkably small. From the magnitude of the circular dichroism and the best estimate which I could make of the extent of reduction, the equilibrium constant for the reaction

$$(+)^\circ + (-)^- = (+)^- + (-)^\circ$$

$$K = \frac{[(+)^-]\,[(-)^\circ]}{[(+)^\circ]\,[(-)^-]} = 1.005 \pm 0.002$$

The symbols (+) and (−) stand for the enantiomers, the superscripts for the charges. The standard free energy for the reaction is only −3 cal/mol.

In the succeeding equilibria involving the more highly charged species, much larger effects are observed, but their quantitative interpretation awaits measurements of the absolute values of the circular dichroism of the species involved. The circular dichroism of only the neutral hexahelicene is required for estimation of the equilibrium constant for the reaction.

A number of control experiments were carried out. No circular dichroism peaks were found at either the absorption maxima of triphenylene (a related but nonchiral hydrocarbon) or anions on reduction in DMB. This experiment suggests that the large but as yet unanalyzed peaks at the absorption maxima of the anions of hexahelicene arise from selective reductions rather than from different induced optical activities in the anions. Finally, reduction of racemic hexahelicene in nonchiral dimethoxyethane yielded no observable optical rotation or circular dichroism.[7]

Although the effect here reported corresponds to a free-energy difference of only 3 cal/mol, it is nevertheless easily measured. Clearly the data do not permit unique determination of the nature of the interaction between the solute and solvent, but they eliminate all models in which the stereochemistry requires differences between free energy of reduction of the two enantiomers greater than 3 cal/mol.[8]

Acknowledgment. I am indebted to Professor Melvin Newman for a gift of racemic hexahelicene and to Dr. Douglas Daniel for preparation of (+)-2,3-dimethoxybutane from (+)-2,3-butanediol. The work has been supported by the National Science Foundation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—(+)-2,3-Dimethoxybutane, 1565-60-2; (−)-hexahelicene, 19253-33-9; (+)-hexahelicene, 17486-32-7.

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(6) S. I. Weissman and R. Chang, *J. Am. Chem. Soc.*, **94**, 8683 (1972).
(7) This experiment may not be quite as silly as the reader would be justified in thinking it is. Recent work on the effect of the non-parity-conserving neutral current interaction on atomic and molecular properties suggests that all materials may have chiral properties. Professor Henry Primakoff has kindly made an estimate of this effect on the reduction of hexahelicene and concludes that at best for the reaction here considered $K - 1 = 5 \times 10^{-11}$, far below the sensitivity of the present measurement. However, the effect depends strongly on the atomic numbers of the elements involved and may yet become measurable. For references to work on this subject and a recent attempt at an experimental observation see D. C. Soreide, D. E. Roberts, E. G. Lindahl, L. L. Lewis, G. R. Apperson, and E. N. Fortson, *Phys. Rev. Lett.*, **36**, 352 (1976).
(8) One could interpret the difference to a difference in the anion charge–solvent dipole interaction. For a mean distance of 3 Å between a singly charged ion and a dipole of 0.5 D, a difference in distance greater than 0.01 Å would lead to a difference in free energy greater than the observed 3 cal/mol.

Enolate Route to 5,10-Disubstituted Indeno[2,1-*a*]indene

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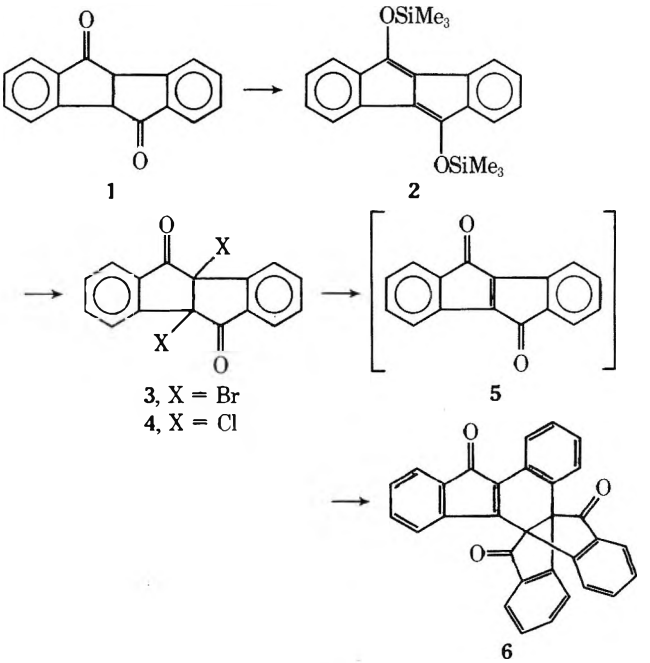
Although 5,10-dialkyl- and diarylindeno[2,1-*a*]indenes are readily prepared from the dione **1**,[1] reported attempts[2] to prepare these 4n π-electron systems by trapping the enolate of **1** have been less successful.



Direct conversion of **1** to the bis(silyl enol ether) can be accomplished by treating **1** with chlorotrimethylsilane in the presence of DBN.[3] The orange product **2** exhibits a uv–visible spectrum typical of an indeno[2,1-*a*]indene chromophore. Silyl ether formation does not occur in the presence of either triethylamine (method of House and co-workers[4]) or *N*-ethylpiperidine. Presumably the more basic amidine, DBN,

is necessary to initiate the silylation by enolizing **1**. Alternatively, bis(silyl ether) **2** can be prepared by treating **1** with excess *N,O*-bis(trimethylsilyl)acetamide in the presence of a catalytic amount of DBN. Attempts to prepare the bisenamine, 5,10-bis(dimethylamino)indeno[2,1-*a*]indene, using trimethylsilyldimethylamine, a reagent reported[5,6] to convert ketones to enamines, led instead to the bis(silyl ether) **2**. Here, as in previous cases,[7] trimethylsilyldimethylamine gave a silyl enol ether rather than an enamine.

Bromination of **2** affords the dibromodione **3** while chlorination gives the dichlorodione **4**. Debromination of the **3** with zinc yields the known red trione **6**[8] previously shown to arise from the dimerization–decarbonylation of the enedione, **5**.[9]

Experimental Section

5,10-Bis(trimethylsiloxy)indeno[2,1-*a*]indene (2). To a warm solution (~50 °C) of 1.20 g (5 mmol) of dione **1** in 50 ml of benzene was added 10 ml of chlorotrimethylsilane followed by a solution of 1.5 g (12 mmol) of DBN in 25 ml of benzene. After 20 min at 50 °C the reaction mixture was allowed to cool to room temperature over 4 h. The DBN hydrochloride was filtered from the reaction mixture. After washing the filtrate with 2 × 25 ml of 4% aqueous HCl it was dried over Na_2SO_4 and then the benzene removed on a rotory evaporator. The orange residual solid was extracted with hot hexane (1 × 50 ml, 1 × 10 ml). Cooling in a freezer gave 0.512 g of orange crystals: mp 132–133 °C; λ_{max} (ether) 411 nm (ϵ 19 600), 387 (14 500), 366 (6700), 303 (32 800), 293 (32 100), 267 (29 700), 262 (27 700), 250 (24 000), 232 (17 200); ^1H NMR (CCl_4) δ 0.33 (9 H, s, $SiCH_3$), 6.76–7.17 (4 H, m, aromatic); mass spectrum M^+ *m/e* 378. Partial evaporation of the hexane mother liquor followed by cooling gave a second crop of 0.494 g. The yield base on 0.325 g of recovered **1** was 68%.

Anal. Calcd for $C_{22}H_{26}O_2Si_2$: C, 69.79; H, 6.92. Found: C, 70.26; H, 6.67.

Halogenation of 2. To a solution of 617 mg (1.6 mmol) of **2** in 20 ml of carbon tetrachloride was added 1.24 g (7.8 mmol) of bromine dissolved in 5 ml of carbon tetrachloride. After standing for 10 min, the reaction mixture was stripped of solvent. The pale yellow solid was air dried yielding 563 mg of **3** (90% yield). The analytical sample was prepared by crystallization from carbon tetrachloride: mp 206–208 °C (reported[10] mp 204–206 °C); ir (CCl_4) 1735 (C=O), 1595 cm^{-1} (aromatic C=C); mass spectrum $M^+ - Br$ *m/e* 311, 313.

Anal. Calcd for $C_{16}H_8Br_2O_2$: C, 49.01; H, 2.06. Found: C, 48.95; H, 2.18.

Chlorination of **2** affords **4**: mp 192–193 °C (white crystals from methanol); mass spectrum M^+ *m/e* 302, 304, 306.

Anal. Calcd for $C_{16}H_8Cl_2O_2$: C, 63.39; H, 2.67. Found: C, 63.32; H, 2.66.

Registry No.—**1**, 50703-54-3; **2**, 60428-11-7; **3**, 25117-53-7; **4**, 60428-12-8; chlorotrimethysilane, 75-77-4.

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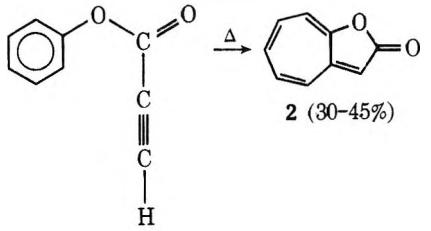
Formation of Tropolone Derivatives (2*H*-Cyclohepta[*b*]furan-2-ones) by the Pyrolysis of Aryl Propiolates

Summary: The flash vacuum pyrolysis of several aryl propiolates gives a 30–45% yield of various 2*H*-cyclohepta[*b*]-furan-2-ones; this reaction thus provides a method for converting phenols to cycloheptane derivatives.

Sir: A few years ago we reported that the flash vacuum pyrolysis (FVP) of phenyl propargyl ether at 460 °C gives substantial yields of 2-indanone (26%) and 1,2-dihydrobenzocyclobutene (31%).[1] The mechanism for the formation of 2-indanone was shown to involve a number of steps which results in a major but well-defined reorganization of atoms.

As an extension of this study we pyrolyzed phenyl propiolate (**1**).[2,3] Surprisingly, the FVP of **1**, carried out at 650 °C and ~10^{-4} Torr as previously described,[4] did not give the expected products analogous to those obtained from the ether but gave instead a fair yield of the tropolone derivative 2*H*-cyclohepta[*b*]furan-2-one (**2**). Lactone **2**[5] and substituted ones[6] have

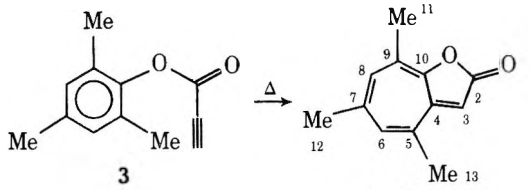


2 (30–45%)

1

been synthesized from 2-chlorotropone and have been converted to a number of cycloheptane derivatives including 2-methyltropone[5] and substituted azulenes.[7] Thus the preparation of **2** from **1** provides the basis for a general procedure for converting phenols to cycloheptane derivatives.

Pyrolysis[4] of 2,4,6-trimethylphenyl propiolate (**3**) (mp 57–58 °C)[2,8] gave a 45–50% yield of **4** (mp 185–186 °C dec): ir

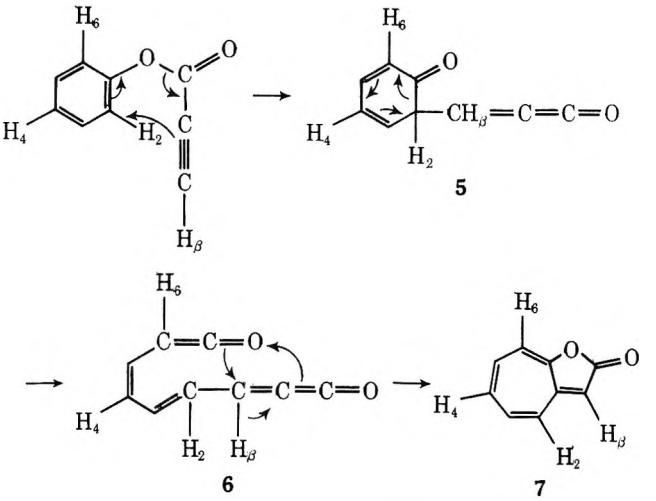


3 **4** (45–50%)

(CCl_4) 1765, 1508, 1239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (s, 1 H), 6.78 (s, 1 H), 5.58 (s, 1 H, H_3), 2.42 (s, 3 H), 2.33 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.84 (C_2), 151.36 (C_4 and C_{10}), 139.08, 137.58, 137.06, 133.94, and 125.17 (C_5 to C_9), 95.42 (C_3), 27.39 (C_{12}, q, J_{C-H} = 128.0 Hz, of t, J_{C-H} = 6 Hz), 24.27 (q, J_{C-H} = 128.0 Hz, of d, J_{C-H} = 7.4 Hz) and 19.72 (q, J_{C-H} = 129.4 Hz, of d, J_{C-H} = 5.9 Hz) (C_{11} and C_{13}).[9] The ^1H NMR signal at δ 5.58 indicates that the three methyl groups are on the seven-membered ring. Long-range proton coupling to the carbon atoms of the methyl groups was used to assign their positions.[10] Two of the methyl group quartets were split into doublets and one of them was split into a triplet. Only the distribution of methyl groups shown will account for these long-range splittings.

The mechanism shown in Scheme I accounts for the positions of the methyl groups of **4**. The formation of intermediate

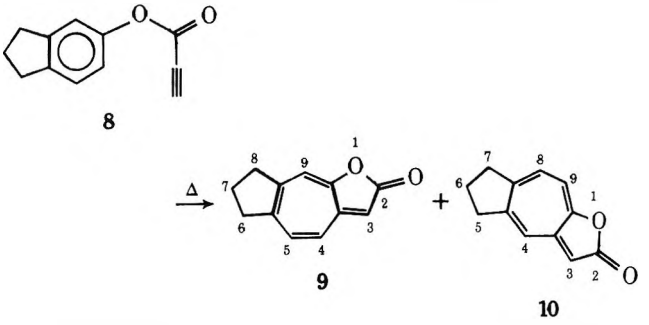
Scheme I



5 **6** **7**

5 by a Claisen-type rearrangement is reasonable even for acetylenic systems[1,11] and methylene ketenes have been observed recently.[12] The sequence of atoms of intermediate **5** is the same as that of the product (**7**) except for the position of H_β. Several reasonable pathways leading from **5** to **7** can be written and the one shown is presented simply to indicate the overall bond changes.

Also consistent with the mechanism shown in Scheme I is the observation that the FVP of **8** (mp 69–70 °C)[2,8] gave a 20% yield of **9** and a 20% yield of **10**. Lactones **9** and **10** were sepa-



8 **9** **10**

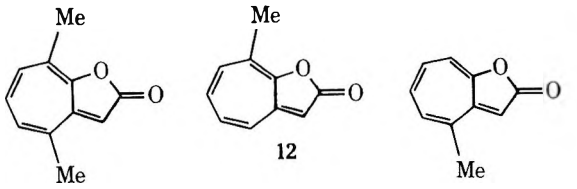
rated by thick layer chromatography using multiple elutions with 25% ethyl acetate in hexane.

Lactone 9: more rapidly moving; mp 118–123 °C dec; ir ($CHCl_3$), 1750, 1615, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 and 7.00 (AB pattern, J_{AB} = 11 Hz), 6.95 (m, 1 H), 5.65 (m, 1 H), 3.0 (m, 4 H), 2.0 (m, 2 H).[9]

Lactone 10: less rapidly moving; mp 96–98 °C dec; ir ($CHCl_3$) 1750, 1600, 1520, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (br s, 1 H), 6.9 (br s, 2 H), 5.60 (s, 1 H), 2.95 (m, 4 H), 2.0 (m, 2 H).[9]

Structure **9** is assigned to the isomer with the low field AB pattern and structure **10** is assigned to the other one with a singlet at δ 7.28 since the following results establish that the ^1H NMR signals at *ca.* δ 7.2 are due to the H_4 protons.

The ^1H NMR spectra of **4** and **11**,[8] which was prepared from the FVP of 2,6-dimethylphenyl propiolate,[2,8] show no signal at *ca.* δ 7.2 and therefore the signals at about δ 7.2 for **9** and **10** must result from the H_4 or H_9 protons. In an effort to assign these signals to either the H_4 or H_9 protons, lactones **12** and **13** were prepared in 50–60% yield by the FVP of o-methylphenyl propiolate (**14**).[2,8] The isomeric lactones were obtained



in a 3:1 ratio and were separated by column chromatography. The major isomer [mp 116–117 °C; NMR ($CDCl_3$) δ 7.40–6.70 (m, 4 H), 5.70 (s, 1 H), 2.43 (s, 3 H); ir ($CHCl_3$) 1740, 1600, 1500, 1265 cm^{-1}][9] was assigned structure **12** because hydrolysis to the acid and decarboxylation of the acid, using a modification of Seto's method,[5] gave 2,7-dimethyltropone[13] [NMR ($CDCl_3$) δ 7.40–6.65 (m, 4 H), 2.30 (s, 6 H); ir ($CHCl_3$) 2980, 1620, 1570, 1365, 1150 cm^{-1}]. The minor isomer **13** [mp 116–116.5 °C (lit.[14] mp 116.5–117.5 °C); NMR ($CDCl_3$) δ 7.21–6.67 (m, 4 H), 5.68 (s, 1 H), 2.39 (s, 3 H); ir ($CHCl_3$) 1750, 1595, 1495, 1260 cm^{-1}][9] gave 2,3-dimethyltropone [mp 59–60 °C (lit.[14] mp 58–59 °C); NMR ($CDCl_3$) δ 7.08–6.67 (m, 4 H), 2.31 (s, 3 H), 2.21 (s, 3 H); ir ($CHCl_3$) 2980, 1630, 1560, 1470, 1365, 1110 cm^{-1}] when submitted to the hydrolysis-decarboxylation procedure. The NMR spectral data of **12** and **13** establish that the signals from **9** and **10** which are shifted slightly downfield from those for the other seven-membered-ring protons result from the H_4 protons.

The comparable yields of **9** and **10** indicate that the fused ring of **8** does not significantly affect the direction of the initial Claisen rearrangement and that both pathways are equally facile. However, the 3:1 ratio of **12** to **13** observed in the FVP of **14** most likely results from a steric effect of the *o*-methyl group.

The production of **10** is especially significant since it possesses the ring system of several guaianolides and pseudoguaianolides, two important classes of sesquiterpene hydroazulenic lactones.[15]

It is not clear why the pyrolysis of aryl propiolates gives different products from those obtained from the pyrolysis of aryl propargyl ethers.[1] It should be noted, however, that the pyrolysis temperatures for the esters are ~200 °C higher than those for the ethers and this temperature difference could be an important factor in accounting for the different reaction pathways.

Acknowledgments. We thank the Mobil Foundation for partial support of this work.

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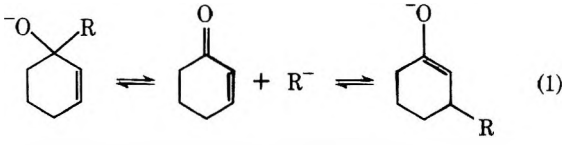
Conjugate and Direct Addition of Ester Enolates to Cyclohexenone. Selective Control of Reaction Composition

Summary: Direct addition of ester enolates to 2-cyclohexen-1-one at −78 °C is reversible at higher temperatures to give products of conjugate addition.

Sir: Reactions of stabilized carbanions with α,β-unsaturated carbonyl systems have received considerable attention during the past decade. Both 1,2 and 1,4 additions have been realized with conjugated enones. For example, dithianes undergo exclusive 1,2 addition;[1] anions of protected cyanohydrins give mixtures of 1,2- and 1,4-addition products.[2] Thioacetal monosulfoxides derived from formaldehyde undergo 1,2 addition; however, higher homologues give predominately 1,4 addition.[3] Although these reactions have been developed into important synthetic methodology, experiments which clearly identify the requirements of direct and conjugate addition have not been described. We wish to communicate our findings concerning reaction of ester enolates with 2-cyclohexen-1-one which, for the first time, demonstrate the importance of experimental parameters in partitioning direct and conjugate addition with stabilized carbanions.

At the outset of our work with ester enolate addition to enones, we had reason to believe that an equilibrium might be established between direct and conjugate addition products (eq 1).[4] Furthermore, we felt that, if kinetic addition occurs



(1)

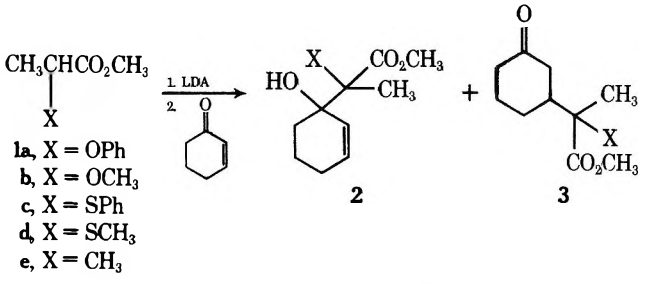
at the carbonyl carbon atom and equilibration leads to conjugate addition, then selective product formation might be possible by careful control of reaction temperature. As the following experiments demonstrate, this is indeed the case for reaction of ester enolates with 2-cyclohexen-1-one.

The ester enolate of methyl-2-phenoxypropionate (**1a**) is generated by addition of a tetrahydrofuran (THF) solution of **1a** to 1 equiv of lithium diisopropylamide (LDA), prepared in the usual manner[5] in THF at −78 °C. Addition of 1 equiv of 2-cyclohexen-1-one and stirring for 30 min, followed by careful quenching with saturated ammonium chloride solution at −78 °C, gives allylic alcohol **2a** (89% yield) and ketone **3a** (7%, bp 142–146 °C at 0.07 mm).[6] On the other hand, if the reaction mixture is warmed to 25 °C before quenching with water, ketone **3a** is the major reaction product (84% distilled yield). When a solution of pure **2a** (isolated as an oil by preparative, medium pressure, liquid chromatography) is added to 1 equiv of LDA at −78 °C and then is warmed to 25 °C, **3a** can be isolated in 91% yield.

Table I. Product Distribution as a Function of Reaction Temperature for Addition of Ester Enolates to 2-Cyclohexen-1-one

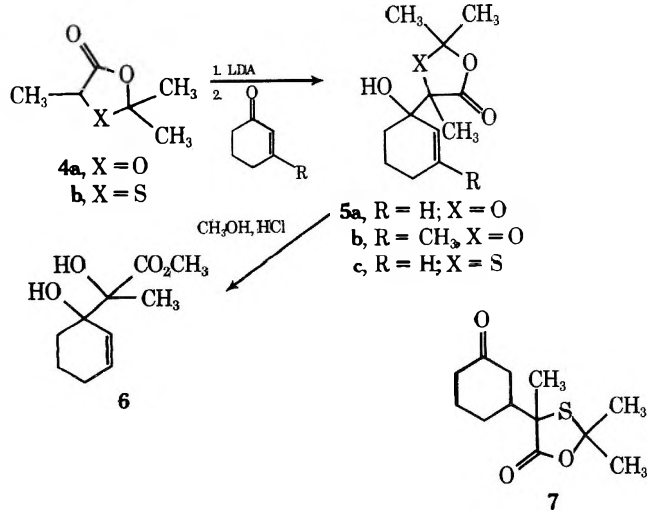
	−78 °C reaction		25 °C reaction	
Ester	% 1,2 addition	% 1,4 addition	% 1,2 addition	% 1,4 addition[a]
1a	88	8		84
1b	75	12	5	62[b]
1c		75		86
1d	63	7		85
1e	88	5	7	83

[a] Isolated yields; all other yields were determined by NMR and VPC analysis. Our limits of detectability were estimated to be ≤2%. [b] With shorter reaction time, yields were ~85–90%; however, much more 1,2-addition product was present.



We also have examined the reactivity of four other enolates derived from α-substituted methyl propionates and the results are presented in Table I. With ester enolates derived from **1b, 1d,** and **1e,** the 1,2-addition products **2b, 2d,** and **2e** were isolated and, as with **2a,** undergo conversion to **3b, 3d** and **3e,** respectively when treated with LDA at −78 °C and then warmed to 25 °C. Thus, kinetic addition is predominately (if not exclusively) taking place at the carbonyl carbon atom. Conjugate addition products arise by reversible formation of 1,2 adducts and subsequent 1,4 addition. With the ester enolate of methyl-2-thiophenoxypropionate (**1c**), however, equilibration occurs even at −78 °C (see Table I).

An interesting change in enolate reactivity was observed with the acetonide **4a.** Reaction with cyclohexenone at either −78 or 25 °C over prolonged reaction times gives only the product of 1,2 addition, **5a** (82% isolated yield, bp 93–95 °C



at 0.05 mm, chemical ionization mass spectrum *m/e* 227). Substitution of 3-methyl-2-cyclohexen-1-one for cyclohexenone gives only **5b,** isolated in 80% yield. When reaction of the ester enolate of **4a** with cyclohexenone is performed as usual, but is followed by addition of 1 equiv of 3-methylcyclohexenone with stirring for 1 h at 25 °C, only **5a** and unreacted 3-methylcyclohexenone are recovered. Clearly, with the enolate of **4a** and cyclohexenone, 1,2 addition is irreversible under these reaction conditions. With thiaacetonide **4b,** however, 1,2 addition is reversible and gives the product of conjugate addition **7** at 25 °C.

Thus, we have shown that, by simple structural modifications (e.g., **1a** and **1b** compared to **4a**) and careful control of reaction temperature, it is possible to direct ester enolates to either direct or conjugate addition with cyclohexenone. Furthermore, we note that the product of acetonide 1,2 addition, **5,** may be converted to the allylic pinacol **6** in nearly quantitative yield on treatment with methanolic hydrogen chloride, thus providing an exceptionally simple synthesis of this useful functionality.

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA 16624-02).

References and Notes

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(2) G. Stork and L. Maldonado, *J. Am. Chem. Soc.,* **96,** 5272 (1974), and references cited therein.
(3) J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.,* 3271 (1973).
(4) This type of equilibration may occur in the addition of other stabilized carbanions to enones; for example, see ref 2.
(5) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.,* **93,** 2318 (1971).
(6) For examples of conjugate addition of simple ester enolates to Michael acceptors in which 1,2-addition is precluded, see J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Lett.,* 4711 (1973). A dithiane ester enolate derived from ethyl glyoxalate undergoes 1,4 addition with 5,5-dimethyl-3-chloro-2-cyclohexen-1-one, presumably at −78 °C, in 94% yield: J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *ibid.,* 2599 (1973). In light of this example, note our results with the ester enolate derived from **1c.**

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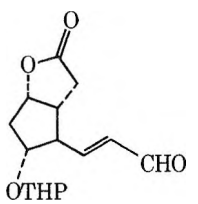
Prostaglandin Metabolites. Synthesis of E and F Urinary Metabolites

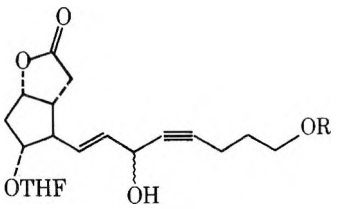
Summary: The synthesis of major urinary metabolites of E prostaglandins, 11α-hydroxy-9,15-dioxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid (**7a**), and F prostaglandins, 9α,11α-dihydroxy-15-oxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid δ-lactone (**8a**) is described.

Sir: The structure of the major human urinary metabolites of PGE_2[1] and $PGF_{2\alpha}$[2] has been determined by mass spectral analysis. The synthesis of those various metabolites have been reported.[3] We wish to report a highly efficient synthesis of one of the major human urinary metabolites of the PGE series, 11α-hydroxy-9,15-dioxo-2,3,5,20-pentanor-19-carboxyprostanoic acid (**7a**), and PGF series, 9α,11α-dihydoxy-15-oxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid δ-lactone (**8a**).[4]

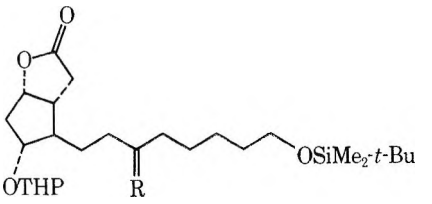
The synthesis was designed to meet three important considerations: (1) the incorporation of deuterium or tritium could be easily accomplished, to enable synthesis of labeled metabolites; (2) the steps involved should be simple and efficient; (3) the intermediates should be flexible enough to allow for possible variations. The present synthesis meets those criteria and allows the synthesis of both E and F metabolites from a common precursor, **6a.**



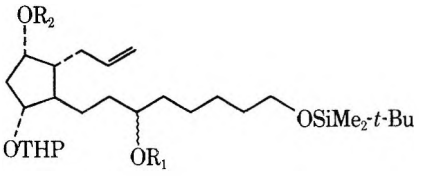
1



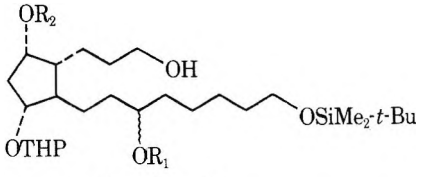
2a, R = $SiMe_2$-*t*-Bu
b, R = $SiMe_3$
c, R = H



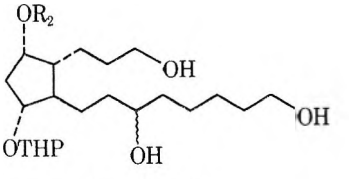
3a, R = OH, H
b, R = $OSiMe_2$-*t*-Bu, H
c, R = O



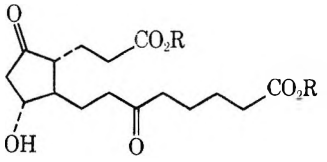
4a, R_1 = R_2 = H
b, R_1 = $SiMe_2$-*t*-Bu; R_2 = H
c, R_1 = $SiMe_2$-*t*-Bu; R_2 = THP



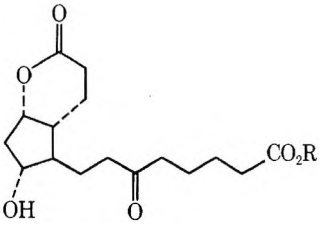
5a, R_1 = R_2 = H
b, R_1 = $SiMe_2$-*t*-Bu; R_2 = THP



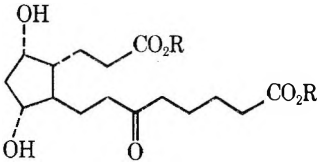
6a, R = H
b, R = THP



7a, R = H
b, R = CH_3



8a, R = H
b, R = CH_3



9a, R = H
b, R = CH_3

The synthesis started from a versatile lactone–aldehyde intermediate, **1**.[5] When the lactone–aldehyde reacted with 1~1.2 equiv of 1-dimethyl-*tert*-butylsilyloxy-4-pentynyllithium[6] at −70~−60 °C in THF (20–30 min), the adduct, **2a**, was isolated in 65~75% yield: ir (cm^{-1}) 3420, 2220, 1775, 975; NMR (CCl_4, δ) 5.72~5.52 (m, 2 H, –CH=CH–), 5.14~4.52 [m, 3 H, –OCHO–, –CHOCO–, –C=CCHC≡C–], 0.86 (s, 9 H, –OSi-*t*-Bu); high resolution mass spectrum (as TMS derivative) $M^+ - C_4H_9$ 493.2433 (calcd for $M^+ - C_4H_9$, $C_{22}H_{41}Si_2O_6$, 493.2442).[7] Catalytic (5% rhodium on alumina, in ethyl acetate) hydrogenation of **2a** yielded 63% **3a** and 25% **3c** (ir 1780, 1710 cm^{-1}). On the other hand, when the hydrogenation was followed by sodium borohydride reduction (−10~0 °C in methanol), **3a** was obtained in better than 90% yield: ir (cm^{-1}) 3460, 1775; NMR (CCl_4, δ) 5.10~4.80 (m, 1 H, –CHOCO–), 4.76~4.54 (m, 1 H, –OCHO–), 4.18~3.28 (m, 6 H, –CHO–, $-CH_2O-$), 0.88 (s, 9 H, –Si-*t*-Bu).

The extension of the upper side chain by one extra carbon was easily accomplished via the following sequence. Diisobutylaluminum hydride reaction of lactone **3a** (−70~−60 °C in toluene, 1 h) followed by Wittig reaction (ylide generated from methyltriphenylphosphonium bromide and *n*-butyllithium in THF, 4 h at room temperature) afforded the diol, **4a**, in 75% yield: ir (cm^{-1}) 3440, 3080, 1640; NMR (CCl_4, δ) 6.30~4.80 (m, 3 H, $-CH=CH_2$); high resolution mass spectrum (as TMS derivative) $M^+ - C_5H_9O$ 543.3726 (calcd for $C_{28}H_{59}Si_3O_4$, 543.3721). Hydroboration-9-BBN oxidation[8] gave the triol, **5a**, in 90% yield after purification by high pressure liquid chromatography: NMR ($CDCl_3$, δ) 4.76~4.54 (m, 1 H, –OCHO–), 4.24~3.24 (m, 9 H, –CHO–, $-CH_2O-$), 0.88 (s, 9 H, –Si-*t*-Bu); high resolution mass spectrum (as TMS derivative) $M^+ - C_5H_9O$ 633.4208 (calcd for $C_{31}H_{69}Si_4O_5$, 633.4222). Treatment of the triol, **5a**, with tetra-*n*-butylammonium fluoride in THF[9] yielded the tetraol,[10] **6a**: NMR ($CDCl_3$, δ) 4.80~4.50 (m, 1 H, –OCHO–), 4.30~3.30 (m, 9 H, –CHO–, $-CH_2O-$); high resolution mass spectrum (as TMS derivative) M^+ 676.4410 (calcd for $C_{33}H_{72}Si_4O_6$, 676.4406). The most difficult steps in the sequence were the conversion of the tetraol, **6a**, to the final products (**7a** and **8a**). Difficulties in purification and isolation of the diacid (**7a**) and lactone–acid (**8a**) added to the problem. Jones oxidation (−10~0 °C, 10 min) followed by hydrolysis [HOAc–THF–H_2O (3:1:1) at 40 °C for 4 h] and purification via high pressure liquid chromatography afforded 30~35% **7a** and 20~25% **8a** in pure form. The structure of **7a** was confirmed by analysis of the dimethyl ester, **7b**: ir (cm^{-1}) 3500, 1750, 1740, 1710; NMR ($CDCl_3$, δ) 4.32~3.80 (m, 1 H, –CHO–), 3.68 (s, 6 H, $-CO_2CH_3$); high resolution mass spectrum (as TMS derivative) M^+ 428.2224 (calcd for $C_{21}H_{36}SiO_7$, 428.2230). The GC–mass spectrum of **7b** (as methyl oxime–TMS derivative) showed a pattern identical with that obtained from the authentic PGE_2 urinary metabolites, M^+ 486.[1,11] The structure of **8a** was also confirmed by analysis of its methyl ester, **8b**: ir (cm^{-1}) 3460, 1740, 1715; NMR ($CDCl_3$, δ) 4.90~4.50 (m, 1 H, –CHOCO), 4.10~3.60 (m, 1 H, –CHO–), 3.68 (s, 3 H, $-CO_2CH_3$); high resolution mass spectrum (as TMS derivative), M^+ 398.2101 (calcd for $C_{20}H_{34}SiO_6$, 398.2125). The GC–mass spectrum of **8b** (as methyl oxime–TMS derivative) also showed a pattern identical with that obtained from the authentic $PGF_{2\alpha}$ urinary metabolites, M^+ 427.[2,12]

The structure of lactone–ester, **8b**, was further confirmed by an independent synthesis. Protection of the free hydroxyl group **3a** by dimethyl-*tert*-butylsilyl group[9] gave **3b**. Without purification of **3b**, diisobutylaluminum hydride reduction was followed by Wittig reaction to give **4b** (84%). Protection of the new free hydroxyl group as its tetrahydropyranyl ether (**4c**, 95%) followed by hydroboration–9-BBN oxidation[8] afforded **5b** (93%). Removal of the dimethyl-*tert*-butylsilyl groups (tetra-*n*-butylammonium fluoride),[9] Jones oxidation, hydrolysis, and methylation with diazomethane gave **8b** in 31% overall yield. Spectral analyses and TLC mobility were identical with those of **8b** obtained from **8a** described previously.

Procedure for 6a → 7a + 8a. A solution containing 776 mg (2.0 mmol) of **6a** in 20 ml of acetone was cooled to −10~5 °C and 4.5 ml (12 mmol) of Jones reagent (2.67 M) diluted with 60 ml of acetone was added dropwise over a period of 5 min. After stirring an additional 5 min at −5~0 °C, the reaction was stopped by addition of 5 ml of 2-propanol (or aqueous sodium bisulfite). Acetone was removed under reduced pressure and the residue was extracted with ethyl acetate (3 × 300 ml). The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration in vacuo afforded the oxidation product. Without purifying, this product was stirred in 10 ml of HOAc–H_2O–THF (3:1:1) at 40~45 °C for 5 h. The reagent was removed under reduced pressure with occasional addition of toluene to facilitate the removal of acetic acid and water. The residue was purified by HPLC [68 g of 30~50-μ silica gel; the column was washed with 300 ml of 5% HOAc in EtOAc, followed by 300 ml of EtOAc–hexane (3:1) before the injection of sample; 30 ml/fraction was collected; EtOAc–hexane (3:1) elution, fractions 1–40; EtOAc elution, fractions 41–100]. The fractions homogeneous on TLC analysis [A-IX[13]–HOAc (10:1)] were collected. The following were isolated: pure **7a** (fractions 19–47, 234 mg, 35%, amorphous solid), NMR ($CDCl_3$ + 10% CD_3OD, δ) 4.32~3.80, (m, 1 H, –CHO–); **8a** (fractions 52–100, 135 mg, 21%), NMR ($CDCl_3$, δ) 4.72 (br s, 2 H, $-CO_2H$, –OH), 4.90~4.50 (m, 1 H, –CHOCO–), 4.10~3.60 (m, 1 H, –CHO–). The diacid, **7a**, is stable at room temperature for only a few

days. A very slow formation of less polar product (A-type metabolite) is observed. In the freezer, the dehydration occurs considerably slower. The δ-lactone–hydroxy acid, **8a**, by standing at room temperature, forms additional polar spot on TLC. It appears that the equilibrium mixture of δ-lactone–hydroxy acid and dihydroxy diacid is formed.[4]

Acknowledgment. The author wishes to thank Mr. J. R. Boal for running the GC–mass spectra and also Dr. R. C. Kelly and Dr. H. A. Karnes for making the starting material available. Helpful discussions with Dr. J. E. Pike of these laboratories are also acknowledged.

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(1) (a) M. Hamberg and B. Samuelsson, *J. Am. Chem. Soc.*, **91**, 2177 (1969); *J. Biol. Chem.*, **246**, 6713 (1971). (b) M. Hamberg, *Biochem. Biophys. Res. Commun.*, **49**, 720 (1972).
(2) (a) E. Granström and B. Samuelsson, *J. Biol. Chem.*, **246**, 5254 (1971); (b) J. C. Cornette, K. T. Kirton, W. P. Schneider, F. F. Sun, R. A. Johnson, and E. G. Nidy, *Prostaglandins*, **9**, 323 (1975).
(3) (a) J. R. Boot, M. J. Foulis, N. J. A. Gutteridge, and C. W. Smith, *Prostaglandins*, **8**, 439 (1974); (b) D. Taub, Z. S. Zelawski, and N. L. Wendler, *Tetrahedron Lett.*, 3667 (1975); (c) E. G. Nidy and R. A. Johnson, *J. Org. Chem.*, **40**, 1415 (1975).
(4) Treatment of **8a** with base followed by reaction with diazomethane gave **9b**. However, it always resulted in equilibrium mixture of lactone (**8b**) and hydroxy ester (**9b**). (Observation by Dr. W. P. Schneider of these laboratories.)
(5) The synthesis of this versatile intermediate (with natural prostaglandin configuration) will be published shortly by Dr. R. C. Kelly of these laboratories.
(6) 1-Dimethyl-*tert*-butylsilyloxy-4-pentynyllithium was obtained in situ by reacting the corresponding alkyne with methyllithium at −20∼−10 °C for 10 min. The alkyne, 1-dimethyl-*tert*-butylsilyloxy-4-pentyne [bp 65 °C (9 mm)] was easily obtained by silylation[9] of 4-pentyn-1-ol (Farchan Co.).
(7) A similar result was obtained when 1-trimethylsilyloxy-1-pentyne was used (**1** → **2b**). Hydrolysis of trimethylsilyl group gave lactone–diol (**2c**) in 85% overall yield.
(8) C. G. Scouten and H. C. Brown, *J. Org. Chem.*, **38**, 4092 (1973).
(9) E. J. Corey and A. Venkateswarlu, *J. Org. Chem.*, **94**, 6190 (1972).
(10) Because of the similar solubility of both the tetraol, **6a**, and the reagent toward solvent and water, it became very difficult to remove the excess reagent. One solution to this problem was to prepare the TMS derivative directly from the reaction mixture. Extraction with hexane followed by aqueous washing removed the reagent. TMS groups were easily removed by stirring in 5% potassium carbonate in methanol–water (4:1).
(11) We thank Dr. E. G. Daniels of these laboratories for providing the GC–mass spectrum of the authentic sample for the comparison. He has identified this metabolite from the urine of single dose injection of PGE_2 into rats and rhesus monkeys: private communication from Dr. E. G. Daniels.
(12) We thank Dr. F. F. Sun and Dr. W. P. Schneider of these laboratories for providing us with the GC–mass spectrum of the authentic sample for the comparisons. See also F. F. Sun, *Biochim. Biophys. Acta*, **348**, 249 (1974); F. F. Sun and J. E. Stafford, *ibid.*, **369**, 95 (1974).
(13) M. Hamburg and B. Samuelsson, *J. Biol. Chem.*, **241**, 257 (1965).

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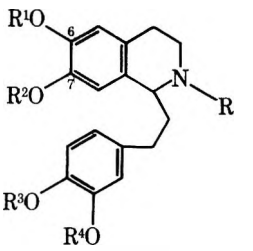
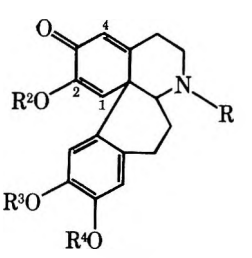
Novel Nonphenol Oxidative Coupling of Phenethylisoquinolines[1]

Summary: Oxidative coupling of nonphenolic phenethylisoquinolines **1a–c** with VOF_3–TFA gave homoaporphines **4a,g,h** in high yields via homoproerythrinadienone intermediates (e.g., 8).

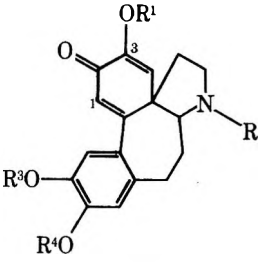
Sir: Nonphenol oxidative coupling reactions which yield spirodienone intermediates and products are currently subjects of great interest.[2–8] The first practical syntheses of this type involved electrooxidative coupling of benzylisoquinolines to morphinandienones.[2–4] Recent reports have also described the chemical intramolecular coupling of nonphenolic benzylisoquinolines with vanadium oxytrifluoride in trifluoroacetic acid (TFA) and demonstrated that the oxidations proceed via morphinandienone intermediates.[6–8] We report herein novel nonphenol oxidative coupling reactions



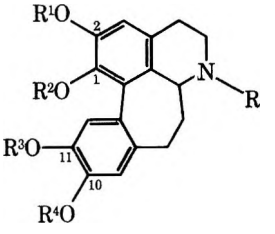
1a, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
b, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
c, $R^2 = CH_2Ph$; $R^1 = R^3 = R^4 = CH_3$; $R = COCF_3$
d, $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$; $R = COCF_3$
e, $R^2 = R^3 = H$; $R^1 = R^4 = R = CH_3$
f, $R^1 = R^2 = R^3 = R^4 = R = CH_3$



2a,c,d



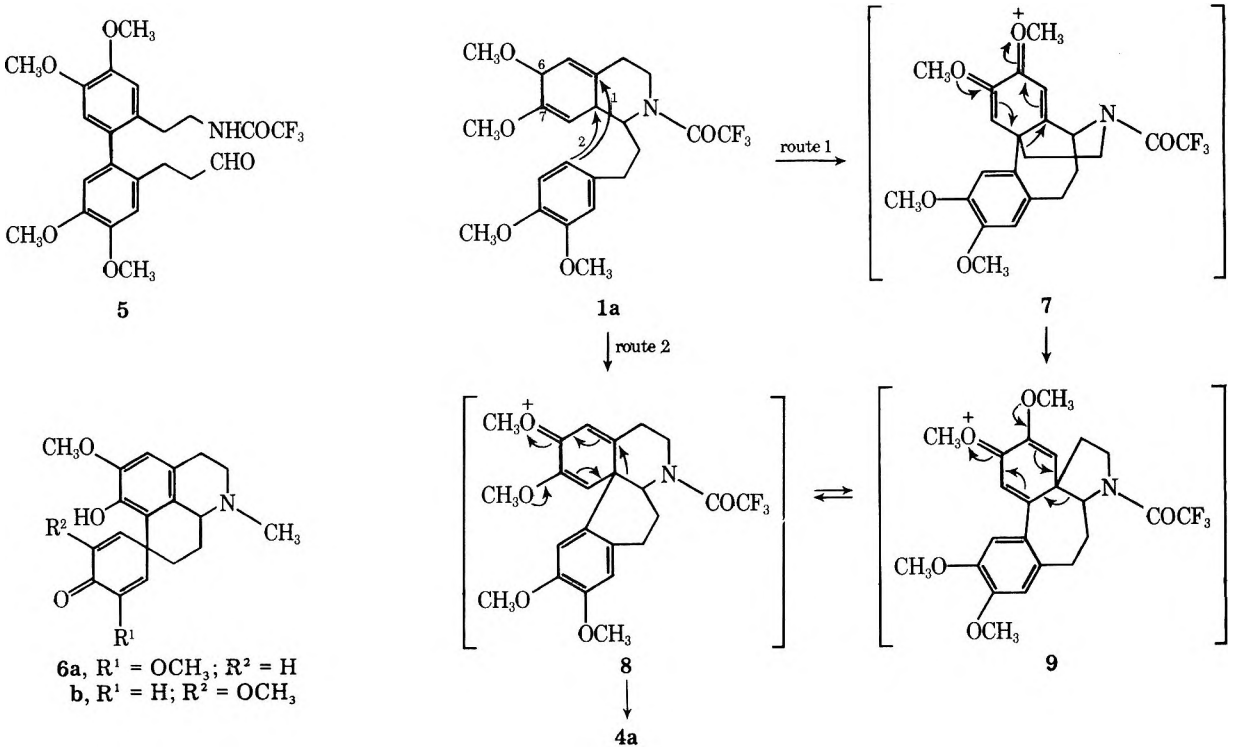
3a,b



4a,e,f
4g, $R^1 = H$; $R^2 = R^3 = R^4 = CH_3$; $R = COCF_3$
h, $R^2 = H$; $R^1 = R^3 = R^4 = CH_3$; $R = COCF_3$

of phenethylisoquinolines **1a–c** using VOF_3–TFA which yield homoaporphines **4a,g,h** via homoproerythrinadienone intermediates (e.g., 8).

Treatment of a solution of (±)-*N*-trifluoroacetylhomonorlaudanosine (**1a**)[9,10] in CH_2Cl_2 and TFA[11] at −10 °C with VOF_3 in TFA for 10 min followed by aqueous workup gave homoproerythrinadienone **2a** (5%, mp 161–162 °C), homoneospirinedienone **3a** (64%, mp 171.5–172 °C), homoaporphine **4a** (2%, mp 167–169 °C), and aldehyde **5** (22%, mp 143–144 °C). To confirm the structure of **2a**, diphenolic precursor **1d** was first oxidized with VOF_3–TFA to homoproerythrinadienone **2d**[12] (78%); subsequent O-methylation of **2d** with diazomethane gave **2a**. In contrast to the acid-catalyzed rearrangement of proerythrinadienones to neospirinedienones,[13] homoproerythrinadienone[14] **2a** and homoneospirinedienone **3a** rearranged to homoaporphines **4g** (87%, mp 221–222 °C) and **4h** (84%, mp 200–201 °C), respectively, upon treatment with BF_3–Et_2O in CH_2Cl_2 at room temperature for 24 h. Treatment of **4g** and **4h** with diazomethane yielded **4a**. The structure of 1,2,10,11-tetrasubstituted homoaporphine **4a** was confirmed by an unambiguous synthesis. Thus oxidation of **1e** with VOF_3–TFA gave diastereoisomeric homoproaporphines[15] **6a** (38%, mp 193–194 °C dec; melting point, ir, uv, and NMR in good agreement with those of (±)-kreysiginone[16a]) and **6b** [30%, mp 198–200 °C dec (lit.[16a] mp 202 °C dec)]. Treatment of **6a** with BF_3–Et_2O in CH_2Cl_2 afforded diphenolic homoaporphine **4e** [87%, mp 185.5–187 °C (lit.[17] 185–187 °C)], which on methylation with diazomethane gave tetramethoxyhomoaporphine **4f**[18] (70% as the hydrochloride; mp 222–224 °C dec; melting point, mixture melting point, TLC, uv, NMR, and mass spectrum identical with those of a sample prepared by alkaline hydrolysis of **4a** followed by N-methylation with HCHO–$NaBH_4$).



5

1a

7

6a, R^1 = OCH_3; R^2 = H
b, R^1 = H; R^2 = OCH_3

8

4a

9

The rearrangement of homoneospirinedienone **3a** to 1,2,10,11-tetrasubstituted homoaporphine **4h** indicates the intermediacy of a homoproerythrinadienone (e.g., **8**), a route supported by the observed facile rearrangement of homoproerythrinadienone **2a** to homoaporphine **4g.** The demonstrated conversions[7] of (±)-*N*-acylnorlaudanosines to (±)-*N*-acylmorphinandienones and thence to (±)-*N*-acylneospirinedienones in nonphenol oxidative coupling of benzylisoquinolines with VOF_3–TFA led us to consider also the possibility that the conversion of phenethylisoquinoline **1a** to homoaporphine **4a** might proceed via route 1: **1a** → **7** → **9** → **8** → **4a.** To investigate this possibility the 6-benzyloxy (**1b**) and 7-benzyloxy (**1c**) analogues of (±)-*N*-trifluoroacetylhomonorlaudanosine (**1a**) were oxidized with VOF_3–TFA for 10 min. Thus **1b** gave **2a** (50%) and **3b** (42%, mp 169–170 °C, 3-benzyloxy analogue of **3a**), whereas **1c** gave **2b** (3%, mp 134–134.5 °C, 2-benzyloxy analogue of **2a**) and **3a** (60%). These results preclude route 1, via homomorphinandienone-type intermediates (e.g., **7**), and confirm route 2, via homoproerythrinadienone-type intermediates (e.g., **8**), for the formation of homoneospirinedienones **3a,b** from phenethylisoquinolines **1a–c.** Furthermore, the homoproerythrinadienone-type intermediates (e.g., **8**) and homoneospirinedienone-type intermediates (e.g., **9**) appear to be in equilibrium in the reaction medium. It was thought that isolation of **2a** and **3a** in high yields in the oxidations of **1b** and **1c,** respectively, could indicate shifts of equilibria due to easy cleavage of the benzyl groups from the corresponding benzyloxonium ions. This was confirmed by isolation of **2a** (71%, no appreciable amount of **3b**) and **3a** (65%, no appreciable amount of **2b**) upon treatment of **1b** and **1c,** respectively, with VOF_3–TFA for ~1 h.

The foregoing mechanistic considerations and demonstrated facile rearrangement of homoproerythrinadienone **2a** and homoneospirinedienone **3a** to homoaporphines **4g** and **4h,** respectively, suggested that homoaporphines might be obtained directly from the phenethylisoquinolines if enough time were allowed for rearrangement of the corresponding homoproerythrinadienone-type (e.g., **8**) and homoneospirinedienone-type intermediates (e.g., **9**). Indeed, the phenethylisoquinolines **1a, 1b,** and **1c** gave homoaporphines **4a** (84%), **4g** (80%), and **4h** (65%), respectively, upon treatment with VOF_3–TFA for several hours.

The conversion of homoproerythrinadienone **2d** to dibenz[*d,f*]azecine, a key homoerythrina alkaloid precursor, has recently been reported.[19] In view of the close similarity in structure of homoproerythrinadienones and homoneospirinedienones, the latter may as well be a precursor of dibenz[*d,f*]azecine. Studies aimed at efficient synthetic routes to homoerythrina alkaloids using homoproerythrinadienones and homoneospirinedienones are in progress.

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(1) This investigation was supported by grants from the National Cancer Institute (CA-12059) and the American Cancer Society (CI-102K).
(2) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **93**, 5941 (1971); **95**, 2651 (1973).
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(5) M. Sainsbury and R. F. Shinazi, *J. Chem. Soc., Chem. Commun.*, 718 (1972).
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(7) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *J. Am. Chem. Soc.*, **97**, 5622 (1975).
(8) S. M. Kupchan and C.-K. Kim, *J. Am. Chem. Soc.*, **97**, 5623 (1975).
(9) Phenethylisoquinolines **1a–c** were prepared by the Bischler–Napieralski procedure and subsequent N-acetylation with trifluoroacetic anhydride in pyridine. Cf. S. Teitel and A. Brossi, *J. Heterocycl. Chem.*, **5**, 825 (1968); A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J. Chem. Soc., Perkin Trans. 1*, 1741 (1972).
(10) All new compounds were characterized by concordant analytical and spectral data. The structural formulas containing asymmetric atoms refer to racemic mixtures.
(11) In a typical oxidation 1 mmol of the substrate [0.05 M solution in methylene chloride containing 20% TFA–TFAA (20:1 by weight)] was treated with 2.5 molar equiv of VOF_3 [dissolved in a minimum volume of a 1:1 solution of ethyl acetate and TFA–TFAA (20:1 by weight)].
(12) The homoproerythrinadienone **2d** was previously obtained in 35% yield by oxidation of **1d** using $VOCl_3$ in CH_2Cl_2.[14]
(13) T. Kametani, R. Charubala, M. Ihara, M. Koizumi, K. Takahashi, and K. Fukumoto, *J. Chem. Soc. C*, 3315 (1971); T. Kametani, K. Takahashi, T. Honda, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, **20**, 1793 (1972).
(14) J. P. Marino and J. M. Samanen, *Tetrahedron Lett.*, 4553 (1973).
(15) The homoproaporphines **6a,b** were previously obtained in 31% and 36.6% overall yield by oxidation of **1e** using potassium ferricyanide[16a] and ferric chloride,[16b] respectively.
(16) (a) A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Commun.*, 934 (1967); A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *J. Chem. Soc., Perkin Trans. 1*, 1394 (1974). (b) T. Kametani, K. Fukumoto, H. Yagi, and F. Satoh, *Chem. Commun.*, 878 (1967); *J. Org. Chem.*, **33**, 690 (1968).

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(18) The tetramethoxyhomoaporphine **4f** was also obtained in 40% yield by treatment of **1f** in FSO_3H, CH_2Cl_2, and TFA with VOF_3 in TFA.
(19) J. P. Marino and J. M. Samanen, *J. Org. Chem.*, **41**, 179 (1976).

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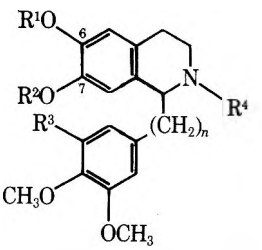
Efficient Intramolecular Monophenol Oxidative Coupling[1]

Summary: The remarkably efficient intramolecular oxidative couplings of monophenolic benzyltetrahydroisoquinolines **1a,b** to aporphines **4a,b** and of monophenolic phenethyltetrahydroisoquinolines **1c–g** to homoaporpines **4c–f**, spirodienones **2c–f**, and **6** are described.

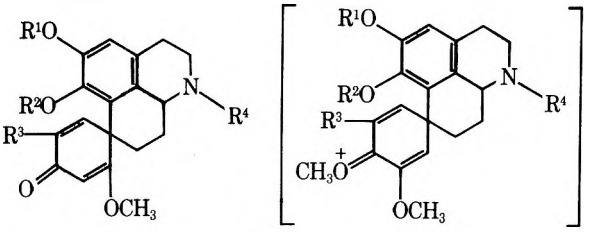
Sir: The important role played by diphenol oxidative coupling in the biosynthesis of alkaloids has been well documented and reviewed.[2] In general, laboratory attempts to effect intramolecular oxidative coupling of diphenols have suffered from low yields, mainly attributable to overoxidation. Recently, attention has been directed toward utilization of monophenolic substrates in an attempt to develop effective intramolecular oxidative coupling methods for use in alkaloid synthesis.[3–5] We report herewith the remarkable efficiency of the monophenol oxidative coupling method using VOF_3 for the syntheses of aporphines **4a,b**, homoproaporphines **2c–f**, homoaporphines **4c–f**, and homoproerythrinadienone **6**.

Treatment of a solution of (±)-*N*-trifluoroacetylnorcodamine (**1a**)[6,7] in CH_2Cl_2 with VOF_3 in trifluoroacetic acid (TFA)[8] at −10 °C for 10 min followed by aqueous workup gave (±)-*N*-trifluoroacetylwilsonirine[9] (**4a**, 70%, mp 196.5–197 °C) along with morphinandienone **5a**[10,11] (8%, mp 179.4–181.5 °C). Under the same conditions, oxidation of (±)-codamine (**1b**) gave a complex mixture of products from which only (±)-thalicmidine [**4b**, 38%, mp 191–193 °C dec (lit.[12] 190–192 °C)] was isolable. In contrast, an 80% overall yield of (±)-thalicmidine (**4b**) was obtained upon treatment of the borane complex[13] of **1b** with VOF_3–TFA (15 min at −10 °C) and subsequent removal of the blocking group by heating with anhydrous Na_2CO_3 in methanol under reflex. Morphinandienone **5b** could not be detected by thin layer chromatography in either of the latter experiments. The facile and high-yield conversions of **1a,b** to **4a,b** constitute the most efficient reported route to 1,2,9,10-tetrasubstituted aporphines.

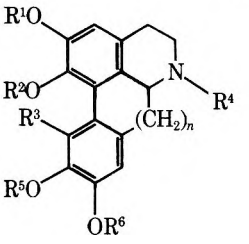
To evaluate the potential of the monophenol oxidative coupling method for the syntheses of homoaporphines and of homomorphinandienones such as the colchicine precursor *O*-methylandrocymbine,[14] 7-hydroxy-1-phenethyltetrahydroisoquinolines **1c–f** were prepared[7] and oxidized with VOF_3–TFA at −10 to −15 °C for 5–10 min. Thus the oxidation of **1c** yielded homoaporphine **4c**[15] (40%) along with homoproaporphine **2c** (18%, mp 192.5–193.5 °C), and **1d** gave homoproaporphine **2d** [42%, mp 200–201 °C dec (lit.[16] 200–202 °C)] along with homoaporphine **4d** [14%, mp 190–192 °C (lit.[17] 195–196 °C)]. Only one isomer of homoproaporphine **2c** or **2d** was obtained, in contrast to the diasteroisomeric mixture obtained by oxidation of diphenolic precursor **1d**.[15,16,18] Similarly, oxidation of **1e** yielded homoaporphine **4e** (46%, mp 161–162 °C) along with homoproaporphine **2e** (4%, mp 207–210 °C dec), and **1f** gave homoproaporphine **2f** [54%, mp



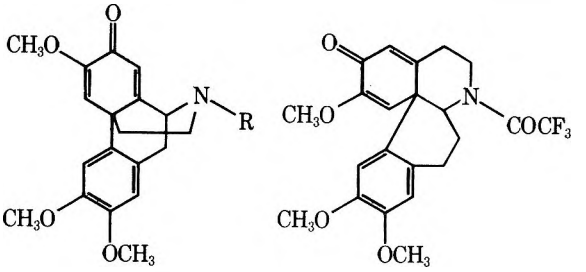
1a, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = COCF_3$; $n = 1$
b, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$; $n = 1$
c, $R^1 = CH_3$; $R^2 = R^3 = H$; $R^4 = COCF_3$; $n = 2$
d, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$; $n = 2$
e, $R^1 = CH_3$; $R^2 = H$; $R^3 = OCH_3$; $R^4 = COCF_3$; $n = 2$
f, $R^1 = R^4 = CH_3$; $R^2 = H$; $R^3 = OCH_3$; $n = 2$
g, $R^1 = R^3 = H$; $R^2 = CH_3$; $R^4 = COCF_3$; $n = 2$



2c–f **3c–f**



4a–f, $R^5 = R^6 = CH_3$
h, $R^1 = R^5 = CH_3$; $R^2 = R^3 = R^6 = H$; $R^4 = COCF_3$; $n = 2$
i, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = R^6 = H$; $n = 2$
j, $R^1 = R^6 = CH_3$; $R^2 = R^5 = H$; $R^3 = OCH_3$; $R^4 = COCF_3$; $n = 2$
k, $R^1 = R^4 = R^6 = CH_3$; $R^2 = R^5 = H$; $R^3 = OCH_3$; $n = 2$



5a, $R = COCF_3$
b, $R = CH_3$ **6**

174–176 °C (lit.[16] 176–178 °C)] along with (±)-kreysigine [**4f**, 16%, mp 185–186 °C (lit.[16] 187–189 °C)]. No homomorphinandienone could be detected by thin layer chromatography in any of the above experiments. Homoproaporphines **2c**, **2d**, **2e**, and **2f** underwent smooth dienone–phenol rearrangements[16,19] upon treatment with BF_3–Et_2O in CH_2Cl_2 at room temperature[20] and afforded homoaporphines **4h** (93%, mp 167–168 °C), **4i** [70%, mp 241–242 °C dec (lit.[19] 241–242 °C)], **4j** (87%, mp 208–208.5 °C), and **4k** [(±)-multifloramine, 72%, mp 185–188 °C dec (lit.[16] 190–192 °C dec)], respectively. The formation of homoproaporphines **2c–f** and of homoaporphines **4c–f** in the oxidations of phenethyltetrahydroisoquinolines **1c–f**, and the demonstrated facile acid-catalyzed rearrangements of homoproaporphines **2c–f** to homoaporphines **4h–k** suggested that the formation of homoaporphines **4c–f** from monophenolic phenethyltetrahydroisoquinolines **1c–f** may proceed via homoproaporphine-type intermediates (**3c–f**)

and, in part, via direct coupling. Thus, the homoaporphines **4c–f** might be obtained in high yields if enough time were allowed for rearrangement of the corresponding homoproaporphine-type intermediates. Indeed, the phenethylisoquinolines[21] **1c, 1d,** and **1e** gave homoaporphines **4c** (77%), **4d** (60%), and **4e** (54%), respectively, upon treatment with VOF_3–TFA for 30–50 min.

Finally, 6-hydroxy-1-phenethyletetrahydroisoquinoline **1g** was subjected to the VOF_3–TFA oxidation (10 min at −10 °C) and homoproerythrinedienone **6**[15] was obtained in 98% yield.

The smooth intramolecular oxidative coupling reactions of monophenolic benzyl- and phenethyltetrahydroisoquinolines contrast remarkably with the results of most prior studies of oxidative cyclization of diphenolic precursors.[2] Further investigations are in progress to evaluate the potential of the monophenol oxidative coupling reactions for the synthesis of other alkaloids.

References and Notes

(1) This investigation was supported by grants from the National Cancer Institute (CA-12059) and the American Cancer Society (CI-102K).

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(3) M. A. Schwartz, B. F. Rose, and B. Vishnuvajjala, *J. Am. Chem. Soc.*, **95,** 612 (1973).

(4) S. M. Kupchan and A. J. Liepa, *J. Am. Chem. Soc.*, **95,** 4062 (1973).

(5) U. Palmquist, A. Nilsson, V. D. Parker, and A. Roland, *J. Am. Chem. Soc.*, **98,** 2571 (1976).

(6) Benzyl- and phenethyltetrahydroisoquinolines **1a–g** were prepared by a standard method, i.e., condensation of benzyloxyphenethylamines and acids to the corresponding amides followed by Bischler–Napieralski cyclization, $NaBH_4$ reduction, N-acetylation or N-methylation, and subsequent debenzylation by hydrogenolysis.

(7) All new compounds were characterized by concordant analytical and spectral data. The structural formulas containing asymmetric atoms refer to racemic mixtures.

(8) In a typical oxidation 1 mmol of the substrate [0.05 M solution in methylene chloride containing 20% TFA–TFAA (20:1 by weight)] was treated with 2.5 molar equiv of VOF_3 [dissolved in a minimum volume of a 1:1 solution of ethyl acetate and TFA–TFAA (20:1 by weight)].

(9) Alkaline hydrolysis of **4a** and subsequent N-methylation ($HCHO$–$NaBH_4$) afforded (±)-thalicmidine[12] (**4b,** 80%).

(10) The structure of **5a** was confirmed by alkaline hydrolysis to the secondary amine, conversion of the secondary amine to the *N*-methyl dienols by treatment with $HCHO$–$NaBH_4$, and subsequent oxidation of the dienols to (±)-*O*-methylflavinantine[11] (**5b,** 65%).

(11) S. M. Kupchan and C.-K. Kim, *J. Am. Chem. Soc.*, **97,** 5623 (1975).

(12) S. M. Kupchan, V. Kameswaran, and J. W. A. Findlay, *J. Org. Chem.*, **38,** 405 (1973).

(13) The borane complex of **1b** was prepared[3] as an amorphous solid (99%) by treatment of **1b** in $CHCl_3$ with BH_3–THF and passage through a silica gel column using $CHCl_3$ as eluent.

(14) A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J. Chem. Soc., Perkin Trans. 1,* 1741 (1972).

(15) S. M. Kupchan, O. P. Dhingra, C.-K. Kim, and V. Kameswaran, *J. Org. Chem.*, preceding paper in this issue.

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(20) Rearrangements of **2c–e** to **4h–j** were complete within an hour. However, conversion from **2f** to **4k** was very slow and required a much longer reaction time (overnight).

(21) The compound **1f** failed to give homoaporphine **4f** in high yield even after longer reaction time, probably owing to slow rearrangement[20] of homoproaporphine-type intermediate **3f.**

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Additions and Corrections

Vol. 37, 1972

Stanley J. Padegimas and Peter Kovacic*: *endo*-7-Aminomethylbicyclo[3.3.1]nonan-3-ones from Rearrangement of 1-N-Substituted *N*-Haloadamantanamines by Aluminum Chloride.

Page 2676, column 2, line 25. "J_{BX} = 15 Hz" should be $J_{BX} \simeq 11$ Hz.

Vol. 38, 1973

Lawrence R. Green* and Jack Hine: Isobutyraldehyde. The Kinetics of Acid- and Base-Catalyzed Equilibrations in Water.

Page 2802. In the last full sentence the words "absence" and "presence" should be exchanged.

Page 2803, line 5. "0.337" should be 0.454.

Vol. 39, 1974

John A. Tonnis,* Thomas A. Wnuk, Michael J. Dolan, and Peter Kovacic*: Behavior of *endo*-7-Aminomethylbicyclo[3.3.1]-nonan-3-one under Reducing Conditions.

Page 768. Experimental Section, column 1, line 16. "0.48" should be 0.048. Column 2, line 3. "J_{BX} = 16 Hz" should be $J_{BX} \simeq 11$ Hz.

Frank I. Carroll,* Gordon N. Mitchell, Joseph T. Blackwell, Asha Sobti, and Ronald Meck: Configuration and Conformation of *cis*- and *trans*-3,5-Dimethylvalerolactones.

Page 3895, column 1. Line 17. "I" should be II. Line 25. "II" should be I. Line 27. "I" should be II.

Vol. 40, 1975

Thomas A. Wnuk, John A. Tonnis,* Michael J. Dolan, Stanley J. Padegimas, and Peter Kovacic*: Diazotization of *endo*-7-Aminomethylbicyclo[3.3.1]nonan-3-ols and *endo*-7-Aminomethylbicyclo[3.3.1]non-2-ene.

Page 447, column 2, line 9. "20^4" should be 10^4.

Page 448, column 1, line 11. "J_{BX} = 13–14 Hz" should be J_{BX} = 10–11 Hz.

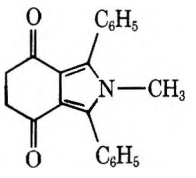
Rodger N. Jenkins and Leon D. Freedman*: Dihydrophenophosphazine Ring System.

Page 768. Column 1, line 1. The letters "aoton" should be a proton.

Page 768. Column 2, line 30. "8.2 g" should be 2.0 g.

John A. Myers,* Wendell W. Wilkerson, and Samuel L. Council: 1,3-Dipolar Addition of an Oxazolium 5-Oxide to Cyclopentadienequinone and to Anthracenequinone.

Page 2875, column 2. The structure assigned to compound **9** is incorrect. A structure in better accord with the available evidence is that shown below. The authors acknowledge Dr. R. S. Atkinson for first suggesting the discrepancy.



Page 2876. Because the structure of **9** was incorrect, Scheme I is also incorrect.

Peter Beak,* Jiro Yamamoto, and Charles J. Upton: Heterophilic Additions to Carbonyls and Thiocarbonyls. Scope and Stereochemistry.

Page 3056, column 1. Lines 24 and 25 should read as follows. increased for the products from the other isomer. However, the value of K which accounts for the observed 82% retention found for the first experiment in Table II leads to a prediction of 69% retention for the second experiment in the table. Conversely, a value of K which accommodates the observed 120% retention in the second experiment leads to a prediction of 50% retention for the first experiment in the table. Accordingly, the predicted extent of.

Page 3056, column 2, line 49. "100%" should be replaced by 67%.

C. Max Hull* and Thomas W. Bargar: Transfer of Oxygen to Organic Sulfides with Dimethyl Sulfoxide Catalyzed by Hydrogen Chloride. Preparation of Disulfoxides.

Page 3152. By-line. "Thomas W. Bargar" should be Thomas M. Bargar.

Page 3154. Reference 12a should have cited H. Nieuwenhuyse and R. Louw, *J. Chem. Soc., Perkin Trans. 1,* 839 (1973), which reverses these authors' previous assignment of configurations for 1,2-bis-(methylsulfinyl)ethane (1); accordingly, they find that the α form is actually the meso diastereoisomer.

Vol. 41, 1976

William F. Berkowitz* and Seth C. Grenetz: Cycloaddition of an Enamine to an Activated Cyclopropane.

Page 13, ref 12. The carbethoxylation of 3,3-dimethylcyclopentanone **16** was done using the procedure of A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 198.

Hanne Eggert, Craig L. VanAntwerp, Norman S. Bhacca, and Carl Djerassi*: Carbon-13 Nuclear Magnetic Resonance Spectra of Hydroxy Steroids.

Pages 72–74. The following entries in Table I were interchanged: for compound **10,** C-9 and C-14; for **21,** C-1 and C-17; for **29,** C-14 and C-17. In Table II for 6β-AcO-Androstane, C-3 and C-4 should be reversed. Table III: for 5α entry "0.0 (19) t" should be 3.9 (19) t; for 12β entry "1.2 (9) t" should be −1.2 (9) t.

K. T. Potts* and J. L. Marshall: Thiazolo[3,4-*b*]indazole, a Ring-Fused Tetravalent Sulfur Thiazole System.

Page 129. In structure **3,** the group, SC(Ph)=NH_2–, shown in the upper left is in error and should be replaced by R (as shown in structure 4).

G. S. Bajwa, K. Darrell Berlin,* and H. A. Pohl: Synthesis of $\Delta^{2,2'}$-Bis(1,3-benzodithiolidene) Derivatives and Complex Salts Therefrom with 7,7,8,8-Tetracyanoquinodimethane.

Pages 145 and 146. In the title as well as in the last line of the right column of page 145 and the fifth line of the left column of page 146, the correct ending for the name is benzothiolidene.

Richard Baltzly: Studies on Catalytic Hydrogenation. I. The Influence on Reaction Rates of the Metal–Carrier Ratio, of Solvents and Acidity.

Page 925, Table III, footnote *a*. The third word should be starting.

Page 926, Table VII. The upper part of this table should have a subheading reading as follows: Cyclohexene, 0.1 mg of Rh.

Richard Baltzly: Studies on Catalytic Hydrogenation. II. Poisoning by Nucleophiles.

Page 932, Table V, column 5 of table. All exponents in this column should be −7 (the first three are given as −7 and the next four as 7).

Pankaja K. Kadaba: Role of Protic and Dipolar Aprotic Solvents in Cycloaddition Reactions Involving Anionic 1,3-Dipoles, Action of Inorganic Azides on Imidoyl Chlorides.

Page 1073, column 2. In structure A, the bonding between the Cl and C and between C and the N of azide should be shown as dotted lines rather than as solid lines.

Vinayakam Subramanyam,* Eileen H. Silver, and Albert H. Soloway: Reaction of Phosphoranes with Formate Esters. A New Method for Synthesis of Vinyl Ethers.

Page 1272. It is regretted that, at the time of writing the paper, the authors were unaware of Dr. LeCorre's work [*Bull. Soc. Chim. Fr.,* Nos. 9–10, 2005 (1974); *C. R. Acad. Sci. Paris,* 963 (1973)] showing that vinyl ethers are formed when the two stabilized phosphoranes, benzylidene and ethoxycarbonylmethylene, react with formate esters.

Wojciech J. Stec,* Bogdan Uznański, Karol Bruzik, and Jan Michalski*: Protic Acid Catalyzed Thiono–Thiolo Rearrangements of Phosphorus Esters.

Page 1291, column 2, bottom. 1 + $H^+ \rightarrow$ **5** should be 1 + $H^+ \nrightarrow$ **5**.

Charles D. Hufford* and William L. Lasswell, Jr.: Uvaretin and Isouvaretin. Two Novel Cytotoxic *C*-Benzylflavanones from *Uvaria chamae* L.

Page 1297. The name uvaretin has also been chosen for a C-benzylated dihydrochalcone from another species of *Uvaria:* J. R. Cole, S. J. Torrance, R. M. Weidhopf, S. K. Arora, and R. B. Bates, *J. Org. Chem.*, **41**, 1852 (1976). Since the received date of our communication was later than that of Cole et al., we have agreed to change the names of our flavanones from uvaretin to chamanetin and isouvaretin to isochamanetin. The correct botanical authority for *Uvaria chamae* is P. Beauv.

Samuel P. McManus,* P. Judson Kelly, William J. Patterson, and Charles U. Pittman, Jr.: Reaction of Lactones and Thiolactones with 2-Amino-2-methyl-1-propanol. Synthesis and 2-Substituted 2-Oxazolines.

Page 1643, Table I. The calculated values for the elemental analysis of **5a** are incorrect. The values for C, H, and N should be 61.12, 9.62, and 8.91, respectively.

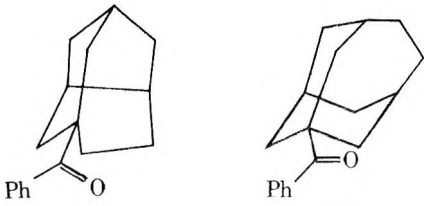
Toshiaki Yoshimura, Tetsuo Omata, Naomichi Furukawa,* and Shigeru Oae: Preparation and Physical and Chemical Properties of "Free" Sulfilimines.

Page 1729. Table I: run 7, before (35–36)^c the number 80 should be added; run 10, the number 55 should be moved down to run 11; run 19, after 95 (191) the superscript *d* should be added; footnote e, "mp 111 °C" should be corrected to mp 104 °C. Column 1. In lines 5 and 6, "(runs 9, 14)" should be corrected to (runs 10, 15). In line 18, "(runs 10, 12, 13, 15–18)" should be corrected to (runs 11, 13, 14, 16–19).

Page 1730. In Table II, after *p*-$CH_3C_6H_4$ c-C_3H_5 (cyclopropyl) should be added. Column 1. In line 13, the numbers "11, 19" should be corrected to 12, 20. In paragraph 3, lines 10 and 11, "longer wavelength" should be corrected to higher wavenumber.

H.-G. Heine,* W. Hartmann, F. D. Lewis, and R. T. Lauterbach: Photochemical Reactivity of Some Bridgehead Phenyl Ketones.

Page 1908. The structures of ketones 1 and 2 in Table I should appear as follows:



1 2

Sergio Alunni, Enrico Baciocchi,* and Piero Perucci: Kinetic Study of Elimination Reactions Promoted by Crown Ether Complexed Potassium *tert*-Butoxide in *tert*-Butyl Alcohol.

Page 2637. In Table II, line 21 should read as follows: 2,2-d_2 (Substrate); 30 (Temp, °C); 1.09 × 10^{-2} ([*t*-BuOK], M); 2.31 × 10^{-2} ([18C6], M); 0.31 (k_2, M^{-1} s^{-1}).

Page 2638, column 2. In footnote 7, line 2, "ref 3" should be ref 4.

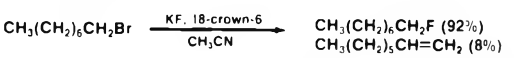
Shyam K. Gupta: New Reactions and Reagents. 5. Ketalization of 1,3-Dihydroxy-2-propane with Alkanols. Formation of Acyclic and Cyclic Ethers Derived from Pyruvic Aldehyde.

Page 2646, ref 18. We wish to call attention to two additional references pertaining to work described earlier by J. Gelas: J. Gelas and A. Thialliers, *Carbohydr. Res.*, **30**, 21 (1973), and J. Gelas, P. Calinaud, D. Horton, and J. D. Wander, *J. Chem. Soc., Perkin Trans. 2*, 1145 (1974).

Crown Ethers

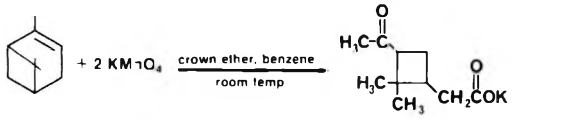
- 15-Crown-5: specific for Na^+
- 18-Crown-6: specific for K^+
- Dibenzo-18-crown-6
- Dicyclohexyl-18-crown-6

Since the discovery of their remarkable ability to dissolve alkali metal salts in non-polar solvents, crown ethers,[1a,b] a class of macrocyclic polyethers, have found novel application in synthesis. **18-Crown-6** promises even greater synthetic utility by virtue of its increased complexing ability.[2] For example, in acetonitrile or benzene effective solvation of the potassium ion of potassium fluoride by **18-crown-6** results in a highly reactive fluoride ion ("naked" fluoride).[2] "Naked" fluoride is a potent base and nucleophile,[2] being capable of converting a variety of alkyl, acyl, or activated aryl halides to their respective fluorides in good yields.



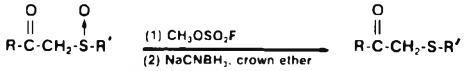
Acetate[3], cyanide[4] and nitrite[4] also display markedly enhanced nucleophilicity in the presence of **18-crown-6**.

In the presence of **dicyclohexyl-18-crown-6,** potassium permanganate readily dissolves in benzene to form a purple solution ("Purple Benzene")[5] which oxidizes alcohols, olefins, aldehydes and aralkyl hydrocarbons in excellent yield under neutral conditions.

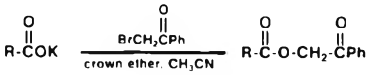


90%, *cis*
(40-60% with no crown ether in an aqueous system)

Alkoxysulfonium salts, formed by alkylation of sulfoxides with Magic Methyl® (methyl fluorosulfonate), are readily reduced with sodium cyanoborohydride in the presence of crown ethers[6] to give sulfides in excellent yield. Similarly, β-ketosulfoxides are reduced to β-ketosulfides,[6] whereas extensive decomposition occurs in the absence of the crown ether.



Phenacyl esters which are difficult to obtain in good yield using classical procedures are formed easily in a refluxing benzene or acetonitrile suspension of acyl salt, crown ether and α-bromoacetophenone.[6]



90% yield

The alkylation of acetoacetic ester enolates gives more *O*-alkylated product in the presence of a crown ether,[7] especially in weakly polar solvents. **Dicyclohexyl-18-crown-6** markedly changes the rates and stereochemical course[8] of alkoxide-catalyzed carbanion-generating reactions; *e.g.,* the reaction of 5-decyl tosylate with potassium alkoxides[9] produces more *trans* olefin in the presence of **dicyclohexyl-18-crown-6.** Crown ethers also find application in the resolution of α-amino acids[10] and show promise for the preparation of organometallics[11] by catalyzing the reaction between metals and C-halogen or acidic C-H compounds. The potassium hydroxide complex of **dicyclohexyl-18-crown-6** reacts with *o*-dichlorobenzene[12] to give *o*-chloroanisole in 40-50% through a non-benzyne mechanism. Finally, crown ethers may be contrasted with our **α- and β-cyclodextrins.** While the cyclodextrins have a lipophilic cavity and hydrophilic shell the reverse is true of the crown ethers.[13]

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